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GASTRIC CANCER  
PRECISION MEDICINE

Editors: Lin Chen  
Seon-Young Kim  
Haruhiko Sugimura



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# Gastric Cancer Precision Medicine

## (FIRST EDITION)

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It is my honor to be the editor of *Gastric Cancer Precision Medicine*. First of all, I would like to express my sincere gratitude to all authors and editors who devoted substantial efforts to publishing this book.

I have been engaging in precision medicine since last year when the Ministry of Science and Technology of the People's Republic of China issued the funding list of the Precision Medicine Key Research Project. For almost thirty years I have devoted myself to the diagnostic and therapeutic field of gastric cancer. Often is the case that patients with same stage of gastric cancer have different prognoses, which makes me realize the significance of precision therapy. We witnessed the evolution of the classification of gastric cancer, from microscopic morphology to the widely-used pathological TNM staging system. People have always been exploring the optimal therapeutic strategy for each subgroup of patients. What we can learn from the recently updated 8<sup>th</sup> edition of TNM staging manual for gastric cancer is that the traditional anatomical classification has constraint in further refining the classification of gastric cancer. The precision medicine, on the other hand, makes its way to emphasize the possibility of accurately sub-classifying the different statuses and processes of gastric cancer patients and identifying the therapeutic target by means of omics technology (e.g., genomics and proteomics) and other sophisticated techniques, and finally achieving precision medicine.

With the coordination of AME Publishing House, the present book invites worldwide experts from 16 countries, including the well-known professor Han-Kwang Yang from Korea and professor Seigo Kitano from Japan, to write this book. The content of this book is novel, covering biology, pathology, treatment and prognosis of gastric cancer, and discussing hot topics like minimally invasive gastric cancer, multidisciplinary team and immunotherapy.

Finally, I hope this book can benefit readers and inspire researchers.



**Lin Chen**

*Chairman of Digestive Tumor Committee, Chinese Research Hospital Association  
Director and Professor of Dept. of General Surgery, Chinese PLA General Hospital*

It is my pleasure to write the preface for this book *Gastric Cancer Precision Medicine*. Professor Chen, the leading Editor of the book, is a distinguished expert in the field of gastrointestinal surgery in China advocating minimally invasive surgery and personalized precision treatment for gastric cancer on the basis of his in-depth research and domain clinical expertise in this field. By assembling the knowledge of numerous experts from world-renowned medical centers, this book will show you invaluable experience of the experts' over the years and the latest progress they have made in precision treatment for gastric cancer.

Gastric cancer is a major burden of disease, particularly in developing countries. To make things more complicated, differences are frequently observed in the ways gastric cancer patients are diagnosed and treated between developed and developing countries. Bridging such differences, therefore, is of utmost importance in facilitating communication and collaboration among physicians from both sides. One major initiative to achieve this goal is the joint publication of such academic books as *Gastric Cancer Precision Medicine*. Organizing international symposiums and conferences is another initiative to accomplish this so that various physicians can exchange their distinctive ideas with one another. For example, the 12<sup>th</sup> International Gastric Cancer Congress (IGCC) to be held in Beijing, China from 20<sup>th</sup> to 23<sup>rd</sup> April, 2017 would provide the experts and physicians worldwide with a promising platform to work together to bridge the differences and improve the management of gastric cancer.

I would like to congratulate the authors, the editors, and any other contributors involved in the publication of this book. I am confident that the diverse thinking among the experts from both developed and developing countries presented by this book will inspire our fellow physicians to provide better gastric cancer care worldwide.



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# Identification of molecular subtypes and significantly mutated genes in gastric cancer using next-generation sequencing

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Gastric cancer is a complex disease that is caused by interactions among multiple genetic and extrinsic factors. The heterogeneous characteristics of gastric cancer make it difficult to select suitable treatment options for individual patients. According to a clinicopathologic perspective, gastric cancer is divided into two subtypes, intestinal or diffuse, which is also known as Lauren's classification. This classification helps to understand the pathogenesis of gastric cancer, but it is insufficient as a predictor of disease prognosis and drug treatment. Thus, more elaborate subgrouping of individual patients is required to develop a personalized therapeutic regimen.

In efforts to stratify gastric cancer patients, recent next-generation sequencing (NGS) studies have identified previously unrecognized molecular subtypes of gastric cancer. As a representative study, The Cancer Genome Atlas (TCGA) network classified gastric cancer into four subtypes, including Epstein-Barr virus (EBV)-positive, microsatellite instable (MSI), genomically stable (GS), and chromosomal instability (CIN) subtypes (1). This study used both sequencing and array-based approaches by investigating exome sequences, copy-number alterations, gene expression, DNA methylation, and protein activities in gastric cancer (2). As a result, this classification provides the most well-defined gastric cancer molecular subtypes to date. Nonetheless, more research is needed to determine significantly mutated genes, druggable targets, or prognosticators that represent each subtype.

In a recent report published in *Cancer Research*, Li *et al.* attempted to define novel molecular subtypes of gastric cancer using methodologies different from those of TCGA (3). In contrast to previous clustering strategies where transcriptome or methylome profiles were generally used, this study used only mutation data for clustering. First, a classification was conducted based on mutation loads by analyzing a total of 544 gastric cancer patients combined from five previous whole genome or whole exome studies. This unsupervised clustering stratified gastric cancer into two subtypes, referred to as regular-mutated (2.4 mutations/Mb; range from 0 to 8.3) and hyper-mutated (20.5 mutations/Mb; range from 9.6 to 200.2). The hyper-mutated subtype from Li *et al.* overrepresented MSI patients, but this subtype appears to be slightly different from TCGA's MSI subtype, as the hyper-mutated phenotype can be generated by defects of various genomic integrity maintenance mechanisms as well as mismatch repair, which is related to the MSI phenotype. Importantly, previous elegant studies from Rizvi *et al.* and Le *et al.* demonstrated that patients with high mutation loads showed sensitive responses to therapeutic blockade against immune checkpoints such as PD-1 (4,5). Thus, the MSI subtype from TCGA or the hyper-mutated subtype from Li *et al.* would clinically benefit from immune checkpoint blockade with PD-1 inhibitors (i.e., pembrolizumab) (5), suggesting the clinical relevance of the hyper-mutated subtype from Li *et al.*

The different mutation loads between subtypes indicate

that tumors from different subtypes may go through different mutation processes during tumor evolution. In fact, mutation signatures between the regular- and hyper-mutated subtypes were distinct. Notably, the regular-mutated subtypes acquired six times more mutations at TpCpA/T sequences than the hyper-mutated subtype (3). Given that TpCpA/T is a sequence motif for the DNA cytosine deaminase APOBEC3B (6), this result suggested that APOBEC3B may be involved in the mutation loads of the regular-mutated or microsatellite stable (MSS) subtypes. Moreover, the number of APOBEC signature mutations positively and significantly correlated with the *APOBEC3B* mRNA level. However, these data were interpreted with caution because the APOBEC signature of the hyper-mutated subtype can be attenuated by other predominant mutation processes, such as a deficiency in mismatch repair. Supporting this suspicion, the *APOBEC3B* mRNA levels were comparable between two subtypes. Therefore, the fact that the APOBEC signature more strongly contributes to the mutation processes of the regular-mutated subtype may be true, but we cannot say that the APOBEC signature is not important in the hyper-mutated subtype.

Li *et al.* further clustered the regular-mutated subtype into two groups, referred to as C1 and C2. This clustering was performed based on a binary mutation status matrix of significantly mutated genes that were found by three algorithms, MutSigCV, MutSigCL, and MutSigFN (7). The C1 cluster contained a significantly high proportion of TCGA's CIN subtype patients, whereas the C2 cluster was enriched with TCGA's GS subtype patients. Reflecting these patterns, *TP53* mutations, which are highly detected in the CIN subtype, were enriched in the C1 cluster, and *RHOA* and *CDH1* mutations, which are the representative mutations of the GS subtype and diffuse-type gastric cancer, were overrepresented in the C2 cluster. More importantly, the C2 cluster displayed poorer prognostic outcome than the C1 cluster, suggesting that the high proportion of GS subtype or diffuse-type GC within the C2 cluster could result in poor survival rates. However, multivariate analysis revealed that C1/2 clusters alone have prognostic value independent of Lauren's classification and the TNM staging. For easier C1/2 clustering, Li *et al.* defined eight genes (*TP53*, *ARID1A*, *CDH1*, *PIK3CA*, *XIPR2*, *APC*, *ERBB2*, and *RHOA*) as a classifier. Because the eight-gene classifier showed enough power to discriminate C1/2 clusters and acted as a significant independent prognostic marker, this method could be applied to gastric cancer patients for clinical uses.

Mutation data combined from 544 gastric cancer patients enabled detection of previously unrecognized significantly mutated genes with a high statistical power. In the regular-mutated subtype, 31 significantly mutated genes were identified. In addition to well-known cancer driver genes such as *TP53*, *ARID1A*, *CDH1*, *PIK3CA*, *APC*, *RHOA*, *SMAD4*, *ERBB4*, *KRAS*, *ERBB2*, and *CTNNB1*, Li *et al.* found unreported significantly mutated genes, including *XIPR2*, *NBEA*, *COL14A1*, *AKAP6*, *CNBD1*, and *ITGAV*. *NBEA* is located on chromosome 13 and is frequently deleted in multiple myeloma (8,9). *COL14A1* is down-regulated by promoter hyper-methylation in renal cell carcinoma (10). *AKAP6* and *CNBD1* are mutated in esophageal adenocarcinoma and gastroenteropancreatic neuroendocrine tumors, respectively (11,12). The functional roles of *XIPR2*, compared to those of other genes, have not been elucidated in the cancer field. Because *XIPR2* is one of the eight genes used in the classifier for C1/2 clustering, preferential functional validation is required to demonstrate the activity and role of *XIPR2* in gastric cancer.

Although this study revealed novel aspects of gastric cancer subtypes, there are several limitations. One limitation of this study is the lack of functional validation of the novel significantly mutated genes that were identified. Another limitation is that the statistical power to detect less frequent mutations (below 2%) is still not high enough with the current 544 samples. Interestingly, Lim *et al.* recently analyzed a total of 629 gastric cancer patients and identified several significantly mutated genes (i.e., *DHFR*, *GHSR*, *GLI3*, *GRM8*, *KIF2B*, and *PREX2*) (2) not reported in the Li *et al.* analysis. With more samples, more significantly mutated genes are expected to be discovered. As another limitation, it is unclear whether the subtyping from Li *et al.* is superior to the TCGA's gastric cancer subtypes. For instance, the C1 cluster from Li *et al.* contained a significantly enriched number of *ARID1A* and *PIK3CA* mutations, which were included in TCGA's EBV subtype, suggesting that the C1 cluster may be a mixture of TCGA's EBV subtype and other subtypes. Even four subtypes from TCGA may oversimplify the complexity of gastric cancer. Therefore, further efforts to categorize each molecular subtype from TCGA and Li *et al.* may be required to facilitate precision medicine of gastric cancer patients.

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### Footnote

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# Muscular metastasis from gastric cancer

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**Abstract:** The association between gastric cancer and muscle metastasis is extremely rare. Few cases have been reported in the literature. We report a case of a 68-year-old man, with a diagnosis of gastric adenocarcinoma by endoscopy and biopsy. A painful nodule on the right thigh became noticeable during chemotherapy sessions, where positron emission tomography and percutaneous biopsy diagnosed a muscle metastasis of gastric adenocarcinoma. This report demonstrates the importance of further investigation of muscle lesion in patients with gastrointestinal cancer and how we can diagnose and treat these lesions.

**Keywords:** Stomach; adenocarcinoma; neoplasm metastasis

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## Introduction

Gastric cancer may metastasize to unusual sites, such as gums, iris, testis, muscle and meninges (1-4). Skeletal muscle metastasis is rare and few sporadic cases have been reported in the literature (5-7).

We report a case of a patient with adenocarcinoma of the stomach and peripheral skeletal muscle metastasis.

## Case presentation

A 68-year-old gentleman with a history of epigastric pain, dysphagia and weight loss for 2 months presented for oncologic evaluation. Upper digestive endoscopy demonstrated a 3 cm ulcerated lesion at the cardia and a large hiatal hernia (*Figure 1*). Biopsy showed a signet ring adenocarcinoma. A tomography scan disclosed a 6.5 cm × 7.5 cm × 5.0 cm tumor at the proximal stomach and multiple enlarged lymph nodes around the esophageal hiatus and the celiac artery (*Figure 2*). Neoadjuvant chemotherapy was started. A positron emission tomography (PET-CT) was not performed at this time.

A painful nodule on the middle third of the right thigh became noticeable during chemotherapy sessions. A 4.0 cm × 2.8 cm × 2.4 cm (volume =14 cm<sup>3</sup>) heterogeneous hypoechoic tumour in deep muscular planes was noticed



**Figure 1** Upper digestive endoscopy disclosing an ulcerated lesion at the cardia and a large hiatal hernia.

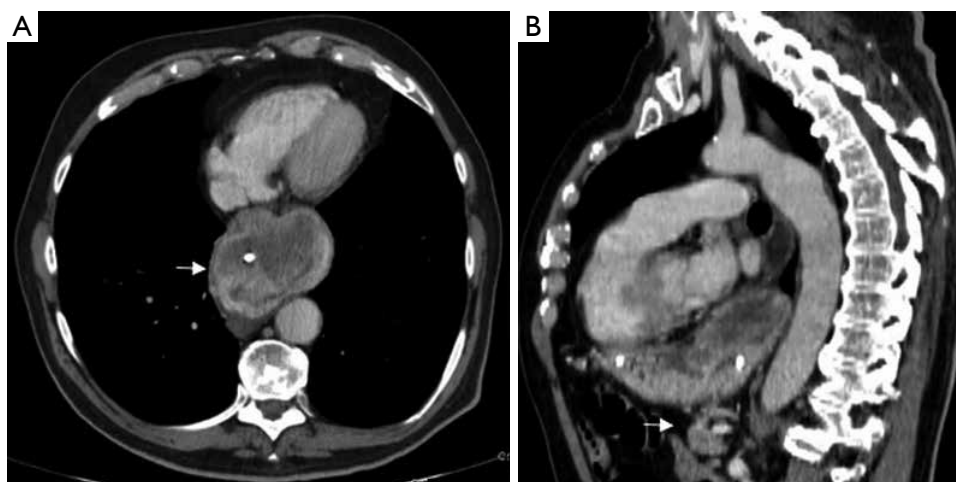
at the ultrasound. PET-CT showed elevated uptake at the gastric tumor site [standardized uptake value (SUV) =9.6 and right thigh (SUV =9.3)] (*Figure 3*). Percutaneous biopsy of the thigh lesion diagnosed a metastatic adenocarcinoma with the same characteristics of the gastric cancer.

Patient is current under chemotherapy.

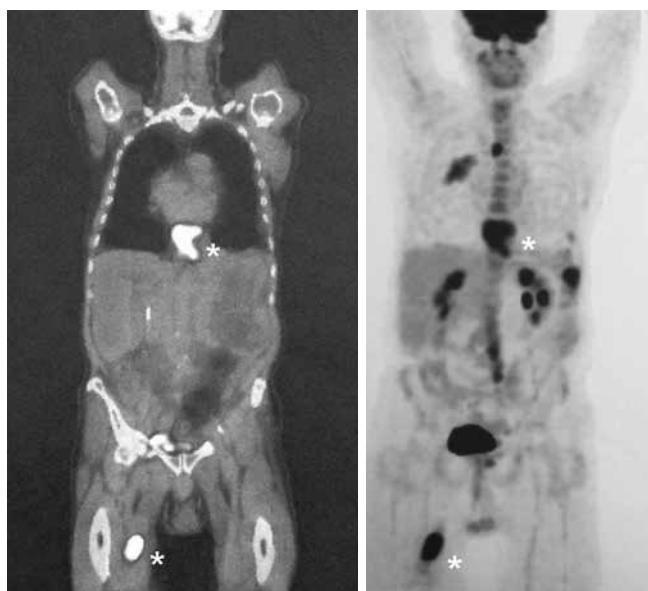
## Discussion

Muscular gastric metastasis is rare. Haygood *et al.* (8)





**Figure 2** Tomography tumor at the proximal stomach (A) (arrow) and multiple enlarged lymph nodes around the esophageal hiatus and the celiac artery (B) (arrow).



**Figure 3** Positron emission tomography showing an elevated uptake at the gastric tumor site and right thigh (\*).

reviewed 262 patients with skeletal muscular metastasis. The authors found that only 14% of the cases originated in the gastrointestinal tract and only one case originated in the stomach. In other study, Tuoheti *et al.* (9) reported two gastric metastasis out of 12 patients with muscular metastasis. The reasons for the rare incidence of muscle metastasis is still not certain since the muscular system

comprises around 50% of the body mass and is highly vascularized. It is believed that frequent changes of blood flow, the destruction of tumor cells by muscle movement, inhibition of tumor proliferation by lactic acid protease and muscle pH may be protective factors (6,7). Also, the portal filter may prevent peripheric spread of the disease without liver metastasis. The proximal location of the tumor may explain the dissemination via porto—azygos shunts in our case; however, the other reports does not state clearly the location of the neoplasm.

Muscle metastasis is usually asymptomatic, but depending on the location and degree of impairment may be associated with generalized muscle pain, muscle swelling, palpable mass, decreased range of motion, fever and weight loss (7). Diagnosis is made by imaging and histopathological examination of the lesion. Magnetic resonance imaging (MRI) is valuable for the detection of muscle metastasis (10). It shows a pattern of hypointense signal on T1 and hyperintense on T2. Some studies showed superiority of MRI compared to CT for detection of muscle metastases (5,7). Surgical resection may be used for symptomatic relief (5). Prognosis is usually poor (5).

In conclusion, skeletal muscle metastasis from gastric cancer is a rare finding. Painful nodules must bring awareness to the possibility of muscular metastasis.

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## Footnote

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# KRAS, BRAF and gastric cancer

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**Abstract:** Gastric cancer (GC) remains a major worldwide health problem and survival rates continue to be poor in patients with advanced stage disease despite multimodal treatment combining different chemo(radio)therapy regimens with surgery or best supportive care. Thus, there is an urgent clinical need to identify new potential drug targets in order to improve survival for GC patients. *KRAS* encodes a small guanosine triphosphatase and point mutations in codons 12 and 13 of *KRAS* have been detected in many human cancers. *BRAF* is a member of the RAF family of protein kinases and has a hotspot for mutations in codon 600 (so called V600E mutation). *KRAS* and *BRAF* proteins are both components of the MAPK/ERK pathway. When mutated, *KRAS* becomes constitutively active resulting in enhanced *BRAF* activity. *KRAS* and *BRAF* mutations in colorectal cancers (CRC) are known predictors of poor response to epidermal growth factor receptor (EGFR) targeting agents. This PubMed and Web of Science based review aimed to analyze and summarize the current literature on mutations in *KRAS* and *BRAF* in GC and their relationship to clinicopathological and molecular variables including *KRAS* amplification. In total, 69 studies were included in this review. The median incidence of a *KRAS* mutation was 6.5% ranging from 0-29%. The median incidence of *KRAS* mutations was similar in studies from the East and the West (East: 6%, ranging from 0-20%; West 7.5%, ranging from 0-29%). *KRAS* amplifications were reported at an incidence of 1-9%. The median *BRAF* mutation incidence in GC was 0%, ranging from 0% to 12%. Due to the low incidence and often small study size, many of the published studies had insufficient statistical power to detect a potential relationship between *KRAS* mutation status and clinicopathological variables including patient survival. In summary, the current literature on *KRAS* and *BRAF* in GC is still limited and very heterogeneous making any comparisons between different studies difficult. *BRAF* V600E mutations are very rare in GC. Interestingly, the incidence of *KRAS* mutations in GC is much lower than that in CRC and there appears to be no difference by ethnicity of the patients. *KRAS* mutations and *KRAS* amplifications seem to be mutually exclusive suggesting the need to screen GC patients for both genetic aberrations. So far, all clinical studies in unselected patients with metastatic GC have failed to show a significant benefit for EGFR targeting therapy. However, there has been a recent report indicating that the subgroup of signet ring cell GC, which is known to be resistant to standard cytotoxic chemotherapy, has a higher incidence of *KRAS* mutations (15%). Thus, EGFR targeted therapy in this particular histological subtype of GC could potentially be a promising treatment option in the future.

**Keywords:** Gastric cancer (GC); *KRAS*; *BRAF*; mutation; gene amplification

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## Introduction

Gastric cancer (GC) is a common cancer with a worldwide incidence of nearly one million cases per year (1). In 2012, there were an estimated 723,100 GC deaths worldwide, making GC the third most frequent cause of cancer related death. There is a large geographic variation in GC incidence, with the highest incidence rates in Eastern Asia (particularly in Korea, Mongolia, Japan, and China), Central and Eastern Europe, and South America and lowest rates in Northern America and most parts of Africa. The incidence of GC in men is about twice as high as in women (2) and approximately 10% of GCs have a familial component (3). *Helicobacter pylori* (*H. pylori*) infection is an established risk factor for developing GC. 89% of cases of non-cardia GC worldwide are attributed to this bacterium (4). Survival of GC patients remains poor. The overall 5-year survival of patients with locally advanced unresectable, recurrent or metastatic GC is 5-20% if treated with cytotoxic chemotherapy (5), increasing to 36% in patients with locally advanced resectable GC treated with peri-operative chemotherapy followed by surgery (6). Thus, there is an urgent clinical need to identify new potential drug targets in order to improve survival for GC patients.

Macroscopically, GCs are categorized according to the Borrmann classification into type I (polypoid), type II (fungating), type III (ulcerating), and type IV (diffusely infiltrating) (7). Histologically, GCs are most commonly categorized using the Lauren classification into intestinal, diffuse and mixed/indeterminate type (8). The intestinal-type occurs more commonly in elderly patients, whereas the diffuse-type is seen in particular in young female patients and has a poorer prognosis (9). In the West, the relative proportion of intestinal-type GC is up to 74% intestinal-type (10) compared to 44% in the East (11). Staging of GC is performed using the International Union Against Cancer (UICC) (12), American Joint Committee on Cancer (AJCC) (13) or Japanese Gastric Cancer Association (JGCA) (14) Tumor Node Metastasis (TNM) staging system which follow same principals but have some minor variations.

Molecular aberrations are known to play an important role in the development of GC. In addition to mutations in oncogenes, such as *TP53*, *APC*, *CDH1*, *p16* and *PTEN*, or tumor suppressor genes such as  $\beta$ -*catenin*, *BRAF*, *KRAS*, *PIK3CA* and *ERBB2* (15), microsatellite instability (MSI) caused by deficient DNA mismatch repair (MMR) has

been identified in 15% to 30% GC (16). DNA aneuploidy, a surrogate marker for chromosomal instability, has been reported in 24-85% GC (17) and Epstein-Barr Virus (EBV) infection has been identified in approximately 9% GCs (18). Several different molecular classifications of GCs have been proposed recently (19). For a recent review on this subject see Tan *et al.* (20).

The focus of this review is on the existing literature on genetic alterations in *KRAS* and *BRAF* in GC. Reported incidence of mutations in *KRAS* and *BRAF* and their relation to clinicopathological and molecular variables including *KRAS* amplification are analyzed and summarized. Literature on *KRAS/BRAF* epigenetic changes has been excluded from this review. Results from GC are compared with studies investigating *KRAS* and *BRAF* mutations in CRC and cancer of the small bowel. Furthermore, the clinical relevance of determining the mutational status and DNA copy number of these genes in relation to GC patient treatment will be discussed.

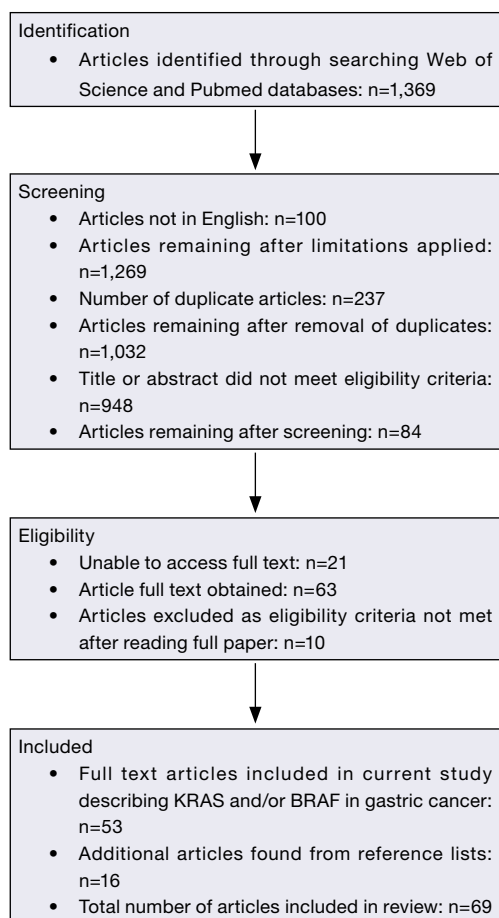
## Methods

The Web of Science (from 1988-14th May 2015) and PubMed (from 1946-14th May 2015) databases were searched for all known gene aliases of *KRAS* and *BRAF* (gene aliases from [www.genecards.org](http://www.genecards.org), accessed on 8th May 2015). These aliases were used as search terms in combination with (“gastric cancer” or “stomach cancer” or “gastric carcinoma” or “stomach carcinoma”, see *Table 1*).

Eligibility to be included in the current review was restricted to original articles reporting GC studies using human tissue, blood or plasma samples irrespective of sample size and stage of disease. Other tumors of the stomach such as lymphomas or gastrointestinal (GI) stromal tumors, and cell line studies were excluded. The reference lists of publications included in this review were searched for further relevant articles. Each article was analyzed for information on study size, geographical origin of patient cohort (East versus West), age, gender, survival, and whether any chemo(radio)therapy was given. With regard to DNA isolation from tumor tissue, the reported tumor cell density, number of blocks used, and tissue processing [frozen versus formalin-fixed paraffin embedded (FFPE)] were analyzed. Furthermore, information on the mutation incidence, the mutation detection method and investigated codons was collected from each study. The relationship of mutation status with clinicopathological variables, DNA MMR status and MSI, and DNA ploidy was noted.

**Table 1** Search terms used in PubMed and Web of Science

Variables	Search term
KRAS	("KRAS" OR "Kirsten Rat Sarcoma Viral Oncogene Homolog" OR "KRAS2" OR "RASK2" OR "V-Ki-Ras2 Kirsten Rat Sarcoma 2 Viral Oncogene Homolog" OR "V-Ki-Ras2 Kirsten Rat Sarcoma Viral Oncogene Homolog" OR "c-Ki-ras" OR "K-Ras 2" OR "CFC2" OR "NS" OR "C-K-RAS" OR "K-RAS2A" OR "K-RAS2B" OR "K-RAS4A" OR "K-RAS4B" OR "KI-RAS" OR "KRAS1" OR "NS3" OR "C-Kirsten-Ras Protein" OR "Cellular C-Ki-Ras2 Proto-Oncogene" OR "GTPase KRas" OR "K-Ras P21 Protein" OR "Oncogene KRAS2" OR "PR310 C-K-Ras Oncogene" OR "Transforming Protein P21" OR "Ki-Ras" OR "c-K-ras") AND ("gastric cancer" or "gastric carcinoma" or "stomach cancer" or "stomach carcinoma")
BRAF	("BRAF" OR "V-Raf Murine Sarcoma Viral Oncogene Homolog B" OR "V-Raf Murine Sarcoma Viral Oncogene Homolog B1" OR "Proto-Oncogene B-Raf" OR "BRAF1" OR "RAF1" OR "NS7" OR "94 KDa B-Raf Protein" OR "B-RAF1" OR "B-Raf Proto-Oncogene Serine/Threonine-Protein Kinase (P94)" OR "Murine Sarcoma Viral (V-Raf) Oncogene Homolog B1" OR "Serine/Threonine-Protein Kinase B-Raf" OR "EC 2.7.11.1" OR "p94") AND ("gastric cancer" OR "gastric carcinoma" OR "stomach cancer" OR "stomach carcinoma")

**Figure 1** PRISMA flow diagram showing the number of studies included at each stage of the review process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

## Results

The initial database searches found 1,369 articles in total. After screening, applying exclusion criteria and including additional articles from references, the final number of articles used for this review was 69. For a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram illustrating the manuscript selection process, see *Figure 1*.

### The KRAS

Mammalian cells encode three functional *RAS* genes: *HRAS*, *KRAS* and *NRAS* (21,22). Although these different isoforms share a similar structure, their expression and/or activation differs by tissue and cancer types (23–25). This review will focus on *KRAS* as it is the most frequently mutated *RAS* gene in GC (26).

Kirsten Rat Sarcoma Viral Oncogene Homolog (*KRAS*) was discovered in 1982 by Chang *et al.* (21). *KRAS* is a tumor suppressor gene which is located on chromosome 12p12 ([www.genecards.org](http://www.genecards.org), accessed 8th May 2015). It has six exons and alternative splicing of exon 4 produces *KRAS4A* and *KRAS4B* which contains 188 and 189 amino acids, respectively (27). *KRAS* encodes a small guanosine triphosphatase (GTPase) protein with a molecular mass of 21.6 kD (28).

The *KRAS* protein contains four domains which determine the interaction with GTP (G-domain, amino

acids 1-165), the anchoring of the protein in the plasma membrane (hypervariable region at the C-terminus, amino acids 165-188) as well as the binding of other regulators and effectors such as RAF and PI3K (28).

KRAS cycles between an inactive GDP-bound state and an active GTP-bound state (29). Activation of KRAS is triggered through a number of different types of receptors including tyrosine kinase receptors such as epidermal growth factor receptor (EGFR), as well as cytokine receptors, T cell receptors, and subunits of heterotrimeric G proteins (30). Active RAS-GTP undergoes a conformational change affecting its interaction with various downstream effector molecules such as RAF and mitogen-activated protein kinase (MAPK) (31) or PI3K/AKT (32). This in turn activates nuclear transcription factors inducing a cascade of cellular processes such as proliferation, angiogenesis, apoptosis, or cell survival (26). Mutant *KRAS* functions as an oncogene inducing malignant transformation of cells due to permanent activation of downstream effectors (33).

*KRAS* mutations have been found in many human cancers. The most common mutations are located in codon 12 or 13 in exon 1, and less frequently in codon 61, 63, 117, 119 and 146 (28). Mutations in codons 12 and 13 are known to result in conformational changes and permanent expression ('activation') of the KRAS protein (34). Overexpression of *KRAS* as a result of loss of p16INK4 or loss of p53 has also been reported (35). For a more general review on *KRAS* mutations in human cancer, see Jancik *et al.* (28).

### ***KRAS* in GC**

#### ***KRAS* mutations**

The first report of a *KRAS* mutation in a single GC was published in 1986. Investigators described the presence of a single mutated *KRAS* allele (gly-12 to ser), together with a 30-50 fold amplification of the other *KRAS* allele (36).

Since this first publication, 64 studies have reported on the incidence of *KRAS* mutations in GC, with the majority of studies (61%) originating from Asia (see *Tables 2,3*). Two studies compared *KRAS* mutations between GC patients from the East and the West (37,38). Forty-five (70%) studies investigated the *KRAS* mutation status in patient cohorts comprising less than 100 patients.

#### **GC cohorts**

The median number of patients per study was 61, ranging from 5 to 712 patients. Excluding three international multicenter studies and two studies that did not mention the

geographical origin of their patients, there were 39 (66%) studies from the East and 22 (37%) studies from the West. Studies from the East had a higher median study size of 66 patients, ranging from 5 to 319 patients compared to studies from the West with a median study size of 33 patients, ranging from 7 to 494 patients. The largest GC study was an international multicenter study including 712 GCs: 278 GC from the United Kingdom, 230 GC from Japan and 204 CG from Singapore (38).

Twenty-five (39%) studies performed *KRAS* testing on samples from multiple centers (19,37-60), 20 (31%) studies used samples from a single center (61-80), and the remaining did not report this information. Twenty-seven (42%) studies were performed using DNA extracted from formalin-fixed paraffin (37-39,41,42,44,45,47,48,50-52) embedded tissue samples (56,61,63-66,68,69,72-74,81-84). With the exception of 11 studies which did not report at all which tissue was used (40,54,77,80,85-91), all other studies used DNA from 'paraffin embedded tissue' (fixation method not reported) (43,92-94), frozen tissue (19,46,53,59,60,67,70,71,75,76,78,79,95-98), blood or plasma samples (99), or a combination of the above (49,55,57,58,62). Of the studies using tissue samples, 37 (59%) used DNA extracted (38,39,44,46,47,50,52-54,60-64,67,68) from resection specimens (70,71,73-76,78-82,84,88-91,93,95-98), ten (16%) used a combination of biopsy and resection specimens (37,40,45,51,65,69,72,87,92,94) and two (3%) used biopsy specimens (77,86). The remaining 14 (22%) did not report on the type of specimen used (19,41-43,48,49,55-59,66,83,85). No study reported extracting DNA from multiple blocks, thus we have assumed that all studies used a single block for DNA extraction. Thirty-seven (59%) studies considered the tumor cell density of the tissue prior to DNA extraction by either performing microdissection or preselecting areas of tumor with tumor cell density ranging from >20% to >80% (19,37-40,44,46-54,61,62,64-71,73-76,81,82,84,89,93,94,98). Twenty-two (34%) studies investigated only subgroups of GC patients, thus eight (36%) studies investigated locally advanced GC (40-44,61,62,82), four (18%) studies metastatic and advanced GC (48,49,81,94), three (14%) studies early GC (45,65,84), two (9%) studies metastatic GC (66,90), two (9%) studies compared early with advanced GC (46,93), one (5%) study intestinal GC (47), one (5%) study MSI GC (85) and one study (5%) investigated GC with concomitant renal cancer (63).

#### ***KRAS* mutation detection methods**

A wide variety of methods was used to detect *KRAS* mutations. Twenty-six (41%) studies used polymerase chain

**Table 2** Published literature on *KRAS* mutation status in gastric cancer excluding studies testing chemotherapeutic agents

Author	Year	Origin	Total, n	mut <i>KRAS</i> , n [%]	Comment
Nagata <i>et al.</i>	1990	Japan	25	2 [8]	–
Victor <i>et al.</i>	1990	South Africa	11	0	–
Kihana <i>et al.</i>	1991	Japan	35	3 [9]	Three of seven adenoma had mut <i>KRAS</i> ; mut <i>KRAS</i> in well diff GC only
Miki <i>et al.</i>	1991	Japan	31	4 [13]	mut <i>KRAS</i> only found in intestinal-type GC
Capella <i>et al.</i>	1991	Europe	14	1 [7]	–
Ranzani <i>et al.</i>	1993	Europe	32	3 [9]	One mut <i>KRAS</i> also had allelic losses
Koshiba <i>et al.</i>	1993	Japan	37	1 [3]	No mut <i>KRAS</i> in 13 adenoma
Craanen <i>et al.</i>	1995	Europe	45	0	Only early GC tested
Sakurai <i>et al.</i>	1995	Japan	19	0	Only early GC tested
Hongyo <i>et al.</i>	1995	Europe	34	7 [21]	Only intestinal-type GC tested; no mut <i>KRAS</i> in stage III
Lee <i>et al.</i>	1995	South Korea	140	11 [8]	mut <i>KRAS</i> more common in DNA aneuploid and in upper third GC
Hosoi <i>et al.</i>	1995	Japan	31	0	Biopsy samples tested
Hao <i>et al.</i>	1998	China	206	0	–
Iwaya <i>et al.</i>	1998	Japan	5	1 [20]	Synchronous primary cancers of the esophagus and other organs
Arber <i>et al.</i>	2000	USA	32	1 [3]	–
Russo <i>et al.</i>	2001	Europe	63	5 [8]	mut <i>KRAS</i> not related to DNA ploidy
Lee <i>et al.</i>	2002	South Korea	71	1 [1]	–
Yoo <i>et al.</i>	2002	South Korea /US	104	10 [10]	mut <i>KRAS</i> related to intestinal-type GC and higher pT
Hiyama <i>et al.</i>	2002	Japan	48	4 [8]	mut <i>KRAS</i> related to well diff histology type, younger age and <i>H. pylori</i> infection
Lee <i>et al.</i>	2003	South Korea	319	9 [3]	mut <i>KRAS</i> related to advanced GC
Brennetot <i>et al.</i>	2003	Europe	82	10 [12]	mut <i>KRAS</i> only seen in MSI not in MSS GC
Kim <i>et al.</i>	2003	South Korea	66	4 [6]	–
Wu <i>et al.</i>	2004	Japan	62	1 [2]	mut <i>KRAS</i> GC related to MSI; <i>KRAS</i> and <i>BRAF</i> mutations were exclusive
Zhao <i>et al.</i>	2004	China	94	8 [9]	Seven of eight GC with mut <i>KRAS</i> were MSI. All mut <i>KRAS</i> in GC from antrum
Yashiro <i>et al.</i>	2005	Japan	180	20 [11]	Only advanced GC tested. mut <i>KRAS</i> more common in well diff GC and Bormann type I. No relationship with <i>H. pylori</i> infection
Oliveira <i>et al.</i>	2005	Europe	25	6 [24]	Only MSI GC tested
Tajima <i>et al.</i>	2006	Japan	133	7 [5]	Only early GC tested; no <i>KRAS</i> mutation in 63 gastric adenoma
Sasao <i>et al.</i>	2006	Japan	55	1 [2]	–
Kusano <i>et al.</i>	2006	Japan	78	4 [5]	–
Gylling <i>et al.</i>	2007	Europe	59	4 [7]	mut <i>KRAS</i> only seen in MSI not in MSS GC
Tajima <i>et al.</i>	2007	Japan	134	8 [6]	Only differentiated GC tested

Table 2 (continued)

**Table 2 (continued)**

Author	Year	Origin	Total, n	mut KRAS, n [%]	Comment
Kimura <i>et al.</i>	2007	Japan	66	3 [5]	–
Liu <i>et al.</i>	2009	China	52	5 [10]	mut <i>KRAS</i> only seen in males
Mita <i>et al.</i>	2009	Japan	86	0	5% <i>KRAS</i> amp
Betge <i>et al.</i>	2011	Austria	12	1 [8]	GC with concomitant renal cancer
Liu <i>et al.</i>	2011	China	58	6 [10]	mut <i>KRAS</i> only seen in males
Corso <i>et al.</i>	2011	Europe	63	11 [17]	Only MSI GC tested; mut <i>KRAS</i> more common in elderly patients
Chen <i>et al.</i>	2011	China	123	12 [10]	<i>KRAS</i> tested in blood
Saxena <i>et al.</i>	2012	India	62	0	–
Deng <i>et al.</i>	2012	Singapore	139	1 [1]	9% <i>KRAS</i> amp
Matsubara <i>et al.</i>	2013	Japan	71	1 [1]	–
Van Grieken <i>et al.</i>	2013	Europe/Japan/ Singapore	712	29 [4]	mut <i>KRAS</i> associated with MMR-deficient GC. In Europe cohort mut <i>KRAS</i> associated with pN, in Japan cohort mut <i>KRAS</i> associated with elderly patients
Kim <i>et al.</i>	2013	South Korea/Japan	30	2 [7]	mut <i>KRAS</i> associated with CIMP
Warneke <i>et al.</i>	2013	Europe	475	17 [4]	mut <i>KRAS</i> associated with worse survival in proximal GC. mut <i>KRAS</i> intestinal-type GC with worse prognosis than <i>KRAS</i> wild-type intestinal-type. 9% <i>KRAS</i> amp
Kim <i>et al.</i>	2014	South Korea	17	1 [6]	Early and advanced GC tested. Missense mutation detected
Kim <i>et al.</i>	2014	South Korea	89	3 [3]	Only metastatic GC tested. <i>KRAS</i> amp in two cases; one case had increased copy number
Peng and Zhao	2014	China	126	9 [7]	Tissue and plasma tested
Palacio-Rua <i>et al.</i>	2014	Colombia	29	2 [7]	–
Qian <i>et al.</i>	2014	China	131	8 [6]	mut <i>KRAS</i> and <i>KRAS</i> amp (5%) mutually exclusive; associated with different outcomes
TGCA	2014	Multicenter	215	36 [17]	–
Ali <i>et al.</i>	2015	USA	116	12 [10]	6% <i>KRAS</i> amp. Includes 36 samples from metastatic sites
Lu <i>et al.</i>	2015	China	156	7 [4]	mut <i>KRAS</i> associated with pN0 GC
Cristescu <i>et al.</i>	2015	South Korea	223	18 [8]	8% <i>KRAS</i> amp
Yoda <i>et al.</i>	2015	Japan	50	4 [8]	8% <i>KRAS</i> amp

mut *KRAS*, mutant *KRAS*; GC, gastric cancer; pT, tumor invasion depth; MSI, microsatellite instability; MSS, microsatellite stable; well diff, well differentiated; pN, lymph node metastasis; CIMP, CpG island methylator phenotype; *KRAS* amp, *KRAS* amplification.



**Table 3** Published literature on *KRAS* mutation status in gastric cancer studies investigating chemotherapeutic agents

Author	Year	Origin	Total, n	mut <i>KRAS</i> , n [%]	Stage of disease	Treatment	Sample type used for <i>KRAS</i> testing	Mutant <i>KRAS</i> relationship to survival
Pinto <i>et al.</i>	2009	Europe	32	3 [9]	Advanced unresectable. Include some junctional cancer	Cetuximab + cisplatin and docetaxel	Not specified	Not reported (no association with ORR)
Han <i>et al.</i>	2009	South Korea	38	0	Recurrent metastatic	Cetuximab + oxaliplatin/leucovorin/5-fluorouracil	Not specified	No mut <i>KRAS</i>
Park <i>et al.</i>	2010	South Korea	30	4 [13]	Metastatic	Cetuximab + chemotherapy	Primary tumor	No association with PFS and OS
Lordick <i>et al.</i>	2010	Europe	52	1 [2]	Metastatic or locally advanced unresectable	Cetuximab + oxaliplatin/leucovorin/5-fluorouracil	Not specified	Not reported
Moehler <i>et al.</i>	2011	Europe	29	0	Advanced	Sunitinib monotherapy	Not specified	No mut <i>KRAS</i>
Rohrberg <i>et al.</i>	2011	Europe	7	2 [29]	Advanced	Erlotinib + bevacizumab	Not specified	No association with PFS, OS and DC
Woll <i>et al.</i>	2011	Europe	13	0	Metastatic or locally advanced unresectable	Oxaliplatin, irinotecan + cetuximab	Biopsies/resected primary tumor	No mut <i>KRAS</i>
Okines <i>et al.</i>	2013	Europe	494	30 [6]	Unresectable and/or metastatic GC. Includes some esophageal and junctional cancer	REAL 3: epirubicin, oxaliplatin and capecitabine ± panitumumab; MAGIC: epirubicin, cisplatin, 5-fluorouracil	REAL 3: pre-treatment biopsies; MAGIC: resections	REAL 3: no association with RR; MAGIC: no association with OS
Richards <i>et al.</i>	2013	USA	40	5 [13]	Metastatic	Docetaxel plus oxaliplatin ± cetuximab	Not specified	Not reported (no association with response)
Takahashi <i>et al.</i>	2014	Japan	164	8 [5]	Advanced	Cisplatin/S-1/5-fluorouracil/5-fluorouracil + methotrexate/paclitaxel + capecitabine + cisplatin ± bevacizumab in metastatic disease	Resection	No association with OS

mut *KRAS*, mutant *KRAS*; PFS, progression free survival; OS, overall survival; DC, disease control; ORR, objective response rate; RR, response rate.



reaction (PCR) (37,43,44,49,60,61,66,70,74,75,80,88,98) or single-strand conformation polymorphism (SSCP) (39,45, 47,52,64,65,71,72,85,93,95,97,99) for mutation screening, followed by confirmatory direct Sanger sequencing. Other methods used to detect *KRAS* mutations included restriction fragment length polymorphism (RFLP) (51,76-78,83,86), next-generation sequencing (NGS) (19,46,48,59,67,81,87,96), pyrosequencing (63,68), Q-PCR (41,94), nested and COLD-PCR (55), denaturing gradient gel electrophoresis (DGGE) (89,91), dot blot hybridization assay (56-58,69,73,82), high-resolution melting analysis (HRMA) (42,50,53,54) and direct Sanger sequencing (62,79). The largest international multicenter study used a combination of HRMA followed by Sanger sequencing, pyrosequencing, and MassARRAY (38). One study used RFLP and SSCP followed by direct sequencing (92), while other studies used a combination of RFLP and dot blot hybridization (84) or a combination of Q-PCR and Sanger sequencing (40). One study did not report which *KRAS* mutation detection method was used (90).

### Investigated *KRAS* codons

Excluding eight studies that performed whole genome sequencing, 49 (88%) studies published information on investigated codons for mutation testing. The remaining seven (13%) studies did not provide any information which codons they investigated, however, they later report only mutations in specific codons. All studies investigated multiple codons, with 49 (100%) investigating codon 12, 45 (92%) codon 13, 18 (37%) codon 61, and 1 codon 146. Only a single study investigated all four codons (codons 12, 13, 61 and 146) (62) and one study investigated codon 59, in addition to codons 12, 13 and 61 (93).

### Incidence of *KRAS* mutations

The overall median incidence of a *KRAS* mutation in GC was 6.5% ranging from 0-29%. The median *KRAS* incidence was similar in studies from the East and the West (East: 6%, ranging from 0-20%; West 7.5%, ranging from 0-29%). Likewise, the largest international multicenter study reported an overall incidence of *KRAS* mutations of 4.2% which did not differ between Eastern and Western countries (UK: 6%, Japan 4%, Singapore 2%) (38).

Of the 36 studies that reported the location of the mutations in *KRAS*, 154 mutations were found in codon 12, 66 mutations in codon 13, six mutations in codon 61. No mutation has been found so far in codon 146. The only study to report *KRAS* mutations in codon 11, was the result

of SSCP and direct sequencing of exon 1. This revealed that two of the seven mutations found in 34 GCs were located in codon 11, all other mutations were in codons 12 and 13 (47). Another study, in addition to identifying one *KRAS* mutation in codon 12 and two *KRAS* mutations in codon 13, also found a K5N mutation in exon 2 and five A59T mutations in exon 4 (93). There was only a single report of a single GC having multiple mutations in codon 12 and codon 13 (78).

### *KRAS* mutation status and clinicopathological variables

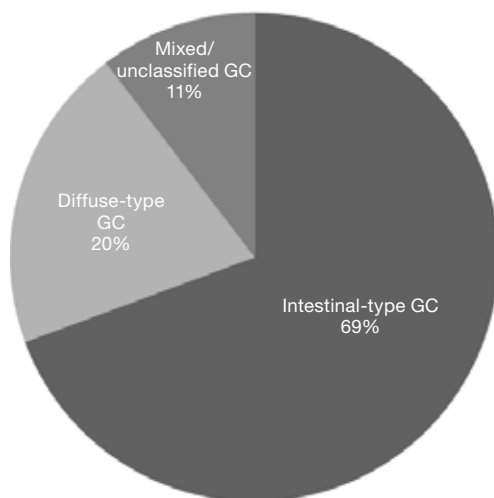
Twenty-nine (45%) studies have investigated the relationship between *KRAS* mutation status (19,37,38,40,46,47,50-54,56,60,62-64) and one or more clinicopathological variables (68,69,71-73,75,76,82,88,91,93,96,98). These included grade of tumor differentiation, Lauren classification, tumor location, tumor invasion depth (pT), lymph node status (pN), Borrmann classification, age, gender, and infection with *H. pylori* or EBV. The most frequent investigated association was found between *KRAS* mutation status and pT, followed by gender and age reported in 33%, 30% and 30% of studies, respectively.

### *KRAS* mutation and age

Nineteen (30%) studies investigated the relationship between patient age and *KRAS* mutation status mostly suggesting that *KRAS* mutations are more frequent in elderly GC patients. Seven (37%) studies reported individual ages or the median age of patients with a *KRAS* mutation (19,46,60,62,63,69,96), whereas the remaining studies stratified patient age into a range of subcategories (38,50,52-55,68,72,76). Only Hiyama *et al.* reported a significantly higher incidence of *KRAS* mutations in patients younger than 60 years (72). One study reported an equal number of *KRAS* mutations in patients  $\leq 65$  years old and  $>65$  years old (54). All other studies found *KRAS* mutations more frequently in elderly patients although this association often did not reach statistical significance (38,50,52,53,55,68,76,98).

### *KRAS* mutation and gender

Nineteen (30%) studies investigated the relationship between gender and *KRAS* mutation status in GC. Although no statistically significant relationship between *KRAS* mutation status and gender was found, most studies seem to suggest that *KRAS* mutations are more frequent in males. Nine (47%) studies found a higher incidence in males (38,46,50,55,62,68,69,72,76), three (16%) studies



**Figure 2** Distribution of *KRAS* mutation incidence in gastric cancer (GC) by Lauren classification.

reported that *KRAS* mutations were exclusively found in males (53,54,63) whereas four (21%) studies found an equal incidence of *KRAS* mutations in males and females (60,75,91,96).

#### ***KRAS* mutation and tumor location**

Twelve (19%) studies investigated the relationship between *KRAS* mutation status and GC location within the stomach. Tumors in the upper third of the stomach had a significantly higher incidence of *KRAS* codon 12 mutations compared to GCs in the middle or lower (3%) third of the stomach (76). Summarizing and interpreting the results from the other studies is difficult as stomach area categorization varied substantially between studies. We therefore defined that GCs located in the cardia or upper third are ‘proximal’ and GCs located in all other regions are ‘distal’. These studies found a higher incidence of *KRAS* mutations in distal GC (19,37,38,60,63,64,68,72,75,91).

#### ***KRAS* mutation and Borrmann classification**

A single study investigated the relationship between *KRAS* mutation status and macroscopic classification according to Borrmann. This study investigated *KRAS* codons 12 and 13 in 108 GC patients with advanced disease and found a significant relationship between *KRAS* mutation status and Borrmann Type 1 (polypoid) GC (82). The incidence of *KRAS* mutation was 6/14 (43%), 8/29 (28%), 2/11 (18%), and 4/54 (7%) in Borrmann type 1 to 4 GCs, respectively. Interestingly all *KRAS* mutations in polypoid

GCs were located in codon 12. This is in contrast to a study investigating 48 GC which did not find any relationship between macroscopic appearance (classified according to the Japanese Research Society for Gastric Cancer) and *KRAS* mutation status (72).

#### ***KRAS* mutation and primary tumor invasion depth (pT category)**

Twenty-one (33%) studies investigated the relationship between *KRAS* mutation status and pT in GC. Unfortunately, different staging systems were used in different publications and some studies compared groups of pT categories against each other making the results interpretation difficult. None of the studies reported a significant association between pT category/stage and *KRAS* mutation status. Overall, there was a higher incidence of *KRAS* mutations in higher pT (pT2-4) GC compared to lower pT (pT1) GC (19,37,38,47,50,53,54, 60,63,68,75,76,82,88,91,93,96).

#### ***KRAS* mutation and lymph node status (pN category)**

Eleven (17%) studies investigated the relationship between *KRAS* mutation status and presence of lymph node metastases with conflicting results. Five (45%) studies found that *KRAS* mutant GCs tended to have either no lymph node metastases (46,50,53,54) or significantly fewer lymph node metastases (38). Whereas other studies report that *KRAS* mutations are more frequent in GCs with lymph node metastases (19,63,68,91,96).

#### ***KRAS* mutation and histological subtype according to Lauren classification**

Seventeen (27%) studies including a total of 2,583 patients investigated the association between *KRAS* mutation status and histological subtype according to the Lauren classification (19,37,38,40,46,47,56,60,62,63,68,72,75, 76,88,91,93). Although 11 (65%) of studies reported a higher incidence of *KRAS* mutations in intestinal-type GC (see *Figure 2*), this association did not reach statistical significance in any of the studies (19,37,38,40,56,60,62,68, 72,75,91).

#### ***KRAS* mutation and grade of tumor differentiation**

Fifteen (23%) studies investigated the relationship between *KRAS* mutation and grade of tumor differentiation reporting discordant results. One (7%) study investigating advanced disease found that *KRAS* mutations were significantly more frequent in histologically differentiated GC (82), three (20%) studies found a higher incidence of *KRAS* mutations

in well-differentiated GCs (47,69,72) whereas nine (60%) studies reported a higher incidence of *KRAS* mutations in poorly-differentiated GCs (38,46,50,53,54,63,73,75,76). Two studies (13%) found the same incidence of *KRAS* mutations in well- and poorly-differentiated GC (40,96).

#### ***KRAS* mutation and survival**

Seven (11%) studies investigated the relationship between *KRAS* mutation status and survival (38,41,62,66,68,76,79). The largest international multicenter study reported a trend towards better survival in patients with a *KRAS* mutant GC (38). In contrast, subgroup analysis in a different study showed that the median survival of patients with *KRAS* mutant proximal GCs was significantly shorter ( $3.5 \pm 3.1$  months) compared with *KRAS* wild-type GCs ( $12.7 \pm 0.7$  months,  $P=0.021$ ) (68). The same study found that *KRAS* mutant intestinal-type GCs had a worse prognosis compared to *KRAS* wild-type intestinal-type GC, however this difference was not significant on univariate analysis ( $P=0.098$ ). Similarly, patients with a *KRAS* mutant GC in the upper third of the stomach may have improved survival over patients with *KRAS* mutant GC in the middle or distal stomach (76).

#### ***KRAS* mutation and chemotherapeutic agents**

Ten (16%) studies investigated the relationship between *KRAS* mutations and the use of chemotherapeutic agents (see Table 3). Four studies (40%) did not find any association between *KRAS* mutation status and progression free survival (PFS) or overall survival (OS) (40,41,62,66), three (30%) studies did not detect any *KRAS* mutations (42,44,94) and two (20%) studies did not find an association between *KRAS* mutations and response to chemotherapy (43,90).

#### ***KRAS* mutation and *H. pylori* infection**

Six (9%) studies have investigated the relationship between *H. pylori* infection and *KRAS* mutation status. Three studies reported a higher incidence of *KRAS* mutations in *H. pylori* infected GCs, but the difference was not significant or statistical analysis was not performed (47,82,97). In contrast, thirteen (87%) *KRAS* mutant GCs were found to be *H. pylori* negative, compared to two *H. pylori* *KRAS* mutant GCs (68). One study reported an equal incidence of *KRAS* mutations in *H. pylori* positive and negative GCs (75). The study by Hiyama *et al.* found that *KRAS* mutations in *H. pylori*-chronic gastritis were significantly more frequent in patients with GC than those without and in patients with *KRAS* mutated GC than in *KRAS* wild-type GC (72).

#### ***KRAS* mutation and EBV infection**

Four (6%) studies investigating a total of 848 GC for *KRAS* mutation status and EBV infection found no relationship between EBV and *KRAS* mutation (19,63,68,97).

#### ***KRAS* mutation status and molecular variables**

##### ***KRAS* mutation and DNA MMR deficiency/MSI (MMR/MSI)**

Thirteen (20%) studies investigated the relationship between *KRAS* mutation status and MMR/MSI with controversial results. One study which included only MSI GC reported that 18% harbored a *KRAS* mutation (98). Eight (62%) studies reported a higher incidence of MSI in *KRAS* mutant GCs (39,63,67,70,74), which was significant in three studies (19,75,91). This finding was supported by one study which found that *KRAS* mutations were more frequent in MMR-deficient GC (38). In contrast, two studies reported that *KRAS* mutant GC were more frequently microsatellite stable (MSS) (46,68).

##### ***KRAS* mutation and DNA ploidy**

Three (5%) studies investigated the relationship between DNA ploidy and *KRAS* mutation status. Two investigated DNA ploidy by DNA flow cytometry. One study investigated *KRAS* mutations in codons 12 and 13 (71), whereas the other study focused on codon 12 (76). Another study investigated DNA ploidy by NGS (19). No associations were reported in any study.

##### ***KRAS* amplification**

Eight (13%) studies investigated *KRAS* amplification in addition to *KRAS* mutations with contradictory results. Three studies found that the incidence of *KRAS* amplification varied between 5% and 9% but was higher than that of *KRAS* mutation in GC (between 0% and 4%) (59,68,80). In contrast, four studies found that *KRAS* mutations are more frequent than *KRAS* amplifications in GC (48,67,87). One study, reported similar frequencies of *KRAS* amplification (6%) and *KRAS* mutation (6%) (79). Interestingly, the 5-year survival of patients with a *KRAS* amplification was worse than that of the patients *KRAS* mutant GC (HR 3.0, 95% CI: 1.3-7.0). Furthermore, *KRAS* amplification and *KRAS* mutation were exclusive. Deng *et al.* reported that patients with GC with a *KRAS* amplification had a significantly poorer prognosis, however, as only one *KRAS* mutation was detected, the relationship between *KRAS* mutation and prognosis could not be analyzed (59).

### The *BRAF*

*BRAF* is a member of the RAF family of protein kinases which has three members: *ARAF*, *BRAF* and *CRAF* (100). All RAF proteins share a common structure (101), but *BRAF* is the only one known to be activated by mutation in human cancer, and therefore the focus of this review (102).

*BRAF* is also known as v-raf murine sarcoma viral homolog B1 (100) and was discovered in 1988 by Ikawa *et al.* (103). *BRAF* is a proto-oncogene and is located on chromosome 7 (7q34) ([www.genecards.org](http://www.genecards.org), accessed 8th May 2015). *BRAF* exists in multiple splicing variants, which seem to exhibit tissue specific expression patterns (104).

The *BRAF* protein is 75 to 100 kDa and has three conserved regions (CR): CR1, CR2 and CR3 (100). CR1 and CR2 are located at the N-terminus and are both regulatory domains, whereas CR3 is a kinase domain and is located at the C-terminus. CR1 is composed of the RAS-binding domain and a cysteine-rich domain binding RAS and membrane phospholipids. CR2 is a serine/threonine rich domain which when phosphorylated can bind regulatory proteins. CR3 is the protein kinase domain which is regulated through phosphorylation (101).

After RAS is activated via extracellular stimuli, it activates *BRAF* by phosphorylation of two residues in the kinase domain. Activated *BRAF* phosphorylates and activates MEK1 and MEK2 which then activate MAP kinases ERK1 and ERK2. ERK1/2 activates numerous cytoplasmic and nuclear targets including transcription factors (100).

More than 65 different mutations have been identified in *BRAF* in human cancer. Most of these mutations are in exon 11 or exon 15 in the catalytic kinase domain (100). The most frequently detected *BRAF* mutation is a single amino acid substitution (V600E) in exon 15 (105). *BRAF* is most commonly mutated in melanomas (67%) and CRC (10%) (105,106). Mutant *BRAF* displays an elevated kinase activity (105) and becomes insensitive to negative feedback mechanisms (107). For a review on *BRAF* mutations in benign and malignant human tumors, see Michaloglou *et al.* (108).

### *BRAF* in GC

In total, 22 studies have investigated the incidence of *BRAF* mutations in GC. Seven (32%) studies screened for *BRAF* mutations by PCR, followed by direct sequencing (43,61,62,68,70,75,98,109). Other detection methods included denaturing high pressure liquid

chromatography, SSCP (39,40,52,93,110), HRMA (42), NGS (46,48,81), amplification-refractory mutation system-PCR, PCR-high resolution melting (50), real-time PCR, immunohistochemistry using a mutation-specific probe (111) or a combination of the above (38,88,112).

Fourteen (64%) studies used FFPE samples (38,39,42,43,48,50,52,61,68,81,88,93,109,111), five (23%) used frozen tissue samples (46,70,75,98,110) and one study used a combination of FFPE and frozen samples (62). Two studies did not report this information (40,112). Excluding the study that performed IHC, ten studies selected areas of tumor with a median tumor cell density of >55%, ranging from >20% to >80% (38,46,48,50,68,70,81,98,109,110). Six studies performed microdissection of the selected area (39,40,52,62,75,93). The remaining five studies did not provide this information (42,43,61,88,112).

All studies investigated the *BRAF* exon 15 'mutation hotspot' (V600E mutation). Some studies extended their mutation search to exon 11 and other regions of exon 15, or whole genome sequencing. The median *BRAF* mutation incidence in GC is 0%, ranging from 0% to 12% (38,39,42,43,46,48,50,52,61,62,68,70,75,81,88,93,98,109-112). Only six of the *BRAF* mutations identified were in V600E of exon 15 (38,40,70,110,112). Six mutations were found in codon 396 and four mutations in codon 608 of exon 15 by Sasao *et al.* (52). Lee *et al.* found two mutations in codon 593 and the remaining five mutations were in codon 599 (V599 M) (93) and Okines *et al.* identified a mutation in V600M and G596D of exon 15 (40).

The highest *BRAF* mutation incidence (12%) was reported in a Korean study of 17 early and advanced GC using whole-genome sequencing by NGS. The two mutations identified were missense mutations; one was detected in a mixed-type early cancer, the other one in an intestinal-type advanced cancer (46). There has been a single publication that used immunohistochemistry and a mutation specific antibody to detect the mutated *BRAF* protein as a surrogate for a *BRAF* mutation. All cases were negative (no evidence suggesting a *BRAF* mutation) (111).

Due to the low incidence of *BRAF* mutations no studies have reported a relationship between *BRAF* mutation status and DNA ploidy or clinicopathological variables. There are three studies that have investigated the relationship between MSI and *BRAF* mutation. *BRAF* mutations were not found in any of 37 MSI GC (110) which was confirmed in a study by Wu *et al.* where the *BRAF* mutant GC was MSS (70). However, in another study the two *BRAF* mutant GC were found to be MSI (46).

### *EGFR pathway in GC*

The EGFR pathway is known to be activated in GC (113). When EGFR is bound to its ligand, it triggers homodimerisation and heterodimerisation of the EGFR receptor. This activates a signaling cascade, including MAPK, through effector molecules RAS and RAF (113). Anti-EGFR monoclonal antibodies block ligand-induced binding EGFR tyrosine kinase activation by binding to the extracellular domain of EGFR (114).

## Discussion

### *KRAS and BRAF mutations in GC*

The current literature reporting on *KRAS* and *BRAF* mutations in GC is very heterogeneous in terms of sample size, patient ethnicity, patient treatment, mutation detection methods, tumor stage and grade of differentiation, as well as other clinicopathological variables.

The majority of studies (70%) investigated the *KRAS* mutation status in less than 100 patients. Such small studies may not be representative of the GC patient population and thus the patient selection bias may significantly influence any results. Thus, two of the smallest studies with five and seven patients reported some of the highest incidence of *KRAS* mutations, of 20% and 29%, respectively (41,95). Similarly, for *BRAF*, the smallest study of 17 patients reported the highest *BRAF* mutation incidence of 12% (46). Furthermore, twenty-two (34%) studies investigating *KRAS* mutations deliberately selected subgroups of GC patients to study the *KRAS/BRAF* mutation status, such as advanced and/or metastatic disease and early disease.

Despite the much higher incidence in the East, the number of studies investigating the relationship between *KRAS* and *BRAF* in GC from the East and the West is almost equal. Nevertheless, potential bias due to differences in the histological subtypes (diffuse-type GC is more prevalent in the East), disease stage (GC is diagnosed at an earlier stage in the East) and patient survival (better OS in the East) (115) needs to be considered when comparing study results, particularly in the twenty studies that performed *KRAS* mutation testing on series from a single center. However, the incidence of *KRAS* mutations between East and West were comparable and do not seem to be related to the differences in GC incidence (38). Thus, bias due to the patient's country of origin appears to have no or minimal influence on the incidence of *KRAS/BRAF*

mutations in GC.

An issue that was not addressed in any of the studies included in this review was the potential influence of tumor heterogeneity on the results. Tumor heterogeneity of *KRAS* and *BRAF* mutations has been described in CRC suggesting that more than one tumor block should be investigated if possible (116). None of the studies investigating *KRAS* and/or *BRAF* mutations in GC seem to have investigated multiple blocks. Studies either did not provide any information or investigated single blocks. Thus, it is impossible to assess whether the incidence of *KRAS* and/or *BRAF* mutations in GC is underestimated based on the current literature.

Over ten different methods were used to detect *KRAS* and/or *BRAF* mutations in GC. It is known that the sensitivity (ratio of mutant to wild-type) of different methodologies varies between techniques (117), with COLD-PCR having the highest sensitivity (1%) and direct Sanger sequencing having the lowest (10-30%). Despite this low sensitivity, Sanger sequencing is considered the 'gold standard' technique due to its ability to detect substitutions, insertion and deletions. The median *KRAS* mutation incidence in GC appears to be similar irrespective of the detection method and thus, the detection methodology does not appear to affect the incidence of mutations detected in GC.

Several of the studies investigating the use of chemotherapeutic agents in the treatment of GC that also performed *KRAS* mutation testing, did not provide sufficient information on the type of tissue used for *KRAS* testing (biopsy/primary resection/recurrent resection/pre- or post-treatment), detection methods used, or codons investigated. Thus it is not possible to accurately interpret the results and make comparisons between such studies. Future studies need to report detailed methodologies in order for conclusions to be drawn from the results.

A recent study suggested that *KRAS* amplifications contribute to the activation of *KRAS* in GC (80) and that activation by *KRAS* amplification may account for the low incidence of *KRAS* mutations in GC compared to other types of cancer (59). However, the results from studies comparing the incidence and relationship of *KRAS* mutations (0-10%) and *KRAS* amplifications (1-9%) in GC remain contradictory (48,59,67,68,79,80,87). Three studies seem to indicate that *KRAS* amplifications and mutations are mutually exclusive (48,79,80) suggesting a need to screen GC patients for both *KRAS* mutations and amplifications.

### ***Incidence of KRAS and BRAF mutations—comparison between GC, small bowel and colorectal cancer (CRC)***

According to the RASCAL collaborative, the incidence of *KRAS* mutation in CRC is 38% (118), and a similar incidence has been reported in other studies. Thus, the incidence of *KRAS* mutations in GC is much lower than in CRC. The incidence of *KRAS* mutations in small bowel adenocarcinomas seems to vary dramatically from 9-43% based on data from four studies investigating each less than 100 patients and is therefore partly comparable to that of GCs and partly similar to CRCs (51,119-121).

In contrast to GC, in CRC many studies have reported a significant association between *BRAF* mutation and either deficient MMR status or MSI (106,110,122-126). This could be related to the fact that *BRAF* mutations are much more frequent in CRC (5-22%) (127) than in GC (0-12%). In adenocarcinomas of the small bowel, the incidence of *BRAF* mutations is comparable to those reported in GC (119-121). Whereas in CRC *KRAS* and *BRAF* mutations appear to be mutually exclusive (128), there are two reports indicating that GC can harbor a *KRAS* and *BRAF* mutations simultaneously (48,93). In summary, *KRAS* mutations in GC are a rare event compared to other cancers of the GI tract. Such differences in the incidence of these mutations between cancers of the GI tract may reflect differences in carcinogenesis.

Although no significant relationship between gender and incidence of *KRAS* mutations has been reported in GC, *KRAS* mutations are more frequently reported in males. In addition, the incidence of *KRAS* mutations is higher in intestinal-type than diffuse-type GC. Both observations may be explained by the fact that the incidence of GC in men is twice as high as in women (2) and that intestinal-type GC is found more frequently in males (129). In CRC, the worldwide incidence is also higher in males but the relative difference is not as prominent as in GC (746,000 new CRC cases per year in males versus 614,000 in females) (2). The relationship between *KRAS* mutations in CRC and gender is not consistent. One study found a higher incidence of *KRAS* mutations in females (130), whereas the QUASAR study did not find a difference (122).

Twelve studies investigated the relationship between *KRAS* mutations and MMR/MSI in GC mostly suggesting a higher incidence of MSI in *KRAS* mutant GC compared to *KRAS* wild-type GC. This is in contrast to CRC, where *KRAS* mutant tumors are found to be less frequent MMR-deficient (118).

In CRC, patients with *KRAS* wild-type cancer seem to have a better survival (131). Few studies (9%) investigated the relationship between *KRAS* mutation status and survival in GC and the results do not concur with those from CRC.

### ***KRAS and BRAF mutations and response to anti-EGFR therapy***

In CRC, *KRAS* mutation and *BRAF* mutation are known predictors of poor response to EGFR targeted agents, such as cetuximab and panitumumab (132) and *RAS/BRAF* mutation screening is now part of routine clinical diagnosis. In contrast, the predictive value of *KRAS* and *BRAF* mutations in GC is far less clear. *In vitro*, several studies in *KRAS* wild-type GC cell lines reported sensitivity to EGFR targeting drugs (133-135). Other investigators report that, both *KRAS* mutant and wild-type GC cell lines were resistant to cetuximab (136). In GC xenografts, apoptosis was only induced in *KRAS* wild-type tumor cells treated with Cetuximab (136). Cetuximab was shown to reduce tumor volume, dissemination and vascularisation in EGFR-expressing, *KRAS* wild-type xenografts (133).

To date, the use of anti-EGFR agents (cetuximab and panitumumab) in phase III metastatic GC trials in patients has either showed no difference (137) or poorer survival than the control group (138). In the REAL3 trial, *KRAS* mutation status did not predict resistance to panitumumab in GC (40).

Due to the low incidence of *BRAF* mutations in GC, a clinical trial which stratifies GC patients according to their *BRAF* status is probably not feasible due to the high number of patients that would need to be screened. Although all studies investigated the V600E mutation, three of the studies that also investigated exon 11 and 15 found *BRAF* mutations other than the hotspot V600E mutation (40,52,93). Thus, there could be an argument for investigating the whole length of the *BRAF* gene for mutations in GC.

## **Conclusions**

In conclusion, despite the decrease in the incidence, GC remains a major worldwide health problem. *KRAS* was one of the first oncogenes discovered in GC in 1986. Nevertheless, the current literature on *KRAS* and *BRAF* in GC is still limited and very heterogeneous making any comparisons between different studies difficult. However, it appears that the incidence of *KRAS* mutations in GC



is much lower than in CRC, does not differ significantly by ethnicity and that *BRAF* V600E mutations are very rare in GC. Due to the low incidence and often small studies, many of the published studies did not have enough power to detect a potential relationship between *KRAS* mutation status and clinicopathological variables including patient survival. Even fewer studies have assessed *KRAS* amplifications as a mechanism for *KRAS* activation. So far all clinical studies in unselected metastatic GC have failed to show a significant benefit for EGFR inhibitors. A recent meeting abstract reported the incidence of *KRAS* mutations in signet ring cell GC is higher (15%) than in other types of GC (139). As the incidence of this histological subtype of GC is increasing, particularly in the West (10) and as this subgroup of GC appears to be highly resistant to standard chemotherapy (140), EGFR targeted therapy in signet ring GC could potentially be a promising treatment option in the future.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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# Implications of epithelial-mesenchymal transition in gastric cancer

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**Abstract:** Gastric cancer phenotypes have been associated with various gene alterations. To identify the phenotypes and basis of gastric cancer, precise information about genetic mutations and molecular associations is needed. Cadherin 1, type 1, E-cadherin (epithelial) (*CDH1*), one of the most commonly mutated genes, is closely involved in phenotypic transitions in gastric cancer. In this review article, we intensively discuss gene alterations and molecular networks in gastric cancer focusing on both *CDH1* and gastric cancer phenotypic diversity [including cancer stem cells (CSCs)] associated with the epithelial-mesenchymal transition (EMT).

**Keywords:** Cancer stem cell (CSC); Cadherin 1, type 1, E-cadherin (epithelial) (*CDH1*); epithelial-mesenchymal transition (EMT); gastric cancer; stem cell

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## Introduction

Gastric cancer has a variety of phenotypes (1). One of its interesting features is the differences between diffuse- and intestinal-type gastric cancers. The epithelial-mesenchymal transition (EMT) might explain these phenotypic differences. Cadherin 1, type 1, E-cadherin (epithelial) (*CDH1*) is commonly up-regulated in intestinal-type gastric cancer. In recent studies, mutations or gene alterations in *CDH1* have been associated with gastric cancer malignancy or metastatic ability. In this review, we describe the biological roles of *CDH1* in gastric cancer association with EMT. Gene expression profiling of gastric cancer has revealed that both cancer grades and stages can be identified via gene signatures (2). In addition, gene and genome alterations have been examined to detect cell phenotypes. Based on a comprehensive analysis of the gastric cancer genome, a number of genes, including *CDH1*, tumor protein p53 (*TP53*), AT rich interactive

domain 1A (SWI-like) (*ARID1A*), mucin 6, oligomeric mucus/gel-forming (*MUC6*), catenin (cadherin-associated protein), alpha 2 (*CTNNA2*), GLI family zinc finger 3 (*GLI3*), and ring finger protein 43 (*RNF43*) have been identified as mutated driver genes (3). These findings suggest the significance of molecular information in cancer prognosis and treatment.

In several diseases, the expression of EMT-related genes, including *CDH1*, has been demonstrated to be negatively regulated (4-8). However, the loss of *CDH1* is insufficient to induce EMT, suggesting that combinations of genes are involved in the EMT process (9). In this review, we focus on the biological roles of *CDH1* in gastric cancer and discuss the cellular phenotypic alterations.

## CDH1 and gastric cancer

*CDH1* is one of the frequently mutated driver genes in gastric cancer, particularly in the diffuse-type gastric

cancers (3,10-13). Generally, *CDH1* is up-regulated in intestinal-type gastric cancer and down-regulated in diffuse-type gastric cancers, whereas cadherin 2, type 1, N-cadherin (neuronal) (*CDH2*) is up-regulated in the diffuse-type gastric cancer (14). Analyses of *CDH1*- and *TP53*-mutated gastric cancers suggest that transforming growth factor-beta receptor 2 (*TGFBR2*) is a candidate driver gene that plays a role as a metastasis suppressor (7). Germline mutations in *CDH1* have been associated with human hereditary diffuse gastric carcinoma (15,16). Analyses using the Catalogue of somatic mutations in cancer (COSMIC) database (<http://www.sanger.ac.uk/genetics/CGP/cosmic/>) have revealed that *CDH1* mutations are also associated with diffuse-type gastric cancer (17). Whereas *CDH1* is mutated in approximately 40% of gastric cancer cases, germline mutations in mitogen-activated protein kinase kinase 6 (*MAP3K6*) have been associated with gastric cancers without *CDH1* mutations (5). The -160C to a promoter polymorphism and haplotypes of *CDH1* have been associated with the risk of developing sporadic diffuse-type gastric cancer (18).

A previous study has shown that *CDH1* expression was increased in gastric cancer cells co-expressing a putative mitogen-activated protein kinase activator with WD40 repeats (MAWD) and a MAWD binding protein (MAWBP), and they were treated with TGF-1 (19). *CDH1*, SMAD family member 4 (*Smad4*) and p53 play important roles in gastric cancer formation (20). The loss of *CDH1* and *Smad4* expression promotes diffuse-type gastric adenocarcinoma and metastasis (20).

Gastrokine 1, a molecule associated with gastric mucosal defense, is reduced in 36.4% of gastric mucosal tissues and is related to miR-185 expression (21). Considering that the Gastrokine 1-miR-185-DNA methyltransferase (DNMT) 1 axis is suggested as a suppressor of gastric carcinogenesis, the influence of gastrokine-regulated methylation on tumor progression should be investigated (21). Indeed, *CDH1* methylation was detected in more than 80% of gastric mucosal tissues examined in this study (21). *CDH1*, claudin-10 and claudin-17 are down-regulated in gastric cancer (22). The down-regulation of *CDH1* might be involved in cancer promotion. Germline variants of *CDH1* have been identified in sporadic gastric cancer patients, and the involvement of down-regulation in *CDH1* is indicated (23). In gastric cancer, *CDH1* is also regulated through cyclooxygenase-2 (*COX-2*) via the nuclear factor (NF)- $\kappa$ B pathway (24). Several somatic mutations of genes, including *erb-b2*

receptor tyrosine kinase 2 (*ERBB2*) (*HER2*) and *CDH1* have been detected in gastric cancer (25). Diffuse-type gastric cancer might arise from the down-regulation of *CDH1* (25). However, the expression of *ERBB2* is preferentially up-regulated in intestinal-type gastric cancers, and the prognostic value of *ERBB2* in gastric cancer remains controversial (25,26). The methylation status of *CDH1* is altered through *Helicobacter pylori* (*H. pylori*) infection (27-29). *CDH1* expression at the plasma membrane is decreased in gastroesophageal junction adenocarcinoma associated with metastasis (30). The metastasis-associated gene (*MTA3*) is also decreased in tumor tissues, suggesting that the EMT pathway is regulated via *MTA3*, a potential prognostic factor in gastroesophageal junction adenocarcinoma (30). Aquaporin 3 (*AQP3*) is overexpressed in gastric cancer tissues, whereas *CDH1* is expressed in normal gastric tissues (31). It has been suggested that *AQP3* induces EMT in gastric cancer cells (31). Appendiceal and intramucosal gastric signet ring cell carcinomas have been identified in diffuse-type gastric carcinoma patients with *CDH1* mutations (32). Thus, whether signet ring cell carcinoma in the appendix is primary or metastatic should be carefully examined (32).

### CDH1 and EMT

EMT is a switching mechanism (33). EMT typically occurs during early embryogenesis, and the mesenchymal-epithelial transition (MET), the reverse phenomenon of EMT, might also occur during the reprogramming of fibroblasts through pluripotent factors (33). Epithelial cells convert into mesenchymal cells during EMT, which involves abundant molecular network alterations (33). Smoking reportedly induces EMT in non-small cell lung cancer through the HDAC-mediated down-regulation of *CDH1* (34). The mechanism of EMT in cancer should be investigated in correlation with *CDH1* (34). As metastasis is one of the causes of cancer progression, metastatic stem cells, which initiate metastasis, are a noteworthy concept (35). Metastatic stem cells may be supported through a stem cell niche, such as hematopoietic stem cells, providing insight into the metastasis mechanism induced by EMT (35).

In EMT-related signal pathways in the neural crest, SMAD-interacting protein 1 (*SIP1*) is a key factor in *CDH1* to *CDH2* switching during development (36). *CDH1* expression is regulated through snail family zinc finger 1 (*SNAI1*) (*SNAIL*) signaling, which induces EMT in gastric



cancer (37). The amplification of *ERBB2*, *MET*, and *FGFR2* is also involved in EMT induction in gastric cancer (37).

*CDH1* is a major marker of epithelial cell states. In BGC823 human gastric cancer cells, *CDH1* was up-regulated through the siRNA-based gene knockdown of N-acetylglucosaminyltransferase V (GnT-V) (38). When considering the expression of other EMT markers, GnT-V might contribute to the metastasis and invasion of gastric cancer (38). *CDH1* is down-regulated during EMT and has been implicated in the induction of pluripotency (39,40). *CDH1* is also down-regulated in human cancer and has been correlated with increased *WNT* expression (41).

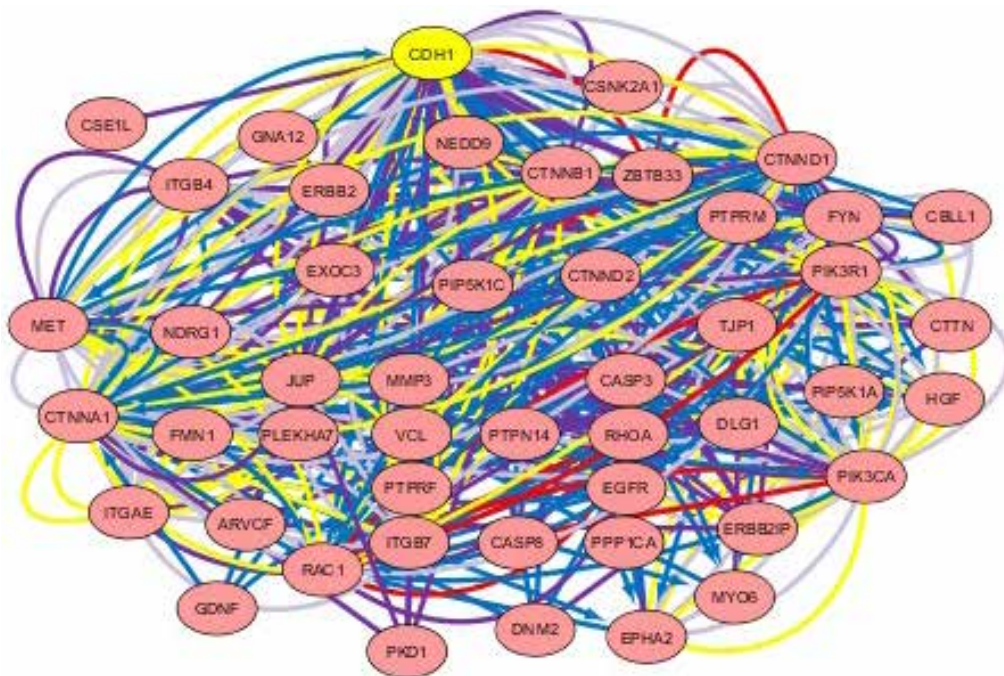
### CDH1 and cancer stem cells (CSCs)

*CDH1* expression is decreased during the EMT process, which might represent an essential mechanism for CSC

maintenance (42). Considering that CSCs and EMT are strongly related, the *CDH1* function might also be involved in CSC development (43). A decrease in *CDH1* expression in hepatocellular carcinomas has been correlated with early recurrent disease (44). *CDH1* network created by cBioPortal may be useful to reveal the cancer mechanism (Figure 1, Table 1) (45,46).

### Conclusions

In conclusion, *CDH1* is a key molecule for the phenotypic transition of gastric cancer cells into mesenchymal states. *CDH1* is up-regulated in epithelial cells, and the down-regulation of *CDH1* leads to EMT. The role of *CDH1* as a marker for EMT detection and the mechanism of EMT via *CDH1* and other molecular signaling should be further investigated to understand gastric cancer and CSCs.



**Figure 1** Network of *CDH1* (analyzed with cBioPortal and cytoscape). Gene network of *CDH1* is shown. The network was analyzed with cBioPortal and cytoscape (<http://www.cbioportal.org/>; <http://www.cytoscape.org/>).

<b>Table 1</b> Genes in CDH1 network created by cBioPortal	
Gene symbol	Gene title
<i>ARVCF</i>	Armadillo repeat gene deleted in velocardiofacial syndrome
<i>CASP3</i>	Caspase 3, apoptosis-related cysteine peptidase
<i>CASP8</i>	Caspase 8, apoptosis-related cysteine peptidase
<i>CBLL1</i>	Cbl proto-oncogene-like 1, E3 ubiquitin protein ligase
<i>CDH1</i>	Cadherin 1, type 1, E-cadherin (epithelial)
<i>CSE1L</i>	CSE1 chromosome segregation 1-like (yeast)
<i>CSNK2A1</i>	Casein kinase 2, alpha 1 polypeptide
<i>CTNNA1</i>	Catenin (cadherin-associated protein), alpha 1, 102kDa
<i>CTNNB1</i>	Catenin (cadherin-associated protein), beta 1, 88kda
<i>CTNND1</i>	Catenin (cadherin-associated protein), delta 1
<i>CTNND2</i>	Catenin (cadherin-associated protein), delta 2
<i>CTTN</i>	Cortactin
<i>DLG1</i>	Discs, large homolog 1 (Drosophila)
<i>DNM2</i>	Dynamamin 2
<i>EGFR</i>	Epidermal growth factor receptor
<i>EPHA2</i>	EPH receptor A2
<i>ERBB2</i>	Erb-b2 receptor tyrosine kinase 2
<i>ERBB2IP</i>	Erb2 interacting protein
<i>EXOC3</i>	Exocyst complex component 3
<i>FMN1</i>	Formin 1
<i>FYN</i>	FYN proto-oncogene, Src family tyrosine kinase
<i>GDNF</i>	Glial cell derived neurotrophic factor
<i>GNA12</i>	Guanine nucleotide binding protein (G protein) alpha 12
<i>HGF</i>	Hepatocyte growth factor (hepapoietin A; scatter factor)
<i>IGF1R</i>	Insulin-like growth factor 1 receptor
<i>IQGAP1</i>	IQ motif containing GTPase activating protein 1
<i>IRS1</i>	Insulin receptor substrate 1
<i>ITGAE</i>	Integrin, alpha E (antigen CD103, human mucosal lymphocyte antigen 1; alpha polypeptide)
<i>ITGB4</i>	Integrin, beta 4
<i>ITGB7</i>	Integrin, beta 7
<i>JUP</i>	Junction plakoglobin
<i>MET</i>	MET proto-oncogene, receptor tyrosine kinase
<i>MMP3</i>	Matrix metalloproteinase 3
<i>MYO6</i>	Myosin VI
<i>NDRG1</i>	N-myc downstream regulated 1
<i>NEDD9</i>	Neural precursor cell expressed, developmentally down-regulated 9
<i>PIK3CA</i>	Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha
<i>PIK3R1</i>	Phosphoinositide-3-kinase, regulatory subunit 1 (alpha)
<i>PIP5K1A</i>	Phosphatidylinositol-4-phosphate 5-kinase, type I, alpha
<i>PIP5K1C</i>	Phosphatidylinositol-4-phosphate 5-kinase, type I, gamma
<i>PKD1</i>	Polycystic kidney disease 1 (autosomal dominant)

**Table 1** (continued)



**Table 1** (continued)

Gene symbol	Gene title
<i>PLEKHA7</i>	Pleckstrin homology domain containing, family A member 7
<i>PPP1CA</i>	Protein phosphatase 1, catalytic subunit, alpha isozyme
<i>PTPN14</i>	Protein tyrosine phosphatase, non-receptor type 14
<i>PTPRF</i>	Protein tyrosine phosphatase, receptor type, F
<i>PTPRM</i>	Protein tyrosine phosphatase, receptor type, M
<i>RAC1</i>	Ras-related C3 botulinum toxin substrate 1 (rho family, small GTP binding protein Rac1)
<i>RHOA</i>	Ras homolog family member A
<i>TJP1</i>	Tight junction protein 1
<i>VCL</i>	Vinculin
<i>ZBTB33</i>	Zinc finger and BTB domain containing 33

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## Footnote

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# The Cancer Genome Atlas output and practice of gastric cancer

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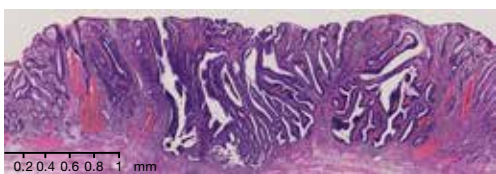
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Any clinical professionals who devote themselves to prevention, diagnosis, therapy, and management of gastric cancer patients are now again facing another achievement by the consortium of The Cancer Genome Atlas (TCGA) (1). In the era of post human genome sequence and massive parallel sequencing technology, every week this kind of huge data draw a transient attention of our colleagues who are very busy with conventional routines. Information like this on the cutting edge of science is not usually related to the action plan next week at the clinic. In a field of lung cancer managements, however, we witnessed the latest fruits of these technologies such as series of discoveries of targetable fused-kinase protein drastically changed clinical practice (2). How influential the results presented here in this article can be to the practice today, tomorrow, and in future? Reasonably, clinicians in any fields of specific organ cancers hope categorization of cancers based on the state-of-the-art technology can specify the fittest therapy in each individual. In the field of gastric cancer research, attempts to delineate genomic characteristics of gastric cancer and to take advantage of these features as potential targets of therapy have been popular in the literatures of the last few years.

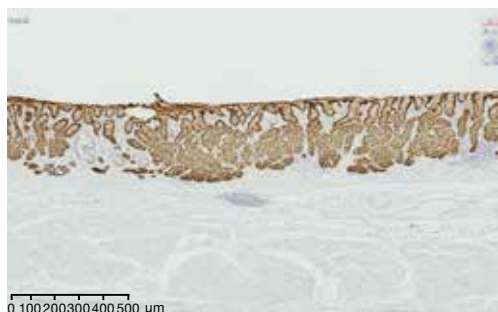
For example, Kubo *et al.* reported re-sequencing and copy number analysis of kinases in gastric cancer (3) and Kiyose *et al.* further applied 400 BAC FISH probes on the tissue microarray of 350 gastric cancers, identified several kinase gene amplification, and suggested the assays could be used as companion diagnosis on pathology archives like Hercep Test<sup>TM</sup> (4). Hillmer *et al.* applied paired-end-tag sequencing approach to four gastric cancers and found structural variations in them (5). Zang *et al.* focused on kinase changes in 14 gastric cancer cell lines (6). Methodologies were various. Deng *et al.* investigated 193 primary gastric tumors by high resolution SNP array and copy number changes in

the tumors. Based on the huge mutational information of gastric cancer obtained by massively parallel short read and DNA paired-end tag sequencing, Nagarajan *et al.* tried to classify gastric cancers into two categories; microsatellite instability-positive gastric cancer and TP53-wild type cancer (7). Then Zang *et al.* did exome analysis of 15 cases and disclosed mutations of chromatin modifier genes such as *ARID1A* and cell adhesion molecule such as *FAT4* (8). As to the MSI positive fraction of gastric cancer, Korean researchers extensively clarified mutation profile (9). In the course of rapid popularity of “genome-wide” approaches applied to each cancer case, a peculiar pathological status became clarified such as *GLO* amplification as a new metabolic marker of gastric cancer (10).

In the paper published in September issue of Nature, TCGA reported the landscape of somatic changes in gastric cancer in comprehensive way. The data they showed include mutations per Mb, copy number changes (somatic copy number alteration SCNA), DNA methylation, mRNA expression profile, micro RNA profile analysis, microsatellite instability, Epstein-Bar virus infection status as well as whole genome analysis for identification of structural changes (such as fusion genes) found in gastric cancer. According to the supplementary table of this paper, out of 295 cases, the cases with T1A and T1B are 11 (3.7%) and the T3 cases are about half of the total cases. This fact implies the idea and consequent strategy for gastric cancer therapy generated by this study are mainly applicable to T3 and T4, an advanced stage gastric cancer, some of which are inoperable. For example, the managements widely recommended in Japan, that is, detection of gastric cancer at early stage by intensive surveillance and endoscopic submucosal dissections (*Figure 1*) for nearly asymptomatic subjects (covered by government-based health insurance),



**Figure 1** An example of the Hematoxylin Eosin stained section of T1A tumor obtained by endoscopic submucosal dissection (Hamamatsu University School of Medicine). The study includes only one case of this stage. The comprehensive genetic study of gastric cancer in this stage is still not available.



**Figure 2** Immunohistochemistry of claudin 18 in human stomach. Monoclonal antibody to CLDN18, a member of tetraspan transmembrane protein of tight junction (Proteintech, Chicago, IL) was used in 200× dilution.

are out of the scope of this costly analysis and therapeutic plan based on it they envisaged here.

The tremendous data set published by TCGA suggested four categories of gastric cancer: (I) EBV positive cases; (II) microsatellite instability (MSI) positive cases; (III) chromosomal instability (CIN) type; (IV) genomically-stable type (near-diploid type). The hallmarks of these four groups can be said in another way: (I) hypermethylation type; (II) KRAS, PTEN, PIK3CA mutations; (III) kinase receptor amplifications; (IV) diffuse type with RHOA mutation, respectively.

For the last two decades, the above four aspects of gastric cancer have been repeatedly investigated both sporadically and systematically in various scale of projects including the very recent studies by two group which identified RHOA mutation (11,12). The genes where mutations were more frequently found than RHOA are TP53, CDH1, SMAD4, and PIK3CA which are consistent with the previous reports, and ARID1A, KRAS, MUC6, and APC followed. The authors highlighted the PIK3CA mutations, extreme

methylation, and amplifications of JAK2, PD-L1, and PDL2 in EBV positive category. As for fusion genes, transcripts involving CLDN18i, which is specifically expressed in gastric epithelium (Figure 2) were detected. Its partners were ARHGAP family genes. The genes involved in this and related pathways have been investigated for years such as involvement of ARHGEF 6 (beta-PIX) and ARHGEF (alpha-PIX) by the researchers of cell signaling (13-16) and the involvement of ARHGAP 6 and 26 in this TCGA paper are mechanistically understandable, especially considering these were found in diffuse type, notoriously invasive subtype of gastric cancers. The finding that the 5' side of fusion transcript is CLDN18, a claudin specifically expressed in the stomach reminds us that SLC34A2 specifically expressed in type II alveolar cell of the lung has been found as a component of fusion transcript in some of lung cancers (17,18).

Based on these data, the authors encourage the readers, and probably themselves, by pointing out that the signaling molecules above-mentioned could be targetable. The involvement of PD-1 and 2, immune checkpoint inhibitors, in EBV related gastric cancer is remarkable considering these molecules are enthusiastically promoted as targets of immunotherapy (especially in malignant melanoma) (19). Obviously the practical feasibility of the management of gastric cancer based on the proposals of this paper warrants further applied and translational researches and assessments by several sectors including academics, industries, health insurance companies, and attending doctors.

The other point to bewilder the practical pathologists is histological sub-classification shown in the supplementary table (1). Sub-classification of gastric cancer ranged from Lauren dichotomy (actually this paper adopts a trichotomy including mixed type) to the Japanese classification systems ([http://www.jgca.jp/pdf/JGCA\\_Jpn\\_Classification\\_3rd\\_Eng.pdf](http://www.jgca.jp/pdf/JGCA_Jpn_Classification_3rd_Eng.pdf), 2011) which morphologically scrutinize very minute attributes up to the level where it sometimes suffers from the Galapagos Syndrome—it has evolved separately from the rest of the world. WHO system would be a wise and modest way when describing the statistics. The most pathologists, however, are very familiar with the morphological heterogeneity in single tumor in advanced stage gastric cancer especially where several blocks (five and more, sometimes 30 to 50) are routinely made for pathological investigation. As expected, the histological sub-classification itself was not related to molecular signature shown here. Thus the cancer, a real challenge we should treat may evade “individualized” therapeutic strategy this

ambitious presentation proposes. On the other hand, in the next stage, the application of the tour de force genetic analyses to the initial stage of gastric carcinogenesis will further provide efficient predictive and preventive measures of this ominous cancer.

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### Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

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# Moving molecular subtypes to the clinic in gastric cancer

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## Introduction

Adenocarcinomas of the stomach and gastroesophageal junction account for a high proportion of worldwide cancer-related mortality. Some progress has been made with the approval of HER2 and VEGFR2 targeted therapies, though the overall prognosis remains poor in metastatic disease with median overall survivals of 12–16 months (1,2). With the well-established understanding that cancer is a disease process owing to the unfettered growth of cells that stems from acquired somatic or germline DNA alterations, multiple investigators have queried the genome to gain insights into novel therapies.

Recently, gastric cancer has been put under the genoscope and distinct molecularly-defined subtypes have emerged (3-7). Prior to molecular classification gastric cancer has largely been characterized by anatomic location and histologic subtype according to Lauren and WHO classification schema (8,9). While histopathologic analyses have observed differing features and prognoses between diffuse and intestinal type gastric adenocarcinomas, genomic data adds detailed information about underlying operative mutational processes and highlights recurrent changes with therapeutic implications.

In the article by Li *et al.*, published in the April 1, 2016 issue of *Cancer Research*, the authors conduct an in depth analysis of genomic level data pooled from five large sequencing studies to establish a study set of 544 annotated gastric cancer specimens (10). Using aggregated genomic

data, the authors sought to increase sensitivity to identify additional recurrently altered genes in gastric cancer and continue to refine the molecular landscape.

## Getting from types to treatment

Results of molecular classification schema are influenced by input data type and sample size, with estimates that 600 samples per anatomic tumor type are needed for complete characterization (11). Combining genomic data from five previously published datasets Li and colleagues identified six previously unreported significantly mutated genes (SMGs) in regular mutated (RM) gastric cancer (3,5-7,10,12) (*Table 1*). Consistent with global incidence patterns well over half of the input data were derived from Asian patients (*Table 1*) (13). To pursue an initial classification scheme, the authors subdivided out 455 RM tumors with a mutation burden averaging around 2.4 mutations per megabase (Mb) pair from 89 hypermutated (HM) tumors with an average of 20.5 mutations/Mb. The classification of tumors into regular and HM signatures led to the observation of mutations at the TpCpW DNA motif (W = A or T; mutated nucleotide underlined) predominating in regular versus HM gastric cancers. Mutations at this motif are typical of the APOBEC cytidine deaminase signature and the authors found a positive correlation with APOBEC3B mRNA levels and TpCpW mutations in the RM subset though not in the HM cancers (14). High levels of microsatellite instability (MSI-H) are found in the HM cohort by Li *et al.*, and define microsatellite instable (MSI) in both the The Cancer

**Table 1** Genomic studies used to derive gastric cancer classification by Li *et al.*, sample size is reported for samples undergoing WES or WGS as some studies included external validation cohorts subjected to targeted sequencing

Series	Sample size	Tissue source	Analysis group	Stage distribution	Treatment status	Lauren subtype	References
Chen <i>et al.</i>	78	Tianjin, China	WES (n=78)	Stage I (n=6); stage II (n=85); stage III (n=97); stage IV (n=106)	Untreated	Diffuse (n=152); intestinal (n=124); mixed (n=18)	(5)
Kakiuchi <i>et al.</i>	30	Tokyo, Japan	WES (n=30)	NR	NR	Diffuse (n=30)	(7)
Wong <i>et al.</i>	49	Seoul, Korea	WGS (n=49)	Stage II (n=1); stage III (n=29); stage IV (n=19)	Untreated	Diffuse (n=31); intestinal (n=18); all MSS	(6)
Wang <i>et al.</i>	100	Hong Kong, China	WGS (n=100)	Stage 0-I (n=10); stage II (n=6); stage III (n=33); stage IV (n=51)	97% Untreated	Diffuse (n=29); intestinal (n=56); mixed (n=14)	(12)
TCGA	295	TCGA Korea (n=31); Vietnam (n=44); Germany (n=39); Poland (n=32); Russia (n=83); Ukraine (n=39); USA (n=24); Canada (n=3)	WES (n=295)	Stage I (n=32); stage II (n=116); stage III (n=111); stage IV (n=20); unknown (n=16)	Untreated	Diffuse (n=69); intestinal (n=196); mixed (n=19); NOS (n=11)	(3)

WES, whole-exome sequencing; WGS, whole-genome sequencing; NR, not reported; MSS, microsatellite stable; TCGA, The Cancer Genome Atlas.

Genome Atlas (TCGA) and Asian Cancer Research Group (ACRG) subgroups; however, there is significant variation in mutation count (mutations/DNA Mb) among the non-MSI groups (3,4). Mutations per DNA Mb has been correlated with response to immune checkpoint inhibitors in several tumor types, providing clinical relevance to mutation burden as a gastric cancer stratification factor (15,16).

Utilizing established computational algorithms, specifically MutSigCV, MutSigCL, and MutSigFN, Li *et al.* identified 31 SMGs causally linked to tumorigenesis among the 455 RM cohorts. Utilizing their large dataset they observed six previously unreported genes recurrently altered, specifically *XIPR2* (7.3%), *NBEA* (7.0%), *COL14A1* (4.4%), *AKAP6* (3.7%), *CNBD1* (3.1%), *ITGAV* (3.1%). These genes have been observed to be altered across alternate tumor types, and involved in diverse cellular processes including actin binding, phospholipid binding, poly(A) RNA binding, ion channel binding, and protease binding (10). While none of these genes are established driver alterations, their identification as SMGs in gastric cancer does support the importance of large sample size for sensitive detection of recurrent alterations. Several large series across cancer types have exemplified the use of large genomic datasets to identify uncommon alterations with

significant therapeutic implications (17,18).

Interestingly, *ERBB2* mutations were found in 3.2% of RM gastric cases from the pooled data, largely consistent with individual prior reports, such as the ACRG in which an *ERBB2* mutation rate of 2.8% was reported in microsatellite stable (MSS) tumors (*Table 2*) (3,4). Of note, the ACRG study also included the 49 patients published by Wong *et al.* that formed part of the present analysis by Li *et al.* Owing to chosen methodological approaches by Li and colleagues the therapeutically important rates of *ERBB2* amplification are not described. As both TCGA and ACRG included array based somatic copy number analysis, *ERBB2* alterations highlight a possible weakness in the study by Li *et al.*, as whole exome sequencing (WES) may not robustly detect gene copy number alterations without specialized computational algorithms. *Table 2* highlights the distribution of key genes in gastric cancer across the reported molecular subgroups.

The confirmation that *CDH1* mutations confer a poor prognosis in diffuse type gastric cancer supports the methodology used by Li and colleagues. The mutation rate of 11.6% identified in the combined genomic analysis is consistent with ranges reported by prior studies, though another large series noted the poor prognosis was



**Table 2** Patterns of distribution for key recurrently altered genes across molecular subtypes of gastric cancer, numbers refer to percentage of samples with the genomic alteration in the primary publication

Gene change	TCGA				ACRG				Li <i>et al.</i> (10)			
	MSI	EBV	GS	CIN	MSI	MSS/EMT	MSS/TP53 <sup>+</sup>	MSS/TP53 <sup>-</sup>	HM	RM	RM C1	RM C2
<i>ERBB2</i> Amp	0	12	3	22	0	0	3.0	17.4	NR	NR	NR	NR
<i>ERBB2</i> Mut	11	4	3	3	16.3	2.8	0	4.7	NR	3.2	NR	NR
<i>MET</i> Amp	2	0	0	7	1.6	0	3.0	3.5	NR	NR	NR	NR
<i>PIK3CA</i> Amp	3	8	2	7	0	0	0	1.1	NR	NR	NR	NR
<i>PIK3CA</i> Mut	42	77	10	3	32.6	8.3	16.9	4.7	40.4	8.4	NR	14.4
<i>KRAS</i> Mut	23	4	9	5	23.3	0	8.5	3.5	21.3	4.4	NR	NR
<i>RHOA</i> Mut	5	8	14	2	0	2.8	6.8	3.5	NR	5.7	NR	9.2
<i>CDH1</i> Mut	8	0	34	3	7.0	2.8	1.7	3.5	NR	11.6	NR	17.5
<i>FGFR2</i> Amp	0	0	7	7	0	4.9	3.0	1.2	NR	NR	NR	NR
<i>BRAF</i> Mut	22	8	0	0	11.6	2.8	1.7	3.5	NR	NR	NR	NR
<i>ALK</i> Mut	9	0	5	2	16.3	0	0	2.4	NR	NR	NR	NR
<i>ARID1A</i> Mut	84	54	16	9	44.2	13.9	18.6	5.9	78.7	13.8	NR	27.5
<i>TP53</i> Mut	39	4	14	70	25.6	33.3	23.7	60	34.8	48.4	89.9	NR
<i>PTEN</i> Mut	25	15	2	1	14	5.6	3.4	3.5	20.2	NR	NR	NR
<i>MTOR</i> Mut	30	4	3	1	14	0	1.7	3.5	NR	NR	NR	NR
<i>APC</i> Mut	36	0	3	12	16.3	2.8	15.3	8.2	NR	6.8	11.1	NR
<i>FBXW7</i> Mut	34	0	5	1	16.3	2.8	1.7	2.4	NR	2.4	NR	NR
<i>SMAD4</i> Mut	8	12	9	7	4.7	2.8	8.5	2.4	NR	6.2	NR	NR

Please see respective references and their supplemental information for complete gene lists. TCGA data is derived from [https://tcga-data.nci.nih.gov/docs/publications/stad\\_2014/](https://tcga-data.nci.nih.gov/docs/publications/stad_2014/) (accessed 5/2016 via cbiportal, <http://www.cbiportal.org>). MSI, microsatellite instable; EBV, epstein-barr virus; GS, genomically stable; CIN, chromosome instability; MSS, microsatellite stable; EMT, epithelial-mesenchymal transition; HM, hypermutated; RM, regular mutated; C1, cohort 1; C2, cohort 2; NR, not reported; TCGA, The Cancer Genome Atlas; ACRG, Asian Cancer Research Group.

associated with both intestinal and diffuse subtypes (19). Differing methodological approaches likely account for differing genomic frequencies of *CDH1* alterations across gastric cancer studies. Along similar lines the large dataset utilized by Li *et al.* allowed for employing an unsupervised clustering method to yield separation of RM gastric cancer into two cohorts with differing prognoses. The investigators noted that cohort 1 (C1) showed overlap with TCGA chromosome instability (CIN) subtype while cohort 2 (C2) was evenly distributed among CIN and genomically stable (GS) subtypes and C1 was associated with a longer median survival (roughly 40 months *vs.* not reached) (10). The study noted that eight differential SMGs (*TP53*, *CDH1*, *ARID1A*, *PIK3CA*, *XIRP2*, *APC*, *ERBB2*, and *RHOA*) could

retain the prognostic significance of the larger SMG list used to characterize C1 and C2 regular-mutated gastric cancer. Notably, this does differ somewhat from the isolated ACRG study that reported MSS tumors with intact p53 activity (MSS/TP53<sup>+</sup>) exhibited better survival than MSS tumors with loss of p53 function due to mutation (MSS/TP53<sup>-</sup>) (4). The ACRG study further classified a MSS/epithelial-to-mesenchymal transition (EMT) subgroup which exhibited the worst survival and contained a relatively high proportion of *ARID1A* mutations. Though the MSS/EMT subgroup was predominantly composed of Lauren classification diffuse subtype histology with peritoneal spread as the most common pattern of recurrence, *CDH1* and *RHOA* mutations were surprisingly rare preferentially

clustering in the MSS/TP53<sup>+</sup> group consistent with the C2 classification. Li and colleagues should be commended on their use of large pooled genomic datasets, but the clinical utility of their classification schema requires further prospective study.

The importance of using genomic data to refine tumor classification is well recognized and pioneered by multiple TCGA studies and pan-cancer analyses (20,21). However, establishing and understanding genomically-defined prognostic subgroups has not yet reliably translated to improved patient outcomes in gastric cancer, as these are inherent tumor features not readily modified. We are not aware of prospective therapeutic studies in which molecular subtype (by TCGA or other) has guided treatment in gastric cancer. Several ongoing trials, particularly with immune-mediated therapies, may clarify the predictive ability of mutational signatures in gastric cancer. In a recent prospective trial of the anti-PD-L1 antibody atezolizumab, higher mutational burden was predictive of benefit from treatment in advanced bladder cancer, helping to validate molecular subgroups as predictive biomarkers (22). Significant work is needed before we can confidently say that immune mediated therapies could/should be restricted based on genomic subtype. Interestingly, computational approaches have suggested that a mutational burden of 10 mutations/Mb may be predictive of tumors more likely to harbor malignancy-associated neoantigens, closely paralleling the TCGA cutoffs (11.4 mutations/Mb) and 8.3 mutations/Mb used to separate HM and non-HM gastric cancers by Li and colleagues (3,10,23).

An interesting observation in the study by Li *et al.* is the breakdown of *PIK3CA* hotspot alterations by regular and HM gastric cancer. RM gastric cancer showed significant enrichment in helical domain mutations (E542K and E545K) whereas HM tumors contained catalytic domain H1047R alterations (4,10). If APOBEC-mediated processes are the main operative method in RM gastric, and defective DNA proofreading and repair dominate HM tumors, then this observation may have larger implications. How, at the fundamental molecular level, mutagenic exposures select for one activating kinase alteration over another is not well understood and begs further investigation in gastric cancer. The distribution of key genes, several with immediate therapeutic implications, across gastric cancer subtypes are yet to be fully exploited (Table 2). In a smaller series of breast and gynecologic malignancies, the H1047R *PIK3CA* alteration was associated with a numerically higher response to PI3K pathway inhibitors than non-H1047R *PIK3CA*

mutations, suggesting possible clinical implications for the observation by Li and colleagues (24).

## Conclusion and future directions

Where should ongoing genomic and clinical studies in gastric cancer go from here to capitalize on refined molecular classification? The development of model systems (patient derived cell lines, etc.) representative of each genomic subtype will be important to functionally validate alterations described by Li and others. For example, do ERBB2 amplified MSS/TP53<sup>-</sup> and MSS/TP53<sup>+</sup> gastric cancer subtypes have similar response rates to trastuzumab, or do the genomic context and concurrent alterations modify the efficacy? As the data from Li *et al.* is drawn predominantly from untreated tumors, the direct applicability of this genomic landscape to treatment-refractory metastatic patients is difficult to discern, and research utilizing samples from more stage IV patients, particularly those with prior therapy (chemotherapy, immunotherapy, radiotherapy, and targeted therapy) may add additional information about possible subtype transformation. Studies relying primarily on genomic data by definition offer only a summative and static view of tumors and we anticipate incorporation of more fluid and functional assays will be needed to realize and optimize the use of genomic data (25). More clinical trials stratified based on molecular classifications should be designed to test the anti-tumor efficacy (i.e., mesenchymal *vs.* non-mesenchymal) to maximize the treatment response for specific target drugs.

The interesting question of whether similar classification schemas can be derived or recapitulated using commercially available hybrid capture based next-generation sequencing assays remains to be determined. Many of these tests incorporate whole exon coverage of 200–400 cancer-associated genes, representing 1–2 Mb of the human genome (3 Gigabases), and have established utility in gastric cancer (26). With improving technological advances, collaborative big data effort, and refined classifications as described by Li *et al.* we hope our patients will reap the ultimate benefit from these research endeavors.

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# Molecular classification of gastric cancer

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Gastric cancer is the world's third leading cause of cancer mortality and the most common cancer diagnosed in men in Japan (1). Clinical work-up of gastric cancer relies in part on imaging modalities, including endoscopic ultrasound and CT/PET, and pathologic analysis of tumor biopsies. Gastric cancer is clinically classified as early or advanced stage, with early disease confined to mucosa/submucosa and advanced carcinoma invading into muscularis propria and beyond (2). Gastric carcinoma is subdivided histologically into intestinal type, which is associated with intestinal metaplasia and *H. Pylori* infection, and diffuse type, which is often linked to familial genetic disorders, such as germline mutations of E-cadherin (*CDH1*) or mismatch repair genes (Lynch syndrome) (3). In 2010, the World Health Organization (WHO) recognized four major histologic patterns of gastric cancer (tubular, papillary, mucinous, and poorly cohesive), but these classifiers have little clinical utility. Recently, molecular profiling of gastric cancers identified potential driver genes for targeted therapy, such as amplified *ERBB2* (4). Clinical trials such as ToGA study found that trastuzumab (anti-Her2 antibody) plus standard chemotherapy demonstrated significantly improved overall survival in Her2-neu-positive patients compared to chemotherapy alone (5). While these results are encouraging, there is an urgent need to develop robust molecular classifiers of gastric cancer to guide clinical decision-making and tailored therapeutic development.

Recently, the Cancer Genome Atlas (TCGA) project reported a four subtype molecular classification of gastric cancer based on molecular profiling of 295 primary gastric adenocarcinomas (6). The cancers were profiled by copy number analysis (array-based), whole-exome sequencing, DNA methylation profiling (array-based), mRNA sequencing, microRNA sequencing, and/or reverse-

phase protein array (RPPA). Roughly one-third of the samples were also profiled by whole genome sequencing. Unsupervised clustering of the data revealed that the gastric cancers could be sub-divided into four groups: (I) cancers with high EBV burden and DNA promoter hypermethylation; (II) cancers with microsatellite instability (MSI), high mutation rate, and promoter hypermethylation; (III) cancers with chromosomal instability (CIN) (i.e., high somatic copy number aberrations); and (IV) cancers with genomic stability (i.e., low copy number aberrations). For clinical decision making, gastric cancers can first be categorized by EBV positivity (group 1, 9% of cases), then by MSI-high status (group 2, 22% of cases), and the remaining cases can be distinguished by copy number aberrations into CIN tumors (group 3, 50% of cases) or genomically stable tumors (group 4, 50% of cases). The distributions of subtypes were similar in patients of East Asian and Western origin.

The EBV-high gastric cancers were largely found in males (81% of cases) and were mostly localized to the gastric fundus and body (7). The cancers were characterized by extreme DNA hypermethylation, distinct from the hypermethylation observed in MSI tumors. EBV-high tumors also showed distinct gene expression profile and mutation spectra compared to the other tumor subtypes. This included *CDKN2A* (*p16<sup>INK4A</sup>*) promoter hypermethylation, *PIK3CA* mutation (80% of cases), and *ARID1A* mutation (55% of cases) (8). EBV-high tumors also displayed *BCOR* mutation (23% of cases) but only rare *TP53* mutations. Interestingly, EBV-high tumors showed amplification of a 9p24.1 locus, which contained *JAK2*, *CD274* (*PD-L1*), and *PDCD1LG2* (*PD-L2*).

The MSI-high cancers were associated with older age and female gender (56% of cases). These cancers displayed high

mutation rate (greater than 11.4 mutations per megabase) and there were ten genes significantly mutated by base substitution mutation in this group, including *TP53*, *KRAS*, *ARID1A*, *PIK3CA*, *ERBB3*, *PTEN*, and *HLA-B*. Additional genes were mutated by insertions/deletions, such as *RNF43*, *B2M*, and *NF1*. MSI-high cancers displayed alterations in major histocompatibility complex class I genes (such as *B2M* and *HLA-B*), likely for evasion of host immune response (9). While non-MSI-high (i.e., non-hypermutated) tumors also carried mutations in these genes, non-MSI-high tumors in addition displayed mutations in the  $\beta$ -catenin pathway (*APC* and *CTNNB1*), TGF- $\beta$  pathway (*SMAD4*, and *SMAD2*) and MAPK pathway (*RASA1*, *ERBB2*).

The CIN tumors were largely localized to the gastroesophageal junction and cardia (65% of tumors) and were largely of intestinal-type histology. CIN tumors contained *TP53* mutations (71% of tumors) and displayed amplification of receptor tyrosine kinases, including *EGFR*, *ERBB2* and *ERBB3*. Other genes that were frequently amplified included *CCNE1*, *KRAS*, *MYC*, *CDK6*, *GATA4*, *GATA6*, and *ZNF217*, which are also amplified in other solid tumor types (10). In contrast, the genomically stable tumors were largely of the diffuse histology (73% of cases) and were associated with younger age of onset. Genomically stable tumors contained *ARID1A* mutations and were enriched for *CDH1* somatic mutations and *RHOA* mutations. Translocations that disrupt *RHOA* signaling were also identified, such as the *CLDN18* and *ARHGA26* interchromosomal translocation. Modulation of *RHOA* and its downstream effectors *ROCK1* and *mDIA* may contribute to the lack of cell cohesion seen in the diffuse tumor histology (11).

The molecular characterization of gastric cancer provides insight into personalized treatments for gastric cancer patients. The primary targets identified in EBV-positive tumors were *PIK3CA*, *JAK2*, and *ERBB2*, which have roles in cell proliferation, apoptosis and survival. *PIK3CA* encodes a catalytic subunit (p100 $\alpha$ ) of the PI3K signaling molecule, and the high incidence of *PIK3CA* mutations in EBV-positive gastric tumors could suggest a targeting strategy for PI3K inhibitors in this subgroup (12). *JAK2* is a cytoplasmic tyrosine kinase which facilitates binding and phosphorylation of STATs to regulate cell proliferation, differentiation, and apoptosis. JAK inhibitors have shown clinical utility in oncology and their use may be warranted in EBV-positive gastric cancers (13). Interestingly, the immunomodulators *PD-L1* and *PD-L2* were also amplified in EBV-positive cancers, raising the

possibility that PD-1/PD-L1 inhibitors may be targeted to this population.

Several RTK amplifications were observed in CIN tumors, including *EGFR*, *ERRB2*, *ERBB3*, *FGFR2* and *MET*. The *MET* gene displayed exon 2 skipping in approximately 30% of cases (correlating with increased activity), while 17% of cases exhibited skipping in exon 18 and/or 19. This provides a novel biomarker for anti-MET therapeutics, such as Rilotumumab (Amgen). Phase III trials for rilotumumab in combination with chemotherapy are currently underway for MET-positive gastric cancer patients (14). Other amplifications in the CIN sub-group include *VEGFA*, *KRAS/NRAS*, and *CDK6*. Recently, a human monoclonal antibody targeting VEGFR2 (Ramucirumab; Eli Lilly and Company) demonstrated improvement in overall survival in patients with advanced or metastatic gastric cancer (15). Further, as in EBV-positive tumors, amplification of *ERBB2* in CIN tumors may likely be a positive predictor of efficacy of HER2-targeted therapies, such as Herceptin. Cell cycle genes (*CCNE1*, *CCND1*, *CDK6*) were also amplified in CIN tumors, which offer additional targeting strategies for this tumor subtype. *CDK4/6* inhibitors are currently in development for a number of cancers types.

In MSI-high tumors, a number of druggable pathways/targets were mutated, such as *PIK3CA*, *ERBB2*, *ERBB3*, and *EGFR*. *PIK3CA* mutations in MSI-high tumors were less dispersed than in EBV-positive tumors and instead occurred at higher incidence at exon 20. Given the high mutation rate of these cancers, the clinical utility of targeted therapeutics in this population remains to be shown. Likewise, few tractable targets were identified in genomically stable gastric cancers. Recurrent mutations were observed in *RHOA*, *CLDN18*, and *CDH1*, which are responsible for cell shape and cell-cell adhesion. While clinical development of novel inhibitors of these targets have been reported, such as the ongoing phase II clinical trial of a monoclonal *CLDN18* antibody (Ganymed Pharmaceuticals), additional targets are likely to be found with continued mining of the gastric TCGA datasets.

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## Footnote

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# Gastric cancer: Classification, histology and application of molecular pathology

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**Abstract:** Gastric cancer remains one of the deadly diseases with poor prognosis. New classification of gastric cancers based on histologic features, genotypes and molecular phenotypes helps better understand the characteristics of each subtype, and improve early diagnosis, prevention and treatment. The objective of this article is to review the new classification of gastric cancers and the up-to-date guidance in the application of molecular testing.

**Keywords:** Gastric carcinoma; classification; histology; HER2; CDH1; DPD; molecular pathology

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## Introduction

Gastric cancer is the fourth most commonly diagnosed cancer and the second most common cause of cancer-related death worldwide (1-2). Although the incidence of gastric cancer has gradually decreased over the last half century, cancer at proximal stomach is on the rise (3,4). Today, gastric cancer is still the seventh most common cause of cancer-related death in the United States (5) and the prognosis of advanced gastric cancer remains poor. Gastric carcinogenesis is a multistep and multifactorial process. While the intestinal type of gastric cancer is often related to environmental factors such as *Helicobacter pylori* infection, diet, and life style, the diffuse type is more often associated with genetic abnormalities. Recent advances in molecular medicine have not only shed light on the carcinogenesis of gastric cancer, but also offered novel approaches regarding prevention, diagnosis and therapeutic intervention.

## Classification of gastric carcinoma

### *Cancers at gastric cardia and gastroesophageal junction (GEJ)*

Gastric carcinoma is clinically classified as early or advanced stage to help determine appropriate intervention, and

histologically into subtypes based on major morphologic component. For the classification based on anatomic location, difficulty often arises when the tumor is located at proximal stomach or cardia, especially when the tumor also involves gastroesophageal junction (GEJ). It is not only because there are shared histologic features and immunophenotypes between the inflamed gastric cardiac mucosa due to *Helicobacter* infection and the metaplastic columnar epithelium-lined distal esophageal mucosa secondary to reflux disease, but also because there is no universal consensus regarding the anatomic definition of gastric cardia (6,7). Several classifications were proposed in order to address this issue. The scheme endorsed by the International Gastric Cancer Association separates gastric cancers into type I, type II and type III, to represent the tumors at distal esophagus, at cardia and at the stomach distal to cardia, respectively (8). This classification, however, has not clearly defined the criteria for each of these anatomic locations. Most recently, the 7th Edition of the TNM classification by American Joint Committee on Cancer (AJCC) has simplified the classification of the carcinoma at proximal stomach based on the location of tumor epicenter and the presence or absence of GEJ involvement (9). The tumor is to be stage grouped as esophageal carcinoma if its epicenter is in the lower thoracic

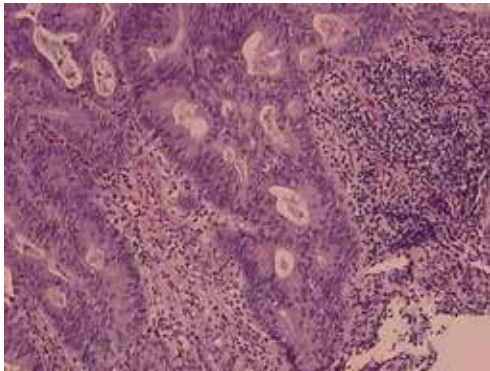


esophagus or GEJ, or within the proximal 5 cm of stomach (i.e., cardia) with the tumor mass extending into GEJ or distal esophagus. If the epicenter is >5 cm distal to the GEJ, or within 5 cm of GEJ but does not extend into GEJ or esophagus, it is stage grouped as gastric carcinoma (9). This classification, although easy for pathologists to follow, could still face some challenges. For example, a bulky gastric cardiac cancer with its epicenter 4 cm below GEJ will still be diagnosed and classified as an esophageal tumor if the proximal end of tumor extends into GEJ by only 0.5 cm (even if the distal end of tumor is 4 cm from the epicenter extending into the stomach). For the operating surgeon who sees the tumor *in situ*, it may be difficult for him or her to accept this tumor as an esophageal cancer. In addition, a recent retrospective study by Huang *et al.* shows that cardiac carcinoma involving GEJ or distal esophagus is more appropriately classified and staged as gastric rather than esophageal cancers, at least in the Chinese population (10). In that study, cardiac carcinomas were staged according to the depth of invasion, status of positive lymph nodes and distant metastasis, as both gastric and esophageal tumors. When the tumor stage is studied and compared with cumulative survival, the findings support that it is more appropriately to group and stage cardiac cancers as stomach in origin (10). To better separate gastric cardiac carcinoma from esophageal or GEJ malignancy, more studies are apparently needed, such as a larger patient sample, molecular profiling of the tumor, clinical follow up data, and defining the tumor location after neoadjuvant therapy as to determine whether the initially bulky tumor was more “gastric” or more “GEJ/esophagus” in origin.

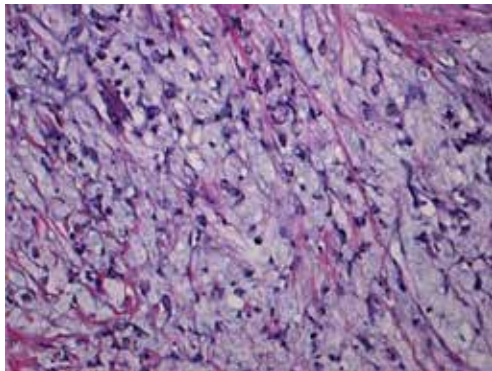
### ***Early and advanced gastric carcinoma***

Early gastric carcinoma is defined as invasive carcinoma confined to mucosa and/or submucosa, with or without lymph node metastases, irrespective of the tumor size (11). Most early gastric carcinomas are small, measuring 2 to 5 cm in size, and often located at lesser curvature around angularis. Some early gastric carcinoma can be multifocal, often indicative of a worse prognosis. Grossly, early gastric carcinoma is divided into Type I for the tumor with protruding growth, Type II with superficial growth, Type III with excavating growth, and Type IV for infiltrating growth with lateral spreading. Type II tumor is further divided to IIa (elevated), IIb (flat) and IIc (depressed), as proposed by the Japanese Endoscopic Society (12). A more recent Paris classification has endorsed three gross patterns

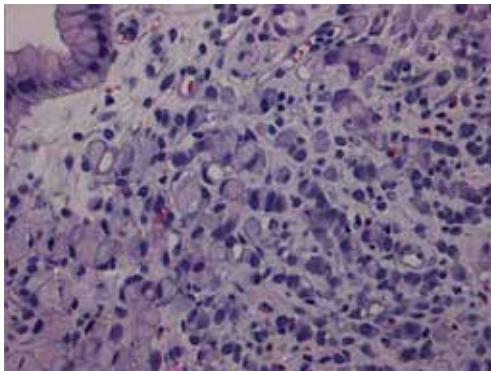
for superficial neoplastic lesions in gastrointestinal tract. Grossly and endoscopically, the tumor is classified as Type 0-I for polypoid growth (which is subcategorized to 0-Ip for pedunculated growth and 0-Is for sessile growth), Type 0-II for nonpolypoid growth (which is subcategorized into Type 0-IIa for slightly elevated growth, Type 0-IIb for flat growth, and Type 0-IIc for slightly depressed growth), and Type 0-III for excavated growth (13). Histologically, the most common forms of early gastric carcinoma are well differentiated, mostly with tubular and papillary architecture. The distinction between well-differentiated carcinoma and high grade dysplasia or carcinoma *in situ* can be challenging when only mucosal tissue is available for histologic assessment. Intramucosal invasion may not be as easily confirmed as an invasive carcinoma into submucosa where stromal desmoplasia is usually evident. The distinction between intramucosal carcinoma and carcinoma *in situ* or high grade dysplasia is important, as the intramucosal carcinoma of stomach, unlike the intramucosal carcinoma in the colon, does metastasize. Generally, the useful histologic features of intramucosal invasion are single tumor cells in the lamina propria and significantly fused neoplastic glands of various sizes. The prognosis of early gastric carcinoma is excellent, with a 5 years survival rate as high as 90% (14). In contrast, the advanced gastric carcinoma which invades into muscularis propria or beyond carries a much worse prognosis, with a 5 years survival rate at about 60% or less (15). The gross appearance of advanced gastric carcinomas can be exophytic, ulcerated, infiltrative or combined. Based on Borrmann's classification, the gross appearance of advanced gastric carcinomas can be divided into type I for polypoid growth, type II for fungating growth, type III for ulcerating growth, and type IV for diffusely infiltrating growth which is also referred to as linitis plastica in signet ring cell carcinoma when most of gastric wall is involved by infiltrating tumor cells. Histologically, advanced gastric carcinoma often demonstrates marked architectural and cytological heterogeneity, with several co-existing histologic growth patterns. The distinction between early and advanced gastric carcinoma before resection is clinically important because it helps decide if a neoadjuvant (pre-operative) therapy which has shown to improve disease free survival and overall survival (16,17) is warranted. While the macroscopic appearance is informative, the most accurate pre-operative staging information is generally obtained with endoscopic ultrasonography (EUS) and computer tomography (CT) (18).



**Figure 1** Tubular adenocarcinoma. Irregular-shaped and fused neoplastic glands with intraluminal mucus and debris.



**Figure 2** Mucinous adenocarcinoma. Clusters and scattered tumor cells floating in the abundant extracellular mucin pools.



**Figure 3** Signet ring cell carcinoma. Signet ring carcinoma cells are predominantly at the superficial lamina propria.

### ***Histologic classification of gastric carcinomas***

Histologically, gastric carcinoma demonstrates marked heterogeneity at both architectural and cytologic level,

often with co-existence of several histologic elements. Over the past half century the histologic classification of gastric carcinoma has been largely based on Lauren's criteria, in which intestinal type and diffuse type adenocarcinoma are the two major histologic subtypes, plus indeterminate type as uncommon variant (18). The relative frequencies are approximately 54% for intestinal type, 32% for the diffuse type, and 15% for the indeterminate type (19). There are indications that the diffuse type gastric carcinoma is more often seen in female and young individuals (20,21), while the intestinal type adenocarcinoma is more often associated with intestinal metaplasia and *Helicobacter pylori* infection (22,23).

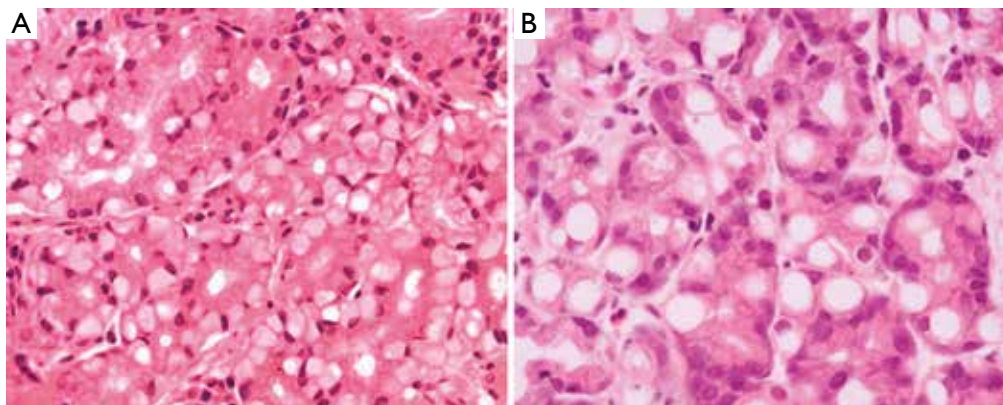
The 2010 WHO classification recognizes four major histologic patterns of gastric cancers: tubular, papillary, mucinous and poorly cohesive (including signet ring cell carcinoma), plus uncommon histologic variants (24). The classification is based on the predominant histologic pattern of the carcinoma which often co-exists with less dominant elements of other histologic patterns.

Tubular adenocarcinoma is the most common histologic type of early gastric carcinoma (*Figure 1*). It tends to form polypoid or fungating masses grossly, and histologically demonstrates irregularly distended, fused or branching tubules of various sizes, often with intraluminal mucus, nuclear and inflammatory debris.

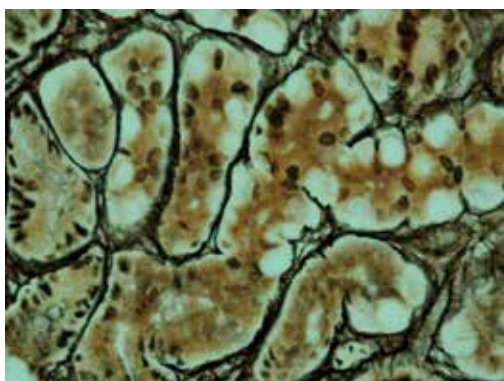
Papillary adenocarcinoma is another common histologic variant often seen in early gastric carcinoma. It tends to affect older people, occur in the proximal stomach, and is frequently associated with liver metastasis and a higher rate of lymph node involvement. Histologically, it is characterized by epithelial projections scaffolded by a central fibrovascular core.

Mucinous adenocarcinoma accounts for 10% of gastric carcinoma. Histologically it is characterized by extracellular mucinous pools which constitute at least 50% of tumor volume (*Figure 2*). The tumor cells can form glandular architecture and irregular cell clusters, with occasional scattered signet ring cells floating in the mucinous pools.

Signet ring cell carcinoma (*Figure 3*) and other poorly cohesive carcinomas are often composed of a mixture of signet ring cells and non-signet ring cells. Poorly cohesive non-signet ring tumor cells are those that morphologically resemble histiocytes, lymphocytes, and plasma cells. Those tumor cells can form irregular microtrabeculae or lace-like abortive glands, often accompanied by marked desmoplasia in the gastric wall and with a grossly depressed or ulcerated surface. When it occurs at the antropyloric region with serosal involvement, the carcinoma tends to



**Figure 4** Pseudo-signet ring cells. The cytoplasm of pseudo-signet ring cells are vacuolated (A) and pale (B) (photos are courtesy of Dr. Caroline Hughes).



**Figure 5** Pseudo-signet ring cells are confined within basement membrane and maintain intact acinar structure with reticulin stain (photo is courtesy of Dr. Caroline Hughes).

have lymphovascular invasion and lymph node metastasis. Because signet ring cell and other poorly cohesive carcinomas at antropyloric region have a propensity to invade duodenum via submucosal and subserosal routes including subserosal and submucosal lymphatic spaces, special attention needs to be paid to those routes when a distal margin frozen section is requested at the time of surgical resection. Special stains such as cytokeratin immunohistochemistry can help detect morphologically occult signet ring cells in the lamina propria. One important differential diagnosis of neoplastic signet ring cells in gastric mucosa is benign pseudo-signet ring cells which can remarkably mimic signet ring cell carcinoma (*Figure 4*). Those pseudo-signet ring cells sometimes can demonstrate cytological atypia, even with mitoses. However, those pseudo-signet ring cells do not reveal invasive pattern with

reticulin stain which highlights pseudo-signet ring cells confined within basement membrane with intact acinar architecture (*Figure 5*) (25).

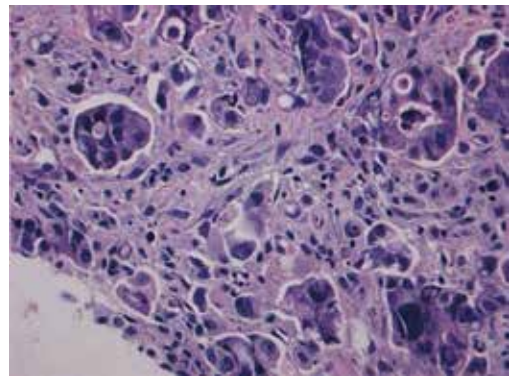
In addition to the above four major histologic subtypes, WHO classification also endorses other uncommon histologic variants, such as adenosquamous carcinoma, squamous carcinoma, hepatoid adenocarcinoma, carcinoma with lymphoid stroma, choriocarcinoma, parietal cell carcinoma, malignant rhabdoid tumor, mucoepidermoid carcinoma, paneth cell carcinoma, undifferentiated carcinoma, mixed adeno-neuroendocrine carcinoma, endodermal sinus tumor, embryonal carcinoma, pure gastric yolk sac tumor and oncocytic adenocarcinoma, all listed in *Table 1*, with Lauren's classification for comparison.

Gastric carcinoma with lymphoid stroma (medullary carcinoma) is one of the uncommon subtypes. It occurs more commonly in proximal stomach and generally follows a less aggressive clinical course. Histologically, this type of carcinoma is characterized by a sharply demarcated advancing margins composed of irregular nests or sheets of polygonal tumor cells associated with a prominent lymphoid infiltrate in a non-desmoplastic stroma. It is interesting that over 80% of gastric carcinomas with lymphoid stroma are Epstein-Barr virus (EBV) positive (26,27), and EBV is only identified in the malignant and dysplastic cells but not in the normal epithelial cells (28). The finding has raised the hope for tumor cell targeting, especially after studies show that Bortezomib, a proteasome inhibitor, can induce EBV kinase by activating EBV lytic protein expression in the infected tumor cells, which in turn renders the infected cells more susceptible to killing by other agents (29). Another group of gastric carcinomas with lymphoid stroma are those



Table 1 Gastric adenocarcinoma classification systems	
WHO (2010)	Lauren (1965)
Papillary adenocarcinoma	Intestinal type
Tubular adenocarcinoma	
Mucinous adenocarcinoma	
Signet-ring cell carcinoma	Diffuse type
And other poorly cohesive carcinoma	
Mixed carcinoma	Indeterminate type
Adenosquamous carcinoma	
Squamous cell carcinoma	
Hepatoid adenocarcinoma	
Carcinoma with lymphoid stroma	
Choriocarcinoma	
Carcinosarcoma	
Parietal cell carcinoma	
Malignant rhabdoid tumor	
Mucoepidermoid carcinoma	
Paneth cell carcinoma	
Undifferentiated carcinoma	
Mixed adeno-neuroendocrine carcinoma	
Endodermal sinus tumor	
Embryonal carcinoma	
Pure gastric yolk sac tumor	
Oncocytic adenocarcinoma	

that demonstrate high microsatellite instability (30,31), resulting from defective function of DNA mismatch repair proteins, usually hMLH1 or hMSH2, but rarely hMSH6 (30,32-34). The number of tumor-infiltrating lymphocytes, while significantly higher than the one in non-microsatellite instability-high cancers, is lower than that in EBV positive carcinoma (34). This group of carcinoma is usually intestinal type by Lauren's classification, and often affects the elderly, with a lower pTNM stage and a low risk of lymph node metastasis. It was suggested that microsatellite instability-high status and EBV infection were the variables which rendered the carcinoma a better prognosis. However, the claims have not been substantiated by other studies. More recent study reveals that the high number of tumor-infiltrating lymphocytes is the only favorable prognostic factor independent of EBV infection and microsatellite instability-high status (34). Also in this investigation, neither EBV positivity nor microsatellite instability-high alone was proved to be an independently favorable prognostic factor. Interestingly, EBV positivity and microsatellite instability-high status, while both share the feature of prominent tumor-infiltrating lymphocytes, are rarely concomitant, suggesting the two are unrelated and involved in distinct



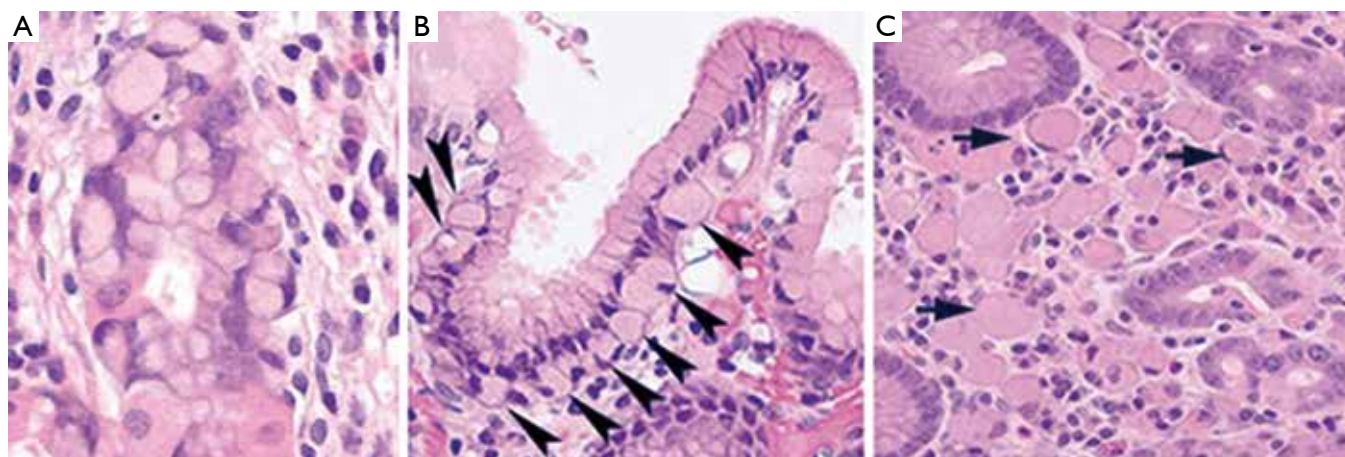
**Figure 6** Micropapillary adenocarcinoma. Small papillary clusters of tumor cells devoid of fibrovascular core and surrounded by empty spaces.

underlying pathways in carcinogenesis.

Micropapillary carcinoma of stomach is a newly recognized histologic variant characterized by small papillary clusters of tumor cells without a distinct fibrovascular core (Figure 6). The micropapillary features are often noted in the deep advancing edge of tumor, surrounded by an empty space mimicking retraction artifact. Micropapillary carcinoma of stomach, as its counterpart at other organs, tends to form endolymphatic tumor emboli and metastasize to lymph nodes. However, the overall survival of gastric micropapillary carcinoma, unlike that in other organs, seems to be not significantly different from conventional gastric adenocarcinoma, although the result may be due to the small patient sample in that study (11 patients) (35). Because of the high incidence of lymphatic invasion and nodal metastasis (up to 82%) (35,36), it is advised that conservative treatment such as endoscopic resection not be used for gastric carcinoma with invasive micropapillary components.

### Application of molecular pathology in gastric carcinoma

An accumulation of genetic and molecular abnormalities occurs during gastric carcinogenesis, including activation of oncogenes, overexpression of growth factors/receptors, inactivation of tumor suppression genes, DNA repair genes and cell adhesion molecules (37), loss of heterogeneity and point mutations of tumor suppressor genes, and silencing of tumor suppressors by CpG island methylation (38). The revelation and understanding of the molecular events and pathways have led to the application of molecular pathology



**Figure 7** A. *In situ* signet ring carcinoma cells confined within basement membrane; B. Pagetoid spread of signet ring cells (arrow heads) below the preserved surface epithelium; C. Focus of intramucosal signet ring cell carcinoma (arrows) in the lamina propria (all three photos are courtesy of Dr. Rebecca Fitzgerald).

in the prevention, early diagnosis, tumor classification and therapeutic intervention. The applications of molecular testing such as the testing of CDH1 gene for hereditary diffuse gastric carcinoma (HDGC) and of HER2 expression in gastric cancers have had significant impact on medical practice, and become standard patient care.

#### ***Hereditary diffuse gastric carcinoma (HDGC)***

About 10% of gastric carcinomas show familial clustering but only approximately 1-3% of gastric carcinomas arise from inherited gastric cancer predisposition syndromes (39), such as hereditary diffuse gastric carcinoma (HDGC), familial adenomatous polyposis, hereditary nonpolyposis colorectal carcinoma (or Lynch syndrome), juvenile polyposis syndrome, Peutz-Jeghers syndrome, Li-Fraumeni syndrome and gastric hyperplastic polyposis (40-42). HDGC is an autosomal dominant disorder with high penetrance. Approximately 30% of individuals with HDGC have a germline mutation in the tumor suppressor gene E-cadherin or CDH1 (43). The inactivation of the second allele of E-cadherin through mutation, methylation, and loss of heterozygosity eventually triggers the development of gastric cancer (44,45). To diagnose HDGS, two or more cases of diffuse gastric carcinoma in first or second degree relatives must be documented, with at least one diagnosed before the age of 50; or there are three or more documented cases of diffuse gastric carcinoma in first or second degree relatives, regardless of the age of onset (46,47).

The histologic phenotype of HDGC in early stage includes patchy intramucosal signet ring carcinoma cells in the lamina propria and its unique feature of carcinoma *in situ* associated with pagetoid spread of tumor cells along the preserved basement membrane (Figure 7). The lesion can be multifocal but usually starts at the junction of antrum and body. The tumor cells often demonstrate hyperchromatic nuclei, with occasional mitoses. Because it is difficult to diagnose HDGC at an early stage both histologically and endoscopically, and because the penetrance of CDH1 mutation is high, with the carrier of this gene conferring over 80% life time risk of gastric carcinoma (47), prophylactic total gastrectomy after confirmation through CDH1 molecular testing is the only recommended way to save patients' lives. According to the updated recommendations for CDH1 testing by International Gastric Cancer Consortium, family members of the following are the candidates for CDH1 testing (48): (I) Two family members with gastric carcinoma, one of which is confirmed diffuse gastric cancer; (II) Three family members with gastric carcinoma in first or second degree relatives including one with diffuse gastric cancer; (III) One member with diffuse gastric cancer before the age of 40; (IV) Personal or family history of diffuse gastric cancer and lobular breast cancer including one diagnosed before 50.

If *in situ* signet ring cell carcinoma with pagetoid spread is identified adjacent to diffuse type gastric cancer and confirmed by expert GI pathologists, the patient should also be tested for CDH1 mutation, because the histologic

**Table 2** Human epidermal growth factor receptor 2 (HER2) scoring criteria for gastric cancer

Score	Surgical specimen-staining pattern	Biopsy specimen-staining pattern	HER2 overexpression
0	No reactivity or membranous reactivity in <10% of tumor cells	No reactivity or no membranous reactivity in any tumor cell	Negative
1+	Faint/barely perceptible membranous reactivity in >10% of tumor cells; cells are reactive only in part of their membrane	Tumor cell cluster with a faint/barely perceptible membranous reactivity irrespective of percentage of tumor cells stained	Negative
2+	Weak to moderate complete, basolateral, or lateral membranous reactivity in >10% of tumor cells	Tumor cell cluster with a weak to moderate complete, basolateral, or lateral membranous reactivity irrespective of percentage of tumor cells stained	Equivocal
3+	Strong complete, basolateral, or lateral membranous reactivity in >10% of tumor cells	Tumor cell cluster with a strong complete, basolateral, or lateral membranous reactivity irrespective of percentage of tumor cells stained	Positive

features have not been reported in sporadic form of gastric carcinoma (49). The confirmation of HDGC through CDH1 mutation can help family members decide if they should consider the similar testing.

Because approximately 4% of these mutation positive families exhibit large germline deletions of CDH1 that cannot be detected by conventional DNA analysis (50), large genomic rearrangements should be sought in addition to conventional direct sequencing. It is also recommended that CDH1 genetic testing on blood for germline mutations should be performed in Clinical Laboratory Improvement Laboratory (CLIA)-certified molecular diagnostic laboratories or research laboratories with expertise in CDH1 gene analysis (48).

In addition to prophylactic total gastrectomy, annual mammography and breast MRI from the age of 35 years are recommended for women with HDGC, due to their increased risk of lobular breast cancer (51).

### *Human epidermal growth factor receptor 2*

Human epithelial growth factor receptor 2 (HER2), a member of the human epidermal growth factor receptor (EGFR) family, is a proto-oncogene located on chromosome region 17q21. It encodes a 185 kD transmembrane tyrosine kinase receptor protein that regulates signal transduction in cell proliferation, differentiation and survival (52,53). HER2 gene amplification was described in gastric carcinoma after its discovery in breast cancer (54). With immunohistochemical stain, it was found that the rate of HER2 overexpression in gastric adenocarcinoma is 12% in a Japanese series (55) and 22.1% in more recent studies (56-58). HER2 overexpression

is more often noted in intestinal type carcinoma (57,59) and in the carcinomas located at proximal stomach or cardia and gastroesophageal junction (24-35%) than in the remaining stomach (9.5% to 21%) (19,59,60). In addition, HER2 status in the carcinomas of stomach and GEJ is relatively homogeneous and rarely shows significant modification from primary site to metastatic foci (61).

Recently, a large scale phase III international clinical trial called ToGA showed that the humanized monoclonal antibody against HER2, Trastuzumab (Herceptin), when combined with chemotherapy (capecitabine or 5-fluorouracil and cisplatin), could effectively prolong overall survival and progression-free survival, and increases the response rate in HER2 positive advanced gastric carcinoma (57). On the basis of these findings, the regulatory approval for trastuzumab was granted in October 2010 in the United States for patients with HER2 positive metastatic adenocarcinoma of stomach or gastroesophageal junction. Now, it is recommended that all patients with gastric cancers should routinely be tested for the HER2 status at the initial diagnosis (57,62).

While HER2 positive status in gastric carcinoma is also defined as either IHC3+ or IHC2+ plus positive FISH, similar to breast cancers, there are several differences in the evaluation of HER2 status in gastric cancers. In gastric or GEJ cancers, only 5 clustered positive cancer cells in a biopsy tissue or a minimum 10% of positive neoplastic cells in a surgical resection specimen are required for defining 3+ score, on the condition that the immunohistochemical stain reveals intense complete, basolateral, or lateral membranous reactivity (62). In order to archive accurate and reproducible HER2 scoring, it is essential that the interpretation of

HER2 expression is strictly based on the criteria originally reported in the Trastuzumab for gastric cancer study, which was published and listed in *Table 2* (57).

In addition, a panel of expert pathologists from the European Union and the rest of the world recommend that if immunohistochemistry is used as the initial test, any specimen type (either surgical resection or biopsy) with <10% strongly stained tumor cells should be subjected to confirmatory *in situ* hybridization testing to preclude false-negative results (62). If the sample is poorly preserved, shows nonspecific staining at cytoplasm and nuclei of the tumor cells, or reveals staining at benign mucosa with intestinal metaplasia, the sample should be retested by FISH to exclude false positive results (62).

Based on the results from ToGA study, the levels of HER2 protein predicts well for the response of gastric carcinoma to Trastuzumab. On the other hand, the tumors with positive HER2 amplification but with low or negative HER2 expression do not respond well to Trastuzumab. Therefore, immunohistochemistry is recommended to be used as the initial testing methodology, and FISH or silver *in situ* hybridization used to retest immunohistochemistry 2+ cases (62).

### *Dihydropyrimidine dehydrogenase*

Dihydropyrimidine dehydrogenase (DPD) is the rate-limiting enzyme in uracil catabolism, and is also the main enzyme involved in the degradation of structurally related compounds like 5-Fluorouracil (5-FU), a widely used drug in treating different kinds of tumor including gastric carcinoma. True deficiency of DPD affects approximately 5% of the overall population (63). Patients with DPD deficiency are at significantly increased risk of developing severe and potentially fatal neutropenia, mucositis and diarrhea (63-65) when treated with 5-FU or capecitabine. In addition, 3% to 5% of the population has a partial DPD deficiency due to sequence variations in DPYD gene, which potentially limits their ability to fully metabolize the drug, thereby resulting in toxicity (66-68). Many studies have addressed and identified the mutations of DPYD and epigenetic alterations of DPYD as the causes of lower levels of DPD or DPD deficiency. Subsequently, different tests have been developed in order to identify the people at risk of DPD deficiency, in the hope that the test results could eventually provide clinical guidance. One of the tests to identify the people with DPD deficiency is DPYD genotyping to detect the important mutations such as DPYD 2A (or IVS14+1 G>A) (66,69). While the individuals

with positive DPYD mutation have an increased risk for DPD deficiency, DPD deficiency is also noted in the people with wild type DPYD, because epigenetic alteration, such as methylation at the regulatory region of DPYD promoter can cause lower DPD level without the mutation at DNA level (70). To make issue more complicated is that the uracil catabolic pathway involves several other enzymes such as dihydropyrimidinase (DHP) (71) and beta-ureidopropionase (BUP1) (72,73). The mutations of those genes which are at the downstream of DPD also impair uracil catabolism. Therefore, uracil breath test which involves DPD, DHP, and DUP1 may reveal more clinical information of potential toxicity in the patients who receive 5-FU treatment (74), because it evaluates the integrity of the entire catabolic pathway of uracil which cannot be archived by DPYD genotyping alone.

Despite the fact that DPYD genotyping is informative for identifying patients with an increased risk of toxicity to 5-FU treatment, and despite the large numbers of studies which attempt to identify molecular predictors of response and toxicity to treatment, none of the tests and molecular markers thus far have been proven to be reliable in prospective clinical trials, and unlike CDH1 and HER2 testing, none of those tests have been validated to permit their use as standard of care in 5-FU therapy. Many questions still remain unanswered and many components in the entire metabolic pathways of FU remain unaddressed. For example, DPD deficiency was noted only in a small percentage of patients with severe 5-FU toxicity, leaving a large numbers of patients with an unexplainable molecular basis of toxicity (75). In predicting who will develop toxicity when treated with 5-FU or capecitabine, much more work has to be done (76).

In conclusion, while gastric cancer remains a deadly disease, the discoveries of new molecular markers, genetic and epigenetic alteration, and novel pharmacogenetic traits have helped improve patients care, fostered hope and led new directions of cure. The newest WHO classification of gastric carcinoma is by far the most comprehensive, describing the morphologic characteristics of each subtype in detail. Hopefully, it will help understand the clinicopathologic entity of each subtype by correlating its histologic feature with molecular profiling and clinical behavior. It is encouraging that the discoveries of some pharmacogenetic traits have opened the door for individualized medicine, promising the future medicine to be more effective and less toxic because it is based on the molecular fingerprint not only of each tumor but of



each human being. Nevertheless, many challenges remain. Some claims to attempt pharmacogenetic prediction based on the pattern of single nuclear polymorphisms (SNP) may be premature and have not been fully validated. Caution should be exercised as some of claims may be biased and could lead to harmful consequences (77,78).

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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# The era of laparoscopic surgery for gastric cancer: what is the present territory and what will be next?

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Since its introduction, laparoscopic surgery has evolved from a new idea into a popular technique that is now the standard of care for many indications. In the treatment of gastric cancer, since Kitano *et al.* first reported a laparoscopic approach for gastric cancer resection in 1994 (1), laparoscopic techniques have become widely adopted by gastric cancer surgeons, beginning in Japan, Korea, and China, and now extending throughout the world. However, at the time laparoscopic techniques were being introduced, conservative surgeons expressed significant concerns about the use of laparoscopic techniques in the treatment of gastric cancer. In the past, many trials failed to show the benefit of chemotherapy for gastric cancer, thus it was considered to be a malignancy refractory to chemotherapy, making complete resection the only strategy for achieving a cure (2). As part of an attempt to completely remove all gastric cancer tumor cells, extended lymph node dissection was previously believed to provide survival benefits. Thus, surgeons were focused on more extended surgery for gastric cancer: a landmark clinical trial that compared D2 versus D2 plus para-aortic lymph node dissection was conducted from 1995 to 2001 (this period was the time that laparoscopic surgery was introduced for gastric cancer) to prove the benefit of extended lymph node dissection (3). Consequently, the argument that laparoscopic surgery might have limited applications in the treatment of gastric cancer because laparoscopic techniques do not permit adequate extended lymph node dissection was reasonable at that time. Even those circumstances, believing that laparoscopic approaches could be used to improve patients' quality of life after surgery with similar oncologic outcomes, smart

and innovative surgeons have developed this laparoscopic technique for gastric cancer. These surgeons initially used laparoscopic techniques to treat very early stage gastric cancers in which limited lymph node dissection would be performed, and over time multiple surgical techniques and new devices have been developed. Also, the advancement of laparoscopic gastric cancer treatment has been further aided by an active exchange of skills and knowledge not only between surgeons within countries (beginning mainly in Japan) but also extending across nations (Japan, Korea, and China). In addition, development and refinement of laparoscopic surgical techniques for the treatment of gastric cancer were further accelerated by the experiences of surgeons working in high volume centers in Korea, where these surgeons have accumulated substantial skill and experience within short periods of time (4). Laparoscopic treatments of gastric cancer have now been propagated across the world, and the use of these methods has been expanded to include even some cases of advanced gastric cancer.

These innovations are now yielding substantial clinical benefits. Interim results of the Korean Laparoscopic Gastrointestinal Surgery Study (KLASS) trial (5), a phase III multicenter, prospective, randomized trial, and the KLASS-01 trial (6) found no differences in mortality and fewer wound complications for laparoscopic surgery compared to conventional open surgery for early stage gastric cancer (clinical stage I). In addition, another large scale case-control and case-matched Korean multicenter study found that the long-term oncologic outcomes of laparoscopic surgery were comparable to those of open

surgery (7). These results suggest that laparoscopic surgery may be considered as a standard procedure for the treatment of early gastric cancer, specifically in distal gastrectomy cases.

But would laparoscopic techniques be applied in cases of advanced gastric cancer? The most recent study entitled “Morbidity and Mortality of Laparoscopic Versus Open D2 Distal Gastrectomy for Advanced Gastric Cancer: A Randomized Controlled Trial” investigating this question has been conducted in China: the Chinese Laparoscopic Gastrointestinal Surgery Study (CLASS). The CLASS group has reported that short-term outcomes in their study cohort have been comparable for cases of advanced gastric cancer treated with laparoscopic surgery for D2 distal gastrectomy compared to cases treated with open surgery (8). To confirm the long-term oncologic outcomes of laparoscopic surgery for advanced gastric cancer, we must wait for the final reports of this and other ongoing trials in Korea, China, and Japan. However, if the quality of laparoscopic resection is the same as conventional open surgery, the expected result would be to find no difference in oncologic outcomes. In the recent CLASS trial and the KLASS II trial (NCT01456598), laparoscopic surgery quality was formally assessed using intraoperative videos and photos, therefore, their primary end point, the long term oncologic outcomes of laparoscopic surgery, would not be inferior to that of open surgery.

Following an extended debate, the D2 level has been set as the cutoff for lymph node dissection in cases of gastric cancer, and D2 lymph node dissection is the standard for gastric cancer treatment as part of either open or laparoscopic surgery, including robotic surgery (9,10). Thus, the maximum level for the application of laparoscopic techniques is D2, and some experienced surgeons are already achieving these technical end points with laparoscopic surgery. A separate problem, however, is that generalizing excellent results of laparoscopic procedures ultimately depend on whether the performance of this procedure can be standardized. The mortality rate for gastric cancer surgery is still high, even for open surgery in the West (11). And according to the United States (US) Graduate Medical Education General Surgery Report from 2012, current US general surgery residency graduates on average performed fewer than five gastrectomy procedures during their 5 years of residency training, suggesting limited exposure to gastric cancer surgery during their training (12). Even in East Asia, where gastric cancer is endemic and D2 gastrectomy has long been a standard surgery, only some qualified surgeons are capable of performing a complete

D2 lymph node dissection using a laparoscopic approach. Therefore, one of the next challenges in laparoscopic gastric cancer surgery, which we must solve, will be standardizing how these procedures are performed.

Current trends in the surgical treatment of early gastric cancer have included minimizing the extent of surgery in highly selected patient (13), for example the use of endoscopic resection, sentinel lymph node navigation surgery, pylorus-preserving gastrectomy, or proximal gastrectomy. One of the aims of laparoscopic approaches in gastric cancer surgery is to minimize surgical extent and improve quality of life for patients, while achieving non-inferior oncologic outcomes. The major premise of all of these minimalist, less invasive surgeries is that there will be no remaining metastases in the lymph nodes in the non-dissected areas. Consequently, the development of methods to accurately predict the presence of lymph node metastases is a current research focus, and this issue must be addressed in order to actively propagate minimally invasive surgery for gastric cancer. Numerous prior studies have tried to predict lymph node metastases preoperatively using various clinical variables (14-16). However, the methods reported in these studies are not yet sufficiently accurate for translation into clinical use. The recent cutting edge technologies, including next generation sequencing (NGS), have enabled characterization of the genetic features of cancers, making it possible to further classify gastric cancers according to their molecular characteristics using multi-omics approaches (17,18). Different methods for treating each gastric cancer may then be applied according to the cancer subtype identified by its molecular characteristics. These genetic analysis methods will be (and in some cases already are) integrated into mainstream cancer research. In the near future, these approaches may make it possible to predict the presence of lymph node metastases at the time of preoperative planning, and such a diagnostic advancement would likely attach wings to the propagation of laparoscopic surgery for gastric cancer.

Last but not least, some of our surgeons must turn their attention to further improving the survival of patients with gastric cancer. Recent studies of gastric cancer surgery have mainly focused on using minimally invasive techniques to achieve non-inferior oncologic outcomes compared to conventional surgical approaches, rather than aiming to improve oncologic outcomes. Except in Korea and Japan, where nationwide screening systems have been established, most patients with gastric cancer are diagnosed at advanced stages. To improve survival in these patients, we need to

collaborate with other disciplines and identify effective adjunctive treatment modalities, including advances in chemotherapy, radiotherapy, and immunotherapy coming from clinical and basic science research. Given that surgery plays a central role in the treatment of gastric cancer and provides the only means of achieving cure, surgeons should acknowledge their pivotal role in conquering this deadly disease. Consilience between disciplines will guide us to victory in the war against gastric cancer.

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### Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

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# Surgical management of gastric cancer: the East vs. West perspective

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**Abstract:** Gastric cancer is a unique malignancy, with definite geographic differences in incidence, pathology, treatment and outcome. While the incidence has been declining in the Western hemisphere, steady rates have been reported in Eastern countries, particularly South Korea and Japan. One of the most profound differences between the East and West centers around treatment strategies, with Western clinicians routinely adopting a neoadjuvant approach, prior to surgical resection. Eastern clinicians, however, favor primary surgical therapy and have pioneered many of the techniques currently used worldwide. From endoscopic therapies to minimally-invasive surgery, including laparoscopic and robotic techniques, the Eastern surgeons have studied their techniques with high-volumes of patients. Western surgeons, practicing in systems where gastric cancer care is not centralized, typically have performed less aggressive surgical resections, although generally see more advanced diseases. In the era where global care is becoming more standardized, however, the differences in surgical practice have lessened. This review compares the surgical techniques and outcomes for gastric cancer practiced in the East with those standard in the West.

**Keywords:** Gastric cancer; surgery; East; West

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## Introduction

The global incidence, screening policies, pathology, management and outcomes of gastric cancer vary significantly by geography, especially between the East and West. While the incidence in the United States (U.S.) is estimated at 21,600 new cases a year (1), the incidence in South Korea, the country with the highest rate in the world, is 33,000 per year, a large number compared to the much smaller size of its population, followed by Mongolia, Japan and China (2,3). Because of the higher incidence in the East, South Korea and Japan, for example, have initiated a screening program for its citizens in an effort to increase rates of early detection. In fact, such systematic efforts in the East have been found to be cost-effective and have resulted in improved gastric cancer survival (4). Meanwhile,

in the West, where the per capita incidence of gastric cancer is far lower, such systematic gastric cancer screening efforts for the entire population has no proven benefit.

There are, however, notable differences between the East and West. The high rate of Barrett's esophagus in the U.S., for example, confers an increased risk of esophageal adenocarcinoma, including gastroesophageal junction tumors, which in the East are often classified as gastric cancer. Because the classification of gastroesophageal junction tumors is a controversial topic, this review will focus only on gastric cancer. The typical patient profile between the East and West differs significantly, guiding the corresponding systematic approaches to gastric cancer. Many of these differences are thought to be due to epidemiologic and environmental risk factors. Even within the U.S. population, patients of Asian descent have been



found to have a higher relative overall survival compared with their counterparts of Caucasian, African-American and Hispanic descent (5-7). These inherent differences contribute to the treatment approaches adopted, which have geographic variance. Here, we review the differences in pathology, surgical and systemic therapy, and outcomes between the East and West.

## Biology

One of the primary differences between the East and West to consider is gastric cancer pathology. Classically, consideration begins with anatomic localization, a factor that guides treatment and correlates with outcomes. From epidemiologic studies, gastric cancer in the West is more commonly located in the proximal stomach and presents at a more advanced stage and has a worse prognosis than in the East, where distal gastric cancers are more common (8). Additionally, lower esophageal and proximal gastric adenocarcinoma has been steadily increasing, a phenomena not observed in the East; this has been postulated to be due to a lower incidence of reflux esophagitis and Barretts metaplasia (8).

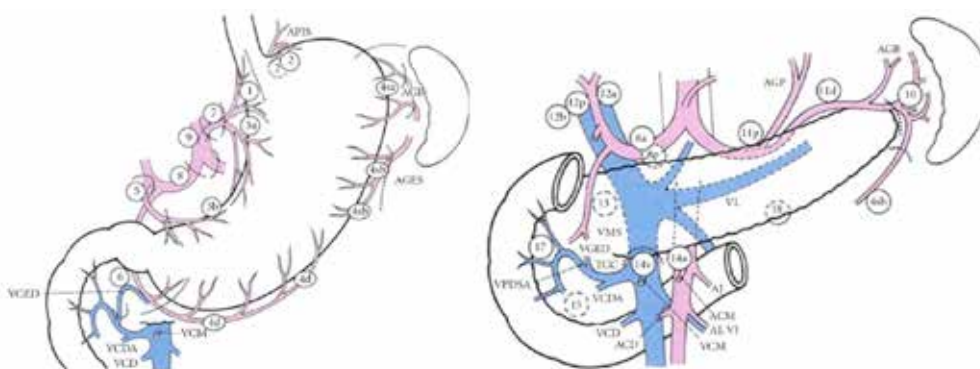
In the West, the incidence of the diffuse and signet ring histologic subtypes occurs more commonly than in the East and are associated with worse prognoses. In addition to the differences in histology, patients in the West tend to present with more advanced disease, whereas nearly half of patients in South Korea and Japan present with early stage disease, a result likely attributable to the national screening programs in those countries. Patients in the U.S. also generally have greater co-morbidities than do patients in the East (9). For example, U.S. gastric cancer patients typically present later in life and have a higher body mass index, factors linked to an increased risk of post-operative complications, all of which are critical to note when comparing outcomes in gastric cancer treatment (9).

Although the etiology and pathogenesis of gastric cancer is an avid topic of investigation without a proven definitive mechanism to date, there are many well described risk factors (10-13). Medical conditions with a known association with gastric cancer include *Helicobacter pylori* (*H. pylori*) gastric infection, chronic atrophic gastritis, intestinal metaplasia, pernicious anemia, gastric adenomatous polyps, and giant hypertrophic gastritis (Ménétrier disease) (10-12). Interestingly, in the U.S., male gender, African American race, low socioeconomic status, obesity, occupational hazards in metal and rubber work, mining, wood and asbestos dust exposure, and cigarette smoking

are associated with gastric cancer, while chronic *H. pylori* exposure and diet have been associated with gastric cancer in the East (10-13). It has also been postulated that in U.S. Caucasian and Hispanic patients, there may be a link between Epstein-Barr virus infection (13). A high salt diet, smoked foods, nitrates, nitrites, poorly preserved foods and secondary amines are thought to alter the gastric milieu, resulting in production of *N*-nitroso compounds which are carcinogenic, factors which are thought to be critical to the increased incidence of gastric cancer in the East (10-13). The role of *H. pylori* infection in the pathogenesis of gastric cancer is a broad and controversial topic beyond the scope of this review, with multiple efforts underway to determine the exact mechanism of this link and what the implications may be for public health efforts in eradicating the organism.

## Endoscopic resection

For advanced gastric cancer and most early-stage gastric cancer, gastrectomy with D2 lymphadenectomy (resection of perigastric lymph nodes and nodes along the named branches of the celiac axis) is considered standard surgical therapy. However, with advancement in techniques for local evaluation of gastric tumors with endoscopic ultrasound, as well as endoscopic resection techniques, endoscopic submucosal dissection (ESD) has become well-recognized as a treatment for early gastric cancers that are at low risk for lymph node metastases. Initial indications for endoscopic resection for early gastric cancer was differentiated histology, <2 cm in diameter, lack of ulceration or scarring, mucosal involvement only, with no lymphatic or vascular involvement (14). More recently, extended indications for ESD are differentiated tumors, without evidence of venous or lymphatic involvement, <3 cm in diameter, and confined to the mucosa or submucosa (15). Expanded criteria to include undifferentiated tumors has yielded excellent long-term survival rates (16,17); ESD is now considered a therapy that could be offered to patients who have early gastric cancer, particularly those limited to the mucosa, without adverse histologic features. Caution must be exercised for tumors with submucosal involvement due to the increased risk for occult lymph node metastases. Lymph node metastases may be present in as many as 20% of patients with early stage gastric cancer, particularly in those patients with lymphovascular invasion and larger tumor size ( $\geq 2$  cm) (18). Therefore, in patients with submucosal disease, gastrectomy with associated lymphadenectomy should be considered



**Figure 1** Lymph Node stations according to the Japanese classification. From Japanese Gastric Cancer Association, Japanese Classification of Gastric Cancer, Kanehara & Co., Ltd, Tokyo, Japan, 14th edition, 2010. (Reprint with permission).

Station number	Location
1	Right paracardial
2	Left paracardial
3	Lesser curvature
4	Greater curvature
5	Suprapyloric
6	Infrapyloric
7	Left gastric artery
8	Common hepatic artery
9	Celiac artery
10	Splenic hilum
11	Splenic artery
12	Hepatoduodenal ligament
13	Posterior to pancreatic head
14	Superior mesenteric vessels
15	Middle colic vessels
16	Paraortic

standard of care. For patients at high-risk for surgery, ESD can be considered an option.

### **D1 vs. D2 lymphadenectomy**

Surgery is the mainstay treatment for early stage gastric cancer and is paramount for achieving cure in patients with gastric adenocarcinoma. Barring an early T1a or *in situ* tumor, gastrectomy including resection of the regional lymph nodes remains the standard surgical procedure. The extent of lymphadenectomy, however, has been a greatly

debated topic of controversy throughout the last few decades. The majority of Japanese and Korean (i.e., Eastern) surgeons would agree that an extended lymphadenectomy (D2) leads to improved outcomes and survival. Certainly, multiple large retrospective studies from those groups have illustrated an impressive overall survival that has not been replicated in Western series (19,20).

The Japanese Gastric Cancer Association (JGCA) published guidelines for surgical treatment and pathologic evaluation that grouped the perigastric and distant draining lymph nodes into 16 stations (*Figure 1, Table 1*) (21). These stations were then categorized into 4 levels (N1 to 4) based on the likely lymphatic drainage from the respective primary tumor location (22). The nodes along the lesser [stations 1, 3, 5] and greater [2, 4, 6] curvatures are included in the perigastric lymph node level (N1). The more distant draining lymph node stations follow the left gastric artery [7], common hepatic artery [8], celiac artery [9], splenic hilum and artery [stations 10 and 11] and are grouped in the N2 level. The most distant, or para-aortic, nodes (N3 or N4) are usually considered distant metastatic disease and are not traditionally included with gastric resections. However, these four categorization levels have recently been abandoned to prevent confusion with the TNM staging systems.

The extent of lymphadenectomy is dependent on the extent of gastrectomy being performed (i.e., total, subtotal/distal, or proximal gastrectomy) (23). For example, historically, a D2 dissection for a total gastrectomy would involve retrieval of lymph node stations 1-12 with a concomitant distal pancreatectomy and splenectomy while a D1 dissection would only require the perigastric nodes at stations 1-7. More recently, proponents have advocated a modified approach to a D2 dissection by sparing the spleen

**Table 2** Selected randomized controlled trials studying the extent of lymph node dissection for patients with gastric cancer

Study	Year published	Region	Extent of lymph node dissection	Patients (n)	Morbidity (%)	Mortality (%)	5-year overall survival (%)
Dent <i>et al.</i> (31)	1988	South Africa	D1	22	22*	0	N/A
			D2	21	43	0	N/A
Bonenkamp <i>et al.</i> (32,33)	1995	Netherlands	D1	380	25*	4*	45
			D2	331	43	10	47
Cuschieri <i>et al.</i> (34,35)	1996	Europe	D1	200	28*	6.5*	35
			D2	200	46	13	33
Wu <i>et al.</i> (36,37)	2004	Taiwan	D1	110	7.3*	0	53.6*
			D3	111	17.1	0	59.5
Sasako <i>et al.</i> (38)	2008	Japan	D2	263	20.9	0.8	69.2
			D2 + PAND	260	28.1	0.8	70.3
Degiuli <i>et al.</i> (39,40)	2010	Italy	D1	133	12	3	66.5
			D2	134	17.9	2.2	64.2

\*P value <0.05. N/A, not reported; PAND, para-aortic node dissection.

and pancreas unless directly involved with the primary tumor. This approach of sparing the pancreas and spleen has shown adequate retrieval of lymph nodes without the morbidity associated with multi-visceral resection (24,25).

A recent retrospective study evaluating 1,377 patients from the Surveillance, Epidemiology, and End-Results (SEER) database looked at the impact of the number of nodes examined and its relationship with survival as a surrogate for accurate staging (26). Total lymph node count and number of positive lymph nodes were two of the independent factors associated with survival. Significant survival benefit was observed for patients who had more than 15 N2 nodes and 20 N3 nodes examined. Although there is no consensus on the level of dissection required (D1 *vs.* D2) in the U.S., pathologic assessment of at least 15 nodes is considered standard of care, and D2 lymphadenectomy is recommended (27).

Japanese and South Korean surgeons routinely perform D2 lymphadenectomy for patients with gastric adenocarcinoma. The surgeon will then meticulously dissect out each lymph node station prior to sending tissue for pathologic evaluation, unlike in the U.S., where surgeons submit the gastrectomy specimen *en bloc* with the lymphadenectomy. Based on the extensive gastric cancer database of 3,843 patients from the experience by the National Cancer Center in Japan, the Maruyama index (MI) was created in order to create estimates for the likelihood of metastases for each lymph node station not removed by the surgeon. The index is based on 8 variables: age, sex,

Borrmann classification, depth of invasion, diameter, location, position and histology (28). Studies of gastric cancer patients undergoing gastrectomy with a MI <5 versus those ≥5, had an improved median overall and relapse-free survival on univariate and multivariate analysis (29,30). Due to the complexity, however, it is infrequently utilized in the West.

Western proponents for a limited D1 resection cite two large randomized controlled trials published in the 1990s from the Netherlands and United Kingdom that were unable to show a survival benefit with extended lymphadenectomy (Table 2). The Dutch Gastric Cancer Group Trial randomized 711 patients undergoing surgery for curative intent to either D1 or D2 lymphadenectomy in 80 centers throughout the Netherlands (32). Participating surgeons were provided an instruction booklet and videotape on how to perform D2 lymphadenectomy, and an experienced Japanese gastric cancer surgeon was present for the first 6 months of the study for instruction. Patients undergoing D2 resections were more likely to have a higher operative mortality (10% *vs.* 4%, P=0.004) and morbidity (43% *vs.* 25%, P<0.001). Mature, 15-year follow-up data showed no overall survival benefit with a D2 lymphadenectomy (41). A subset analysis, however, showed a lower locoregional recurrence rate and fewer gastric cancer related deaths with D2 lymphadenectomy. Similar to the Dutch trial, the United Kingdom Medical Research Council (MRC) Gastric Cancer Surgical Trial (ST01) randomized 400 gastric adenocarcinoma patients to D1 or D2 lymphadenectomy (34). The operating surgeons were

provided with a booklet and instructional video to ensure standardization of the two procedures. Again, this Western study demonstrated higher post-operative mortality (13% *vs.* 6.5%,  $P=0.04$ ) and morbidity rates (46% *vs.* 28%,  $P<0.01$ ) in the D2 lymphadenectomy group as well as a higher chance of undergoing concomitant pancreatectomy and splenectomy. Most notably was the significantly higher rate of anastomotic complications in the D2 dissection group, also including severe pancreatitis, pancreatic fistula, and gastric remnant necrosis. Long-term results showed no difference in overall survival, gastric cancer related deaths, or recurrence-free survival.

These trials may now be less relevant as more recent studies have shown that routine resection of the spleen and pancreatic tail for middle and proximal gastric tumors increases morbidity and perioperative mortality without long term overall survival benefit. The traditional D2 resection involves a distal pancreatectomy and splenectomy for all tumors except in the antral location, in order to adequately resect lymph node stations 10 and 11 surrounding the splenic artery and hilum. In the UK MRC trial, subset analysis of patients undergoing pancreatico-splenectomy, splenectomy alone, or preservation of both organs showed survival difference, with the poorest survival in those undergoing multi-visceral resection (35). Similarly, the Dutch trial performed a multivariate analysis and showed increased mortality associated with splenic or pancreatic resections. This likely contributed to the lack of survival difference between D1 and D2 resections.

More recently, however, studies from the East and West have shown improved morbidity and mortality with avoidance of routine splenectomy and pancreatectomy compared to traditional D2 resection (42-44). The Italian Gastric Cancer Study group randomized 267 patients with gastric adenocarcinoma to a D1 or modified D2 resection (39). Routine splenectomy and pancreatectomy were not performed unless direct extension by the primary tumor (T4) was noted. No statistically significant difference was noted between the groups in regards to morbidity or in-hospital mortality. Due to this most recent data, surgeons in the Eastern hemisphere are routinely adopting a modified technique for D2 resections and preserving the pancreas and spleen.

The difference in survival and results between Eastern and Western surgeons is likely multi-factorial. Some have pointed to the theory of stage migration as the etiology for improved survival with D2 resection with Eastern surgeons. With an extended lymphadenectomy, a greater number of lymph nodes

are retrieved with a higher chance of detecting a positive node. A recent retrospective analysis of 79 patients undergoing D2 *vs.* D1 lymphadenectomy from Kaiser Permanente Los Angeles showed a significantly greater number of nodes retrieved with a D2 lymphadenectomy (mean, 26 *vs.* 9 nodes,  $P<0.0001$ ) (45). Within the D2 lymphadenectomy group, 39% showed additional lymph node metastases in the extended portion of the dissection, altering 16% of the TNM staging. Additional lymph node dissection beyond a D2 is traditionally not recommended. A prospective trial spearheaded by the Japanese Clinical Oncology Group randomized 523 patients with gastric cancer to D2 or D2 plus para-aortic lymph node dissection (38). Although, as expected, the operative time and estimated blood loss were increased with the extended dissection, the overall and recurrence-free survival showed no significant difference.

### Minimally invasive approaches

Since the first minimally invasive distal gastrectomy for gastric cancer was described by Kitano *et al.* (46) in 1994, there have been multiple studies comparing this to the classic open approach. The theoretical benefits of faster recovery time, decreased operative blood loss and lower morbidity rates with minimally invasive gastrectomy are weighed against the concern for oncologic safety with adequate lymphadenectomy for accurate staging.

There are several randomized clinical trials (RCT) (47-51), predominantly out of the East, and the Korean Laparoscopic Gastrointestinal Surgery Study Group (KLASS trial) has published the largest trial to date (48). This group randomized 342 patients with early gastric cancer (limited to T1N0, T1N1, or T2N0 by preoperative staging) to laparoscopic or open distal gastrectomy. The authors showed no difference in post-operative morbidity and mortality between the groups. In regards to oncologic safety, the authors did not evaluate the number of nodes removed between the two groups. However, there was no statistically significant difference in terms of the rate of D1 *vs.* D2 dissection done between the two groups. No long-term results regarding locoregional recurrence or overall survival are currently available.

Due to the small number of randomized clinical trials and the low number of patients in each study, a recent meta-analysis by Vinuela *et al.* (52) included several high quality non-randomized studies (NRCT) comparing laparoscopic and open distal gastrectomy for gastric cancer. Twenty-five studies (including 6 RCTs and 19 NRCTs)

were included for a total of 3,055 patients from both the Eastern and Western hemispheres. Although laparoscopic distal gastrectomies were associated with longer operative times, estimated blood loss was lower, and a decreased length of hospital stay and overall complication rate was demonstrated. There was no difference between groups with respect to in-hospital mortality. Open gastrectomy, however, showed a significantly higher number of lymph nodes retrieved compared to the laparoscopic approach. However, the proportion of patients with less than the 15 nodes was similar in each group. The potential effect on long-term survival with laparoscopic gastrectomy is still unclear. Additionally, since the majority of studies are predominantly focused on early stage disease, a study bias may be present, and it remains to be seen whether minimally-invasive gastrectomy is an effective approach for more advanced stages, especially as seen in the Western hemisphere.

Gastric cancer patients who have a proximal or bulky tumor are not candidates for a distal/subtotal gastrectomy and should be considered for a total gastrectomy. Laparoscopic total gastrectomy is considered technically more difficult than its distal gastrectomy counterpart and, therefore, less widely practiced. However, increasing experience with minimally invasive techniques and better instrumentation has prompted more utilization for gastric cancer patients. A recent meta-analysis looking at 15 NRCT comparing laparoscopic and open total gastrectomies was published (53). Similar to the data for laparoscopic distal gastrectomies, laparoscopic total gastrectomy was associated with lower estimated blood loss and complication rate, although with a longer operative time. No difference in mortality was noted. In addition, oncologic resections were similar, as there was no significant difference in the number of nodes retrieved between the groups. Unfortunately, no data on long-term survival was available. Minimally-invasive gastrectomy, either laparoscopic or robotic, is currently regarded as an approach that should be offered by experienced surgeons who are familiar with these techniques.

### **Cytoreductive surgery and heated intraperitoneal chemotherapy (HIPEC)**

The presence of peritoneal disease is classified as stage IV disease; however, recent data suggests that these patients should not necessarily be precluded from surgical resection. Cytoreduction with the administration of HIPEC has long

been advocated for treatment of peritoneal malignancies related to appendiceal cancer, mesothelioma, and more recently, colon adenocarcinoma and gastric adenocarcinoma. Yang *et al.* published results of a randomized phase III trial in which 68 patients with peritoneal carcinomatosis were randomized to either cytoreductive surgery or cytoreductive surgery with HIPEC using intraperitoneal Cisplatin and Mitomycin C. The rate of adverse events was noted to be similar between groups, and the cytoreductive surgery plus HIPEC patients had an improved overall survival, median of 11 months versus 6.5 with cytoreductive surgery alone ( $P=0.046$ ) (54). The University of Pittsburgh evaluated 23 patients with gastric peritoneal carcinomatosis who underwent cytoreductive surgery with HIPEC using Mitomycin C and observed major morbidity in over 50% of the cohort and a median overall survival of 9.5 months, concluding that cytoreductive surgery with HIPEC may offer survival benefit in a carefully selected population (55).

More aggressive chemotherapy regimens have been recently advocated, with the institution of bidirectional chemotherapy: systemic chemotherapy in addition to the intraperitoneal chemotherapy. Yonemura recently published results from a specialized peritoneal malignancy center in Japan, evaluating 194 patients treated with bidirectional therapy: intraperitoneal docetaxel and cisplatin and oral S-1 for four cycles. Patients who responded to this therapy were then taken for cytoreductive surgery and HIPEC with docetaxel (56). Major complications were observed in 23.6% and an improved median survival of 15.8 months was noted. A meta-analysis of 20 randomized controlled trials using various intraperitoneal agents also demonstrated that HIPEC conferred a 2-year survival advantage (57).

More recently, Rudloff *et al.* randomized 17 metastatic gastric cancer (including those with liver and lung disease) patients to cytoreductive surgery with HIPEC and systemic chemotherapy (FOLFOXIRI: 5-FU, leucovorin, oxaliplatin, and irinotecan) *vs.* systemic chemotherapy alone (58). The median overall survival for the HIPEC group was 11.3 months compared to 4.3 months in the systemic chemotherapy only arm. However, definitive conclusions on the superiority of HIPEC with systemic chemotherapy should be deferred since this study was limited by small numbers of patients.

While cytoreductive surgery and HIPEC is not commonly considered for patients with gastric carcinomatosis, patients with a low peritoneal carcinoma index may have an improved survival with this treatment modality. While most surgeons advocate initial treatment



with systemic therapy, patients with stable disease, low-volume peritoneal disease and good functional status may be considered for this treatment modality. Caution for enthusiasm regarding cytoreductive surgery and HIPEC must be exercised until future research can further clarify the optimal treatment and timing for this diverse population of metastatic gastric cancer patients. The survival of patients receiving systemic therapy only reported in these trials falls short of survival of metastatic patients previously reported in other, larger studies. Therefore, HIPEC should be performed on protocol at institutions that routinely perform HIPEC, in select patients who have demonstrated stability of disease and survival on standard chemotherapies.

### Outcomes

Although both the East and West utilize the American Joint Committee on Cancer (AJCC) staging system for determination of prognosis, relative survival differs markedly even when matched by stage. For example, when comparing Korean and U.S. high-volume centers, disease specific survival after R0 resection was greater in Korea, with a 5-year gastric-cancer-related probability of death of 17% versus 32% in the U.S (59). Interestingly, a subset analysis of a T1N0 cohort at the same institutions demonstrated no difference in rates of death due to gastric cancer (60). A meta-analysis addressing this question, comparing published disease specific survival rates in randomized control trials, demonstrated improved relative 5-year survival in the East with an adjusted odds ratio of 3.22 (95% confidence interval: 1.85-5.58) (61). These results were demonstrated even after adjusting for patient age, chemotherapy, gender, and tumor size, factors historically attributed as reasons for differences in survival outcomes between East and West.

Other than the differences in surgical treatment as discussed above, there are also important differences between East and West in perioperative therapy to consider. Lesions T2 or greater, or with evidence of lymph node disease, are typically treated first with systemic therapy in the West, unlike in the East where surgical resection is typically performed, even for advanced gastric cancer (23,62). Theoretical advantages for pre-operative therapy include: demonstration of an *in vivo* response to therapy, treatment of occult micrometastatic disease, better health of patients who may subsequently receive the full chemotherapy regimen, and increased likelihood of margin-

negative surgical resection of tumor.

The British medical research council adjuvant gastric cancer infusional chemotherapy (MAGIC) trial introduced neoadjuvant chemotherapy as standard of care in the West. The trial demonstrated that patients with operable gastric, esophageal, and gastroesophageal cancer had improved survival when treated with preoperative and postoperative chemotherapy, 23% with surgery-alone versus 36% with surgery and chemotherapy (63). In addition, the authors illustrated a higher curative resection rate (79% vs. 70%, P=0.03) for patients who underwent neoadjuvant therapy. This increase in curative resection rate (R0 resection) for neoadjuvant therapy is mirrored in other studies as well (64,65). While this approach reflects the treatment philosophy in the West, in the East the results were criticized because of the inclusion of esophageal cancers and the limited extent of lymphadenectomy in surgical treatment. It should be noted, however, that phase II and phase III trials of preoperative S-1 and cisplatin in Japanese series, including the extended lymphadenectomy, demonstrated improved survival compared to historical controls (66,67). For patients with bulky nodal or para-aortic nodal disease, improved overall survival was also observed when randomized to neoadjuvant S-1 and cisplatin followed by surgery with an extended lymphadenectomy, but further trials are under way (67,68).

### Conclusions

Although etiologic and pathologic differences exist in the presentation of gastric cancer treated in the West versus the East, surgical techniques developed in countries of high-incidence have become more universal. It is widely accepted that gastrectomy with a modified D2 lymphadenectomy (sparing the distal pancreas and spleen) confers adequate staging information, with the goal of obtaining a minimum of 15 lymph nodes. As minimally-invasive techniques continue to be developed, oncologic safety and equivalence to the standard open gastrectomy remains to be seen. With better efficacy of systemic chemotherapy, more aggressive approaches to surgical resection, including cytoreduction and HIPEC, can also be considered in selected patients. These techniques appear to be applicable to patients in both the Eastern and Western hemispheres.

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## Footnote

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# Ongoing clinical studies of minimally invasive surgery for gastric cancer in Japan

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**Abstract:** Since the development of laparoscopy-assisted distal gastrectomy (LADG) with lymph node dissection for gastric cancer in Japan, this type of surgery is improving and evolving. To establish high-quality evidence of laparoscopic gastrectomy (LAG) in the field of gastric cancer treatments, two large-scale, prospective randomized controlled trials have been performed in Japan; the Japan Clinical Oncology Study Group (JCOG) 0912 for early disease and the Japanese Laparoscopic Surgery Study Group (JLSSG) 0901 for advanced disease. Analyses using mega-data from the National Clinical Database (NCD) have also been carried out as a clinical study to clarify the safety of LAG. Furthermore, as advanced laparoscopic techniques have been developed, prospective clinical studies are being performed with regard to laparoscopy-assisted total gastrectomy (LATG), robotic gastrectomy, and minimally invasive surgery with sentinel node (SN) navigation. This review summarizes the current status of minimally invasive surgeries for gastric cancer based on the latest ongoing clinical trials in Japan.

**Keywords:** Laparoscopic gastrectomy (LAG); randomized clinical trials (RCTs); advanced gastric cancer (AGC)

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## Introduction

Since laparoscopy-assisted distal gastrectomy (LADG) with lymph node dissection for early gastric cancer (EGC) was developed in 1991 in Japan, the number of patients treated using LAG has gradually increased (1,2). In January 2011, the National Clinical Database (NCD) in Japan started to prospectively collect data on surgical procedures. According to the NCD data base, the ratio of LADG and laparoscopy-assisted total gastrectomy (LATG) has reached 45% and 20% of total number of the cases undergone gastrectomy for gastric cancer, respectively.

Initially, major efforts were made to improve the technical safety and improve the standardization of laparoscopic gastrectomy (LAG) (3-7). For the purpose of

improving the laparoscopic technique, the Japan Society for Endoscopic Surgery (JSES) established the Committee for the Endoscopic Surgical Skill Qualification System in 2001 (8,9). With regard to the clinical relevance of this examination, Mori *et al.* demonstrated that surgical complications were significantly fewer in those who passed the examination compared with those who failed (8). Thus, this assessment system may contribute to the standardization of laparoscopic techniques and enhance surgical skills in the field of LAG.

Although advances in techniques and improvement of instruments have led to the standardization of LAG with lymph node dissection among experienced surgeons, surgeons should evaluate as to whether the laparoscopic approach to gastric cancer is adequate and beneficial for

cancer treatment. Therefore, large-scale, prospective studies are needed to answer several clinical questions.

Here we review ongoing clinical studies of LAG for gastric cancer in Japan, and introduce the current status of the latest studies.

#### **Current indication of LAG for gastric cancer according to the Japanese gastric cancer guidelines (version 4)**

Since the Japanese gastric cancer treatment guidelines were established in 2001, LAG has been indicated as an investigational treatment even though the number of LAG rapidly increased in Japan (10). Small-scale randomized controlled trials, a non-randomized study and retrospective studies have demonstrated that LAG has superior short-term and comparable long-term outcomes to open gastrectomy (11-17). As a result, the guidelines were revised based on the latest evidence and trends of cancer treatments in 2014. According to the recent guidelines (version 4), LAG is recommended as an optional treatment for cStage IA gastric cancer not indicated for endoscopic treatment and cStage IB gastric cancer.

However, there are several limitations in this statement. First, the only study with a high level of evidence is a single, small-scale, randomized clinical trial (RCT). Recently, a Japanese phase II clinical trial performed by the Japan Clinical Oncology Study Group (JCOG0703) in patients with cStage IB (including SS, N0) gastric cancer demonstrated that LADG can be performed safely with a minimal risk of anastomotic insufficiency or pancreatic fistula, although most of the patients had cStage IA cancer (18). The technical feasibility of LADG could be statistically proven; on the other hand, data on long-term outcome are not available yet. Second, it should be noted that in the Japanese trial, LADG was performed by surgeons with a high level of relevant experience. Therefore, the indication should be considered in each institution by taking into account not only surgeon' skills but also surgical team organization. Third, the technical safety of LATG is still controversial, particularly in terms of anastomotic complications. Although LAG including distal gastrectomy (DG) and total gastrectomy is covered by Japanese health insurance, LAG currently means LADG in most cases.

Thus, the statements on LAG in the latest guidelines mainly pertain to LADG. Taking the above limitations into consideration, the statements in these guidelines are applicable to practice.

#### **Ongoing clinical studies of LAG for gastric cancer in Japan**

To provide answers to the clinical questions, prospective clinical studies are ongoing in Japan. These contain multicenter prospective randomized trials and a large-scaled prospective cohort study.

##### *Current studies of LADG for EGC*

Since LADG for EGC was introduced in 1991, the technical and oncological feasibility of LAG has been evaluated worldwide. However, most of these studies were limited by having a small sample size, and a short-term follow-up period.

Therefore, a retrospective, multicenter study was performed by the Japanese Laparoscopic Surgery Study Group (JLSSG) to evaluate preliminary short- and long-term outcomes of LAG for EGC (19). A total of 1,294 patients (872 men, 422 women) undergoing laparoscopic surgery were enrolled in this study from 1994 to 2003. The overall morbidity and mortality rates associated with these operations were 14.8% and 0%, respectively. This study showed that the 5-year disease-free survival rate was 99.8% for stage IA disease, 98.7% for stage IB disease, and 85.7% for stage II disease. Although these data may be considered preliminary, they appear to indicate that LAG for EGC yields good short- and long-term oncologic outcomes. In addition, morbidity and mortality rates following LADG are identical to or less than those observed following open distal gastrectomy (ODG) as per the published small randomized clinical trials (RCTs) (14-17).

With regard to prospective studies in Japan, a phase III study (JCOG0912) was performed to confirm the non-inferiority of relapse-free survival of LADG to ODG in patients with the same inclusion criteria used in the phase II study (JCOG0703) (20). Regarding short-term outcome, there were no significant differences between two groups in terms of intra-operative adverse events (G3-4) and in-hospital, non-hematological adverse events (G3-4) (21). The authors concluded that LADG performed by the credentialed surgeons was safe as ODG for cStage I cancer. A large-scale, multicenter randomized trial (KLASS01) regarding the safety of LADG for cStage I cancer from Korea has mentioned that this procedure confers the benefit of a lower occurrence of wound complications compared with conventional ODG (22). Therefore, LADG is safe in terms of short-term outcomes, at least for patients with

cStage I cancer. Regarding the non-inferiority of LADG in terms of long-term outcome, the result should be anticipated from each country.

To establish a risk model for DG in Japanese patients with gastric cancer, the NCD was constructed for risk determination in gastric cancer-related gastrectomy using data from 33,917 cases (1,737 hospitals) (23). As a result, the 30-day, in-hospital, and operative mortality rates were 0.52%, 1.16%, and 1.2%, respectively. The morbidity rate was 18.3%. This study demonstrated that this risk model developed using nationwide Japanese data on DG including both laparoscopic and open approaches for gastric cancer can predict surgical outcomes. Regarding LAG, JSES and JLSSG have performed a nationwide prospective survey to verify the feasibility and safety of LAG (NaSLAG) in 2014. The estimated enrollment number was approximately 8,300, and patient enrollment was finished in September 2015. The short-term surgical outcomes of LAG compared with OG are being evaluated using a propensity score-matched analysis. These results based on mega-data from Japan will be expected to cover the fields of exclusive criteria in our prospective RCT for LAG, such as age (elderly patients), and high BMI.

#### ***Current studies of LADG for advanced gastric cancer (AGC)***

The extent of lymph node dissection in AGC remains controversial. In Asian countries, D2 lymph node dissection is routinely carried out in AGC, the main advantages of D2 lymph node dissection being considered to include prolonged survival and improved staging accuracy (24,25). Techniques for D2 lymph node dissection were recently developed for laparoscopic surgery and used in several Asian institutions (5,26,27). Recent retrospective studies and meta-analysis comparing laparoscopic D2 gastrectomy and open D2 gastrectomy for AGC demonstrated that the laparoscopic procedure may be feasible (11-13,17). However, several questions remained to be answered because the evidence from large-scaled, prospective study is yet to be established. Therefore, a randomized, controlled phase II trial was performed in Japan to confirm the feasibility of LADG in terms of technical safety, and short-term surgical outcomes (registered number, UMIN 000003420, [www.umin.ac.jp/ctr/](http://www.umin.ac.jp/ctr/)) (28). In this study, the eligibility criteria included pre-operatively diagnosed AGC that could be treated using DG with D2 lymph node dissection; MP, SS, SE without the involvement of other organs; N0-2 and M0. Patients aged 20-80 years were pre-

operatively randomized. To proceed to a phase III trial developed to identify the potential non-inferiority of LADG to ODG in terms of short- and long-term outcomes, the safety of LADG with D2 lymph node dissection should be established through a preliminary step, which determines the occurrence of anastomotic leakage and pancreatic fistula as primary endpoints in a phase II trial. For quality control in this study, surgeons operating on patients in the laparoscopic arm had to be certified by the Endoscopic Surgical Skill Qualification System. This accreditation system for gastrointestinal surgery was established in 2004, and the surgical skill assessment system has contributed to the standardization of the laparoscopic technique and has enhanced the surgical skills of laparoscopic surgeons in Japan (8,9). In addition, a central review of the surgical procedure was carried out on the basis of photographs taken after lymph node dissection for all patients and video footage for arbitrarily selected patients (29). This review system may enable surgical standardization in terms of D2 lymph node dissection.

As a result, among the 91 patients in the laparoscopic arm, 86 underwent LADG according to study protocol. Regarding the primary endpoint of the phase II trial, the proportion of patients with either anastomotic leakage or pancreatic fistula was 4.7% (4/86). The morbidity rate of grade 3 or higher, including systemic and local complications, was 5.8%. Conversion to open surgery was required for one patient (1.2%), in the absence of any intra-operative complications. The post-operative mortality rate was 0 and no patient required readmission for surgical complications within 6 months following initial discharge. Hence, the technical safety of LADG with D2 lymph node dissection for locally AGC was demonstrated. A phase III trial to confirm the non-inferiority of this procedure to open gastrectomy in terms of long-term outcomes is ongoing. In East Asia, large-scale, multicenter RCTs are currently ongoing not only in Japan, but also in Korea (KLASS 02: NCT01456598) and China (CLASS 01: NCT01609309). Regarding to short-term outcome from the Chinese trials including CLASS01 study, favorable outcome in LADG as well as ODG for AGC has been demonstrated (30,31). These data in combination will be beneficial for determining the role of LAG.

#### ***Current studies of LATG for gastric cancer***

LATG for upper gastric cancer is performed at a limited number of hospitals in Japan because of its technical

difficulty, particularly for esophagojejunostomy, and concerns regarding subsequent complications. According to the 12<sup>th</sup> JSES survey in 2014, the incidence of intraoperative and postoperative complications in LADG was 1.1% and 7.5%, respectively. On the other hand, the incidence of intraoperative and postoperative complications in LATG was 1.9% and 20.1%, respectively. With regard to the laparoscopic procedure in LATG, Uyama *et al.* first reported in Japan on Roux-en-Y anastomosis using a laparoscopic linear stapler in 1999 (32), and Tanimura *et al.* reported a good outcome for intracorporeal anastomosis using a conventional circular stapling device (33). Kunisaki *et al.* also reported that LATG using the Or-Vil<sup>TM</sup> system (Covidien, Mansfield, MA, USA) was a technically feasible procedure (34). However, no RCT data on LATG are available in Japan, because the standardization of techniques for esophagojejunal anastomosis has proved difficult even for experienced surgeons.

Recently, a multicenter, non-randomized confirmatory study of LATG with lymph nodal dissection for clinical stage I gastric cancer (JCOG1401) was carried out in terms of technical safety-, and short-term surgical outcomes (registered number, UMIN 000017155). The primary endpoint of the study was the proportion of anastomotic leakage because anastomosis-associated complications are great concern in LATG.

In Korea, a feasibility study of LATG in EGC (KLASS03) was performed, and patient enrollment has already finished (NCT01584336). The primary endpoint of the KLASS03 study was to evaluate the incidence of postoperative morbidity and mortality. These studies will lead to the confirmation of the technical safety of LATG for EGC. On the other hand, several issues related to the technical and oncological feasibility still exist regarding LATG for AGC. Recently, Nakauchi *et al.* demonstrated that totally laparoscopic total gastrectomy for AGC performed by expert surgeons is sufficiently feasible and safe, although combined resection of the spleen or distal pancreas for R0 resection was included in their retrospective, single institute study (35). For standardization of these procedures, it will be needed to expand the indication of LATG step by step at this moment.

#### ***Current studies of robotic gastrectomy for gastric cancer***

Robotic surgery in cholecystectomy was first performed in 1997 by Cadière *et al.* (36). Since then, this system has been broadly applied in various fields including not only gastrointestinal surgery but also urological surgery

and other surgical specialties (37). Recently, the clinical relevance of robot-assisted gastrectomy for gastric cancer was reported. The small series of cases have demonstrated that robot-assisted gastrectomy for the treatment of gastric cancer is a feasible and safe procedure in the hands of experienced laparoscopic surgeons (38-41). In contrast, Yoon *et al.* demonstrated that robotic gastrectomy offered no apparent benefit, in terms of surgical and oncological outcomes, given its present technological status (42). A recent meta-analysis of robotic gastrectomy used in 1,875 patients demonstrated that it was similar to that of LAG in terms of short-term outcomes and number of harvested lymph nodes, and it had a longer operative time and lower estimated blood loss (43).

In Japan, Uyama *et al.* demonstrated that this approach using a robotic system can facilitate D2 nodal dissection, particularly in suprapancreatic lymph node dissection (44). Suda *et al.* also showed the short-term outcomes of robotic gastrectomy in a single institutional retrospective cohort study (41). In the robotic surgery group, morbidity and duration of hospitalization following surgery were significantly improved, although the operative time and estimated blood loss were slightly greater. As the number of robotic systems is rapidly increasing in Japan, robotic surgery has spread into many institutions. However, several issues remain to be solved regarding clinical indication, short- and long-term outcomes, cost-effectiveness, and stress of surgeons. Recently, a multi-institutional historically controlled prospective cohort study was conducted to clarify the feasibility, safety, effectiveness, and economical efficacy of robotic gastrectomy for resectable gastric cancer (registered number, UMIN000015388). The primary endpoint of this study includes postoperative complications greater than grade 3 according to the Clavian-Dindo classification. Inclusion criteria with regards to indication are cStage I or II gastric cancer, curably treated by total, distal or proximal gastrectomy with D1+ or D2 lymph node dissection. The estimated enrollment number is 330, and this study is ongoing. The results from the Japanese study are expected to inform decisions on the future direction of robotic gastrectomy for gastric cancer.

#### ***Current studies of minimally invasive surgery for gastric cancer based on sentinel node (SN) navigation***

The SN concept has been focusing on gastric cancer surgery, and many studies, mainly from Japan, have demonstrated the results of SN biopsy for EGC (45,46). A multicenter,

single-arm, phase II study of SN mapping for gastric cancer showed a SN detection rate of 97.5% (387/397), and the accuracy of nodal evaluation for metastasis was 99% (383/387) (47). Only four false-negative SN biopsies were observed. Next, a study of SN navigation surgery for EGC was launched to assess the availability and safety of individualized gastrectomy based on the SN concept for the EGC (registered number, UMIN000014401). The primary endpoint of this study is postoperative 5-year recurrence free survival (RFS) ratio. In this study, strategy of treatment based on SN mapping relied on the division of patient into three groups. Among these, the minimized gastrectomy and sentinel basin resection group included patients whose SNs were negative by intraoperative pathological diagnosis and spread within the confines of the resection range of minimized surgery involved laparoscopic local resection or gastrectomy. Although several issues remain to be resolved for the validation of the SN concept, the combination of less invasive laparoscopic surgery and SN navigation appears contribute to the improvement of long-term quality of life after gastric surgery.

### Future perspective

Since the first LADG for gastric cancer was introduced in Japan, many surgeons have made efforts to improve the technical and oncological safety of LAG. With a view to standardizing LAG, multicenter clinical studies have also been launched to establish high-quality evidence not only in Japan but also in Korea and China. The fruitful data from these studies are expected to decide future directions for the use of LAG for gastric cancer. International cooperation and sharing of information on current issues regarding LAG for gastric cancer will be required.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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# Ongoing surgical clinical trials on minimally invasive surgery for gastric cancer: Korea

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**Abstract:** Since Korean Laparoscopic Gastrointestinal Surgery Study (KLASS) group was activated in 2003, several randomized controlled trials (RCTs) have finished or are ongoing in Korea to evaluate oncologic safety and feasibility of minimally invasive surgery (MIS) for gastric cancer by KLASS group as well as other expert surgeons. MIS in gastric cancer is regarded as one of standard treatment modality for early gastric cancer (EGC) and the indication is going expansion with the accumulation of evidence. This review covers current status of ongoing clinical trials on MIS for gastric cancer in Korea.

**Keywords:** Gastric cancer; minimally invasive surgery (MIS); clinical trial

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## Introduction

Despite the rapid progress in the molecular understanding of gastric cancer and the development of targeted therapies to treat it, currently surgical resection is the only effective treatment option to improve the survival (1-3). Since the first successful gastrectomy for gastric cancer by Theodor Billroth in 1881, the surgical skill has been steadily revising and improving. Remarkable change during recent decades would be the adoption of minimally invasive surgery (MIS) for gastric cancer. Due to the recent improvements in early diagnosis (4), the incidence of early gastric cancer (EGC) in Korea has been increasing and MIS has been rapidly adopted to many Korean gastric cancer surgeons. Moreover, the efforts to build the evidence on feasibility of MIS are being continued. As experience in the use of laparoscopy has accumulated, the inclusion criteria for studies on MIS have been extended to patients with advanced gastric cancer (AGC). Moreover, interests in advanced techniques, such as laparoscopic total gastrectomy (LTG) or extended lymph node dissection has steadily broadened the scope of the studies on MIS. In addition, the effort to find a more suitable surgical treatment option in EGC, such as sentinel node navigation surgery (SNNS) or function

preserving surgery is also continued. The aim of this article is to overview the current status of ongoing clinical trials regarding MIS for gastric cancer in Korea (*Table 1*).

## Laparoscopic gastrectomy for EGC

In Korea, the Korean Laparoscopic Gastrointestinal Surgery Study (KLASS)-01 trials—the first multicenter, large-scale, prospective, randomized controlled trial (RCT) comparing laparoscopic distal gastrectomy (LDG) with open distal gastrectomy (ODG) for EGC—was started in 2006 (NCT00452751). Although several RCTs had been conducted to address the oncologic safety of laparoscopic gastrectomy before commencing KLASS-01, the sample sizes of those studies were not large enough to conclusively demonstrate safety and equivalency compared with open procedures (5-8). The primary end point of the KLASS-01 was 5-year overall survival. The secondary endpoints were disease free survival, morbidity and mortality, quality of life, inflammatory, immune response, and cost-effectiveness. The Enrollment was finished at August 2010; 1,416 patients from 12 centers participated in this study. Recently, the result on morbidity and mortality was reported (9). The overall complication rate was significantly lower in the

Study	KLASS 01	KLASS 02	KLASS 03	KLASS 04	KLASS 05	Robot	SENIORITA
Current status	Enrollment: finished	Enrollment: finished	Enrollment: finished	Recruiting patients	Recruiting participant	Results are reported, data collection for subsequent study	Recruiting patients
Phase	III	III	II	III	III	II (observational matched cohort)	III
Intervention	LDG vs. ODG	LDG vs. ODG	LTG	LAPPG vs. LDG	LPG vs. LTG	RG vs. LG	LSNNS vs. LG
Inclusion criteria	Clinical stage I	cT2-T4a	cT1N0	cT1N0	cT1N0, upper 1/3 location	cT1-T3	cT1N0
Sample size	1,416	1,050	168	256	-	400 (finally 434 were enrolled)	580
Primary endpoint	5-year overall survival	3-year relapse-free survival	Morbidity and mortality	Incidence of Dumping syndrome	-	Morbidity and mortality	3-year disease-free survival
Secondary endpoint	Disease free survival, morbidity and mortality, quality of life, inflammatory and immune response, and cost-effectiveness	3-year overall survival, morbidity and mortality, and postoperative recovery index, and quality of life	The surgical outcomes according to several methods of reconstruction and the postoperative course	3-year relapse-free survival and overall survival, morbidity and mortality, body weight change, fat volume change on abdominal CT scan, change of protein and albumin, quality of life, incidence of gallstone, and gross and microscopic changes measured by gastroscopy	-	Operative time, blood loss, rate of open conversion, recovery of bowel function, length of hospital stay, and financial costs	Morbidity and quality of life
Year started	February 2006	October 2011	October 2012	July 2015	-	May 2011	March 2013
Year of completion (estimated)	August 2015	May 2018	November 2013	June 2023	-	December 2012	December 2022
KLASS, Korean Laparoscopic Gastrointestinal Surgery Study; SENIORITA, Sentinel Node Oriented Tailored Approach; LDG, laparoscopic distal gastrectomy; ODG, open distal gastrectomy; LTG, laparoscopic total gastrectomy; LAPPG, laparoscopy-assisted pylorus preserving gastrectomy; LPG, laparoscopic proximal gastrectomy; RG, robot gastrectomy; LG, laparoscopic gastrectomy; LSNNS, laparoscopic sentinel node navigation surgery.							

LDG group (13.0%) than in ODG group (19.9%) although there was no difference in interim analysis (10). The difference was mainly due to wound complication (LDG *vs.* ODG; 3.1% *vs.* 7.7%,  $P=0.001$ ). The result confirms the minimally invasiveness of laparoscopic surgery. The final results on oncologic safety are expected to be reported soon.

In spite of rapid progress on surgical skill and instruments, LTG in gastric cancer patients is not widely accepted due to the absence of established optimal methods for anastomosis and the technical difficulty of performing complete D2 lymphadenectomy. To investigate the feasibility of LTG in clinical stage I gastric cancer located in upper 1/3, the KLASS group launched the prospective, multicenter phase II trial (KLASS-03) in 2012. The purposes of this study are to evaluate the incidence of postoperative morbidity and mortality, and to evaluate the surgical outcomes according to several methods of reconstruction. Also, the postoperative course of the patients underwent LTG was analyzed. The enrollment of 168 patients was finished in November 2013. The result of this study will confirm the safety of LTG and propose the optimal method of anastomosis in LTG (NCT01584336).

### Laparoscopic gastrectomy for AGC

The standard surgical treatment for AGC is open gastrectomy with D2 lymphadenectomy according to Japanese, NCCN, and ESMO guidelines (11-13). D2 lymphadenectomy is associated with lower loco-regional recurrence and gastric cancer-related death rates compared to gastrectomy with D1 lymphadenectomy (14). However, the actual extent of D2 lymphadenectomy varies among surgeons because of a lacking consensus on the anatomical definition of each lymph node station. It was a big obstacle to perform the RCT comparing laparoscopic and open D2 lymphadenectomy for patients with locally AGC. Therefore, standardization of D2 lymphadenectomy and surgical quality control (KLASS-02-QC, NCT01283893) were accomplished prior to KLASS-02-RCT trial (15) to build a consensus on D2 lymphadenectomy and to qualify surgeons. Six unedited videos of LDG and ODG were submitted by surgeons for participation and reviewed by international experts using evaluation criteria for completeness of D2 lymphadenectomy. Finally, the review committee made decisions on whether a surgeon's qualification was sufficient to participate in KLASS-02-RCT (16). The primary endpoint of the KLASS-02 RCT is non-inferiority in the 3-year relapse-free survival rate after LDG and D2

lymphadenectomy for locally AGC compared with open conventional surgery. The secondary end-points are 3-year overall survival, morbidity and mortality, postoperative recovery index, and quality of life (NCT0146598). The estimated sample size of KLASS-02 is 1,050. The enrollment of patients was finished in May 2015 and the final results are expected to be reported in 2018. The KLASS-02 trial is the first phase III trial to evaluate the efficacy of LDG with D2 lymphadenectomy for AGC. Also in China (CLASS 01, NCT01609309) and Japan (JLSSG0901, UMIN000003420), a multicenter phase III trials are ongoing to compare LDG and ODG in patients with locally AGC.

### Laparoscopic function-preserving surgery

The improved survival rates of cancer patients have increased the interest in patients' post-surgical quality of life. The aim of function preserving surgery in gastric cancer patient is to reduce the functional sequelae of radical gastrectomy such as dumping syndrome, reflux gastroesophagitis and weight loss. Function preserving gastric resections include pylorus-preserving gastrectomy (PPG), proximal gastrectomy (PG), and vagus nerve preserving gastrectomy. With the development of minimally invasive approaches, methods to adopt those function preserving procedures to MIS have been tried.

PPG has been known to have functional advantages in terms of nutritional benefit, lower incidence of dumping syndrome, bile reflux, or gallstone formation, as compared with distal gastrectomy (17-21). However, previous comparative studies between PPG and distal gastrectomy were mostly performed retrospectively by conventional open surgery. In addition, PPG may have potential risks against oncologic safety, including fewer dissected lymph nodes compared to distal gastrectomy (22-24). Although recent large-volume retrospective analyses reported that laparoscopic PPG was oncologically safe and was better than LDG in terms of nutritional advantage and a lower incidence of gallstone formation, prospective RCTs, especially comparing laparoscopic PPG and LDG, are rare (25). To evaluate superiority on postoperative quality of life and comparable survival after laparoscopic PPG compared to LDG in patients with middle-third EGC, KLASS-04 trial is recruiting patients since July 2015 (NCT02595086). The primary endpoint is incidence of dumping syndrome, and secondary endpoints are 3-year relapse-free survival and overall survival, morbidity and mortality, body weight

change, fat volume change on abdominal CT scan, change of protein and albumin, quality of life, incidence of gallstone, and gross and microscopic changes measured by gastroscopy. The estimated sample size is 256. This study will contribute to the wide application of laparoscopic PPG.

Performing PG for gastric cancer has been limited because of anastomosis related complications such as anastomosis stricture and reflux esophagitis, which substantially affected postoperative quality of life after the surgery. Although many investigators reported the various types of reconstructions and feasibility of these methods, there was no RCT comparing laparoscopic PG with LTG (26-28). Recently, double tract reconstruction following PG was reported as feasible and useful method with excellent postoperative outcomes in terms of preventing reflux symptoms (4.65%) and anastomotic stenosis (4.65%) by the investigators in Korea (28). The KLASS group is preparing the KLASS-05 trial comparing Laparoscopic PG with double tract reconstruction and LTG. The primary endpoint is hemoglobin change at post-gastrectomy 2 years, and secondary endpoints are prevalence rate of postoperative reflux esophagitis, anastomotic stricture, incidence of morbidity and mortality, quality of life 2-year after operations and 3-year disease free survivals. The estimated sample size is 180. Currently, recruitment of participating surgeons is in progress.

### Sentinel node navigation surgery (SNNS)

SNNS and function preserving surgery share the concept. SNNS, the individualized minimally invasive treatment, may retain the patients' quality of life by preventing various post-gastrectomy syndromes related to unnecessary prophylactic lymph node dissection in patients without lymph node metastasis. However, clinical application of SNNS remains controversial for years because of different study protocol and results between studies (29-34). Main debatable issue for clinical use of SNNS is high false negative rate. However, a recent multicenter trial from Japan showed quite promising results with a low false-negative rate of SN biopsy in early-staged gastric cancer patients (35). In addition, multicenter quality control study (phase II) has been performed recently in Korea prior to phase III trial and tolerable results were observed (0% false negative rate of laparoscopic sentinel node basin dissection) (36). Based on these results, multicenter phase III trial (Sentinel Node Oriented Tailored Approach, SENORITA) to compare the laparoscopic SNNS with laparoscopic gastrectomy for cEGC (cT1N0, less than

3 cm, not indicated to endoscopic submucosal resection) was launched in March 2013 (NCT01804998). The estimated sample size was 580. The primary end-point was 3-year disease-free survival, and the secondary end-points were morbidity and quality of life. Laparoscopic SNNS is expected to assume an important role in gastric cancer treatment through SENORITA trial. However, there are a number of technical problems to be resolved for clinical use of SNNS. These include the accuracy of intraoperative pathological diagnosis, optimal tracer material or method, and the possible applicability of intraoperative endoscopic resection instead of partial gastric resection. Additional studies on SNNS are still required.

### Robotic surgery for gastric cancer

Da Vinci robot systems (Intuitive Surgical, Sunnyvale, California, USA) was applied to gastric cancer in Korea since 2005 and several investigators have reported that short-term postoperative outcomes and oncologic outcomes of robot surgery were comparable to laparoscopic gastrectomy (37-40). In addition, meta-analysis results revealed that use of robotic surgery for gastric cancer significantly decreases intraoperative blood loss. Also, comparable morbidity and mortality to laparoscopic surgery was reported (41). However, longer operation time and higher cost are the limitations of clinical application of robotic surgery in gastric cancer in spite of technical superiority over laparoscopic surgery such as 3-dimensional imaging, surgical instrument with a high degree of angulation and filtration of resting tremor. The current indications for robotic surgery are similar to laparoscopic surgery due to a lack of evidence. Therefore, a prospective, multicenter comparative study was conducted in Korea and the short-term outcome was reported recently (NCT01309256). There were no significant differences in morbidity and mortality rates, estimated blood loss, rates of open conversion, diet build-up, and length of hospital stay, but significantly higher cost and longer operation time in robot group were observed as expected (42). Studies on the long-term surgical outcomes are on progress.

### Conclusions

This article is a brief outline of ongoing clinical trials on MIS in Korea. Well-designed, large-scale clinical studies had been completed or are actively ongoing. The results of the studies are expected to prove that MIS is as safe



and effective as open conventional surgery. As well as accumulation of evidence, the multicenter prospective studies have contributed to the standardization of the surgical technique. This has also accelerated the subsequent clinical trials. Many unresolved issues of MIS are expected to be addressed in future multicenter prospective studies.

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## Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

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# Surrounding break up after *Helicobacter pylori* eradication to prevent metachronous gastric cancer after endoscopic submucosal resection

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**Abstract:** Still debates exist whether *Helicobacter pylori* (*H. pylori*) eradication can impose the chance of gastric cancer prevention since the effects of *H. pylori* eradication on the development of metachronous gastric cancer (MGC) after endoscopic treatment. Supported with other evidences that eradication can prevent gastric cancer as well as rejuvenation of atrophic gastritis and some improvements of dyspeptic symptoms, in February 21, 2013, Japanese government decided to eradicate *H. pylori* in patients with chronic gastritis. This is largely due to sincere hope either to lessen gastric cancer incidence as well as mortality or improve the quality of life of Japanese people. Though *H. pylori* had been defined as class 1 carcinogen by IARC at 1994, several evidences confirmed that *H. pylori* played promoting actions gastric carcinogenesis rather than as initiator. With the findings that field cancerization is one of core pathways of *H. pylori*-associated gastric carcinogenesis, the answer to debates that eradication alone was insufficient to prevent MGC includes either the discovery of biomarkers to eradicate earlier before stepping into irreversible stage of gastric carcinogenesis or adoption of strategy to perform siTRP (short-term intervention to revert premalignant lesion). Therefore, surrounding break up should be considered as siTRP after the successful eradication to prevent *H. pylori*-associated gastric cancers.

**Keywords:** *Helicobacter pylori* (*H. pylori*); metachronous gastric cancer (MGC); surrounding break up; eradication; gastric cancer prevention

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## Effects of *Helicobacter pylori* (*H. pylori*) eradication on the development of MGC after endoscopic resection of early gastric cancer; never ending story should be finished

*H. pylori* infection, gastric inflammation, and subsequent changes in genetic or epigenetic mutations eventually can develop gastric cancer (1). Though the anticipation for preventing gastric cancer through eradication had

been raised, following clinical studies have revealed its limited effects in these purposes. Practically, the number of metachronous gastric cancer (MGC) that emerges after successful endoscopic treatment of early gastric cancer has decreased with successful eradication in some studies, but not in all, leaving the curiosity about the real effects of eradication in preventing MGC development after endoscopic mucosal resection. Recently, in order to make

clear whether *H. pylori* eradication actually suppresses the development of MGC after endoscopic resection, Kawanaka *et al.* (2) studied to clarify either the molecular markers related to carcinogenesis in intestinal metaplasia (IM) by a cross-sectional study or the changes of those markers by an open labeled randomized controlled trial (RCT) of *H. pylori* treatment. In their studies, they found that microsatellite instability and immunohistochemical staining to Das-1 (7E12H12, IgM isotype) antibody showed significantly higher incidences in both the *H. pylori*-positive and -negative patients compared with the control group, but *H. pylori* eradication did not provide significant reversals of any molecular alterations. Stimulated with the result by Uemura *et al.* (3) that *H. pylori* infection significantly led to gastric carcinogenesis in large Cohort study, the meta-analysis by Fuccio *et al.* (4) showed *H. pylori* eradication seems to reduce the risk of gastric cancer, whereas the analysis by Take *et al.* (5) showed the risk of gastric cancer remains even after *H. pylori* eradication. In a similar way, with respect to the effects of *H. pylori* eradication on the prevention of MGC after endoscopic resection, studies conducted by several Japanese and Korean doctors reported that *H. pylori* eradication significantly reduced the risk of the development of new gastric cancer in patients who underwent ESD (6-8), whereas there are retrospective and prospective open-label trial showing that *H. pylori* eradication did not reduce the incidence of MGC in patients who underwent ESR (9-12).

There were several speculations to explain this discrepancy about the necessity of *H. pylori* eradication in patients who underwent ESD and whether patients presenting with chronic atrophic gastritis (CAG) whether eradication can impose the chance of rejuvenation through eradication. One of the answers come from very recent publication by Jung *et al.* (13) that CAG with intestinal metaplasia, open type CAG and moderate to severe degree of intestinal metaplasia was significantly associated with MGC development in case of eradication failure, signifying that *H. pylori* eradication may be essential in preventing metachronous lesions after ESD for precancerous lesions before carcinomatous transformation. According to Sugimoto *et al.* (14), MGCs were found in 23 of 155 patients following ESD, 3.5% per year, among which the cumulative incidence of MGC was significantly high in patients with intestinal metaplasia and neutrophil infiltrations, especially in the corpus, concluding that the presence of intestinal metaplasia before ESD is closely associated with the development of MGC after ESD. The other explanation

is that the gastritis-like lesion emerging after eradication might determine the chance of MGC development. According to report by Moribata *et al.* (15), the emergence of map-like redness after *H. pylori* eradication, even though in the absence of intestinal metaplasia, was useful endoscopic findings in predicting the development of MGC after ESD. Map-like redness on endoscopic findings denotes “gastritis-like appearance” better seen under narrow band imaging of magnifying endoscopy (16). Lastly, the timing of eradication and the age of patients might affect the outcome of MGC development. According to Watari *et al.* (17) and Jang *et al.* (18), since patients with precancerous lesions with molecular alterations that do not reverse after *H. pylori* treatment, represent the lesion passing “point of no return” and may be at high risk condition, by which earlier *H. pylori* eradication should be considered for preventing gastric cancer prior to the appearance of precancerous lesions. Generally, old age more than 60 years old is also independent risk factor MGC (19).

### ***H. pylori* infection eradication alone is not sufficient to prevent cancer; *H. pylori* as promoter for gastric carcinogenesis**

Debate that *H. pylori* might play a causative role in gastric carcinogenesis still exists in spite of IARC's definition of *H. pylori* as a class I carcinogen. In order to define the exact role of *H. pylori* infection in gastric carcinogenesis, our group (20) established a mice model of *H. pylori* infection. As results, the incidence of gastric cancer at the 50<sup>th</sup> week was 80% in mice treated with both methyl N-nitrosourea (MNU) 240 mg/L and *H. pylori* infection, whereas only 27% in mice treated with only MNU 240 mg/L, concluding *H. pylori* infection promoted gastric carcinogenesis rather than direct carcinogens. Similarly, in order to evaluate the difference in susceptibility to stomach carcinogenesis in relation to age of acquisition of *H. pylori* infection, Cao *et al.* (21) designed an experiment involving inoculation of *H. pylori* ATCC43504 followed by MNU treatment at different ages. As results, the earlier acquisition of *H. pylori* significantly increased gastric chemical carcinogenesis with MNU, as compared to the case with later infection. In Mongolian gerbil models, *H. pylori* infection significantly caused gastric carcinogenesis, whereas the eradication resulted in curtailment of enhancing effects. However, in mice or rats, *H. pylori* infection alone never caused gastric tumorigenesis until 20 months later, suggesting *H. pylori* is not an initiator, but might be a strong promoter

for gastric carcinogenesis (22). A high-salt diet has been revealed to synergistically enhance development of stomach cancer with *H. pylori* infection; the latter exerts stronger promoting effects than the former (23). On serial investigation of *H. pylori*-infected models, long-term *H. pylori* infection developed highly proliferative and dilated glands containing a large amount of mucin, called heterotopic proliferative glands, simulating mucinous adenocarcinoma, but not gastric adenocarcinoma, leading to conclusion that *H. pylori* infection thus appears to have a strong promotional influence but not to initiate gastric carcinogenesis (22). Therefore, translating these findings into the debates that *H. pylori* eradication does not warrant the prevention of MGC development in patients receiving ESD, either the discovery of biomarker or consideration of other strategy such as dietary or nutritional intervention to mitigate promoting contribution should be considered.

### **Still there is no biomarker significantly telling “the point of no return” in *H. pylori*-associated carcinogenesis**

Gastric atrophy and intestinal metaplasia are defined as preneoplastic conditions of gastric cancer, whereas *H. pylori*-associated CAG by itself potentiates a risk for gastric cancer development. Though *H. pylori* eradication in some, overall reduction of GC incidence has been shown. However, this effect is not noted in all (24). Therefore, enormous effects had been thrown to discover biomarkers telling “the point of no return” and right person who can be benefited from successful eradication. Furthermore, MGC after ESD still occurs to some degree even after eradication, Watari *et al.* (25) studied to discover biomarkers related to carcinogenesis expressed in intestinal metaplasia through a hospital-based, case-control study of 75 patients, 50 gastric cancer patients who had undergone ESD, and 25 age- and sex-matched chronic gastritis patients for whom *H. pylori* had been successfully eradicated. As results, microsatellite instability and Das-1 reactivity in intestinal metaplasia strongly predicts the development of MGC. Enomoto *et al.* (26) found serum pepsinogen test and DNA methylation in CpG islands significantly reflected the progression of CAG showing a high likelihood of future cancer development, so called epigenetic “field cancerization” (27). Though global DNA hypomethylation is an early molecular event in *H. pylori*-related gastric carcinogenesis (28), aberrant methylation of CpG islands in promoter regions can permanently inactivate tumor-suppressor genes,

as mutations and chromosomal abnormalities do. For instances, cyclin-dependent kinase inhibitor 2A (CDKN2A), cadherin-1 (CDH1), and mutL homolog 1 (MLH1) are inactivated more frequently by aberrant methylation than by mutations in gastric cancer, of which the amount of methylated DNA molecules in the gastric mucosa significantly fluctuated in active *H. pylori* infection (29), showing the presence of an epigenetic field for cancerization in *H. pylori* infection. Taken together of all these facts, in order to prevent MGC after ESD, eradication of *H. pylori* seems to be supplemented with strategies such as surrounding break up. Combination with anti-oxidative or anti-inflammatory agents, dietary or nutritional intervention to cope with field cancerization, and earlier and effective eradication. In our institute, we have extended our efforts under the siTRP (short-term intervention to revert premalignant lesion).

### **siTRP (short-term intervention to revert premalignant lesion) strategy to prevent gastric cancer**

The conclusion that “prevention might be better than treatment in cancer treatment” is reached after 30 years “war on cancer” initiated by National Cancer Act by President Richard Nixon in 1971. Besides of PhytoCeuticals, life-style modification including non-smoking, non-alcohol, weight reduction, and some natural agents, molecular targeted therapeutics achieved high goal of effectiveness under the concept of therapeutic or preventive “synthetic lethality” of which extended application can be included within the scope of chemoprevention (30). In clinic, siTRP strategy has been applied in patients with *H. pylori*-associated CAG, patients after ESD, and persons who are the first relatives of gastric cancer (31). Fortunately, in contrary to cancer chemotherapeutics, natural agents activating molecular mechanisms for cancer prevention, reversion of premalignant tumors, and even ablation of cancer stem cells, are actively developed, armed with mechanisms such as selective induction of apoptosis, suppression of growth factors, suppression of cell proliferation inhibiting angiogenesis, stimulating mesenchymal-epithelial transition, and hardening the tumor microenvironment.

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## Footnote

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# Long journey to prevent metachronous gastric cancer after endoscopic resection

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The “Perspective” by Drs. Cho *et al.* (1) is a very interesting and informative article for the readers. They have summarized the recent issues regarding the effects of *Helicobacter pylori* (*H. pylori*) on the prevention of metachronous gastric cancer (MGC) after endoscopic resection (ER), including our study (2). We thank them for their kind comments and interest in our article.

## Does *H. pylori* eradication actually prevent MGC from the perspective of basic and clinical evidence?

As Cho *et al.* (1) mention in their paper, there has been great debate about whether *H. pylori* eradication actually prevents MGC. Our recent open-label, randomized, controlled trial (RCT) demonstrated that *H. pylori* eradication did not produce significant changes in the molecular alterations related to carcinogenesis in patients once gastric cancer had occurred in the stomach (2). To date, only a few studies investigated the effects of eradication on molecular alterations in the background mucosa with gastric cancer (3,4). Shin *et al.* (4) reported that a decrease in the *MOS* methylation level was not observed among patients with intestinal metaplasia (IM) or those with gastric cancer, and the methylation level in *MOS* was persistently increased in

patients with gastric cancer even after *H. pylori* eradication (mean follow-up duration, 26.0 months). Choi *et al.* (5) postulated that a long-term investigation (over 5 years) could clarify the exact role of *H. pylori* eradication. One of the limitations in our study was that the intervention period of the RCT was short (1 year), and thus it may be necessary to conduct follow-up for a long time. In Japan, it has been only 3 years since the government approved health insurance coverage for the treatment of *H. pylori* in chronic gastritis in 2013. Therefore, future studies of molecular events with a long-term investigation following eradication are expected to resolve this matter in Japan.

Cancer risk is generally higher in patients who underwent ER than in those with chronic gastritis, because the patients who develop gastric cancer enter the state of “field cancerization”. To date, there have been a few meta-analyses regarding the effects of *H. pylori* eradication on MGC after ER (6,7). These studies concluded that *H. pylori* eradication is associated with a reduction of the incidence of gastric cancer. A recent meta-analysis by Chen *et al.* (8) showed that, for patients without IM at baseline diagnosis, *H. pylori* eradication may halt the progression to a precancerous lesion including IM and reduce the risk of gastric cancer, whereas when IM presents, no preventive effect was observed after eradication, neither in the risk



of gastric cancer nor in the progression to a precancerous lesion. This result supports the study by Wong *et al.* (9).

### **H. pylori infection may be a promoter for gastric carcinogenesis**

In the animal model, *H. pylori* infection alone never causes gastric tumorigenesis, and other factors including methyl N-nitrosourea or salt are needed to develop stomach cancer (10). In addition, the lesions that developed in *H. pylori*-infected models are heterotopic proliferative glands, similar to mucinous adenocarcinoma, different from gastric adenocarcinoma. Therefore, the results from animal models highlight that *H. pylori* is not an initiator, but it might be a promoter of gastric carcinogenesis (11). Taken together, it makes sense to us that *H. pylori* eradication alone cannot prevent the development of gastric cancer, including MGC. Additionally, it may be true that the elimination of the bacteria delays the development of gastric cancer if *H. pylori* infection plays a role as a promoter of gastric carcinogenesis. In any case, it will be best to provide eradication for the chronic gastritis patients who did not pass the “point of no return”.

### **Beyond H. pylori eradication for MGC prevention**

The number of molecular alterations related to gastric carcinogenesis may be approximately 20 at most. However, we still cannot identify the indisputable biomarkers heralding the “point of no return” in *H. pylori*-associated carcinogenesis despite the efforts of many investigators worldwide. Thus, additional efforts are needed for a secondary prevention study of MGC for patients whose *H. pylori* has been eradicated. Actually, a combination of anti-oxidative or anti-inflammatory agents, dietary or nutritional intervention activating molecular mechanisms for cancer prevention, reversion of premalignant lesions, and even ablation of cancer stem cells rather than *H. pylori* treatment is needed, as Cho *et al.* state, as short-term interventions to revert premalignant lesions (siTRP) (1).

In conclusion, patients with IM may not benefit from *H. pylori* eradication with respect to the risk of MGC. Additionally, in view of the present situation, in which we cannot identify a definite biomarker for gastric cancer development, it is appropriate that surrounding break-up should be considered, such as siTRP, rather than *H. pylori* treatment to prevent MGC.

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### **Footnote**

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# Management of high-output chylous ascites after D2-lymphadenectomy in patients with gastric cancer: a multi-center study

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**Background:** This study aimed to propose treatment strategies for high-output chylous ascites (CA) developed after gastric cancer surgery.

**Methods:** The data of patients with CA after gastric cancer surgery in three high volume Training and Research Hospitals between 2005 and 2015 were retrospectively evaluated.

**Results:** Nine patients out of 436 gastrectomies were detected with CA. The mean amount of daily fistula output was 939 mL. Treatment consisted of cessation of oral feeding, total parenteral nutrition (TPN), somatostatin analogs administration, clamping and/or removal of the drainage tube, diuretic administration and diet therapy with medium-chain triglycerides (MCTs) alone or in combination. The mean fistula closure time and length of hospital stay were 23 and 24 days respectively. Hemopneumothorax developed during right subclavian vein catheterisation for TPN implementation in one patient. There was no mortality.

**Conclusions:** Combined cessation of oral feeding and TPN are usually used for treatment of CA as first-line treatment. However, TPN is not harmless. Although our data are limited they do allow us to conclude that diet with MCTs may be used for medical treatment of CA as first-line.

**Keywords:** Chylous ascites (CA); gastric cancer; lymphadenectomy (LA)

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## Introduction

The lymphatic system was described by Asellius in 1627 and chylous ascites (CA) was first reported by Morton in 1691 (1,2). It is defined as the leakage of milk-like triglyceride-rich lymphatic fluid from lymphatic system to the peritoneal cavity (3). CA generally occurs as a result of disturbances of cisterna chyli, the thoracic duct, or their major tributaries (4-6). It may be seen after congenital defects of the lymphatic system, oncological abdominal surgery, abdominal aortic and vena cava surgery, nephrectomy,

retroperitoneal lymphadenectomy (LA), blunt abdominal trauma, portacaval and mesocaval shunt procedures, bacterial peritonitis, pelvic irradiation, pelvic surgery, peritoneal dialysis, liver cirrhosis, abdominal tuberculosis, inflammatory disease, spinal surgery, or after a variety of other benign or malignant processes (1-3,7-11). In this study we aimed to put forward treatment strategies for high output CA with life threatening complications developed after D2-lymphadenectomy (D2-LA) performed for gastric cancer.

## Methods

The data of patients with CA after gastric cancer surgery in three high-volume Training and Research Hospitals between 2005 and 2015 were retrospectively evaluated. Gastric cancer surgery was performed by surgeons experienced in gastric cancer surgery and specifically trained in National Cancer Center (NCC) in Tokyo/Japan. Patients were analyzed for age, gender, tumor localization, surgery type, resected and metastatic lymph nodes number, day of lymphatic leakage (LL), daily fistula output, diagnosis of CA, tumor-node-metastasis (TNM) classification, choice of treatment, morbidity, mortality, day of fistula closure and hospital stay duration. Informed consent were provided in all patients.

## Results

Nine out of 436 patients with gastrectomy were identified with CA (2.06%). Five of these were women and four were men. The mean age of patients was 59.5 (range, 31–73) years. Tumor localization was distal in four patients. Proximal and middle tumour locations were found in two patients and one patient had diffuse gastric cancer. Six and three patients underwent total gastrectomy (TG) and subtotal gastrectomy (STG) plus D2-LA respectively. One patient underwent additional patient mediastinal LA while another patient received additional splenectomy (SP) plus distal pancreas resection. Intraoperative lymphatic fluid leakage was seen in one patient and the lymphatic duct was sutured. The mean number of resected lymph node was 33.8 (range, 20–48) and the mean number of metastatic lymph nodes was 8.7 (range, 0–26). There was no lymph node metastasis in two patients. According to the TNM staging, five patients were Stage III (55.6%), two Stage II (22.2%) and two Stage I (22.2%). Only one patient (11.2%) had early gastric cancer. Interestingly this patient had attended the emergency department with only pyloric stenosis findings. Oral feeding was started postoperatively with the mean time of 3.9 (range, 2–5) days. The mean time of noticing postoperative LL was 5.9 days (range, 5–7). Suspicion of CA was based on the macroscopic appearance of the drainage fluid and was confirmed with biochemical tests. Mean daily fistula output was 939 (range, 600–1,500) cc. The treatment regimen either solely or combined included cessation of oral feeding and total parenteral nutrition (TPN), periferial parental nutrition (PPN), or Sandostatin analogs (Somatosan, CuraMED Pharma GmbH, Karlsruhe,

Germany) administration, removal of the drainage tube, diuretic administration, clamping of drainage tube and diet treatment with medium-chain triglycerides (MCTs) including MCT oil (Ses Handels-Und Service GmbH, Köln, Germany), Basic-f (Numil, Istanbul, Turkey) and Fantomalt (Nutricia, the Netherlands). Meantime to fistula closure was 23 (range, 8–51) days. Mean length of hospital stay was 24 (range, 11–45) days. The detailed features of the patients are seen on *Table 1*. Hemopneumothorax occurred in one patient during right subclavian vein catheterization for TPN implementation and was treated with tube thoracostomy. In addition, grade I Clavien-Dindo surgical complication including wound infection was observed in patient who TPN administration. No mortality was occurred.

## Statistical analysis

Only descriptive analysis was used because of limited of cases.

## Discussion

CA is a rare condition and usually occurs as a complication of abdominal surgery. The incidence is stated as between 0.17–1.10% (12-14) while the level in our study was 2.06%. CA might cause permanent protein loss, nutrition impairment, metabolic complications, prolonged hospital stay, increased costs and life-threatening complications such as sepsis, severe dyspnea and death (6,15).

The lymphatic system is an important route through which protein and liquids pass from the intestinal lumen to vascular system. Another interesting point is, it also plays an important role in the absorption of fat and fat soluble vitamins (1,16). Under normal circumstances lymphatic fluid and interstitial fluid share the same concentration and osmotic pressure (16). Lymphatic fluid flows from the lymph nodes to prenodal collecting lymphatic vessels and then through postnodal lymphatic vessels respectively into lymphatic trunci, cisterna chyli and ends up in ductus thoracicus. This one way flow happens by means of smooth muscles and valves present in the collecting lymphatics (3).

CA might occur for a number of reasons. Crumley *et al.* (17) stated two criteria for postoperative CA in their study; one of them is the impairment of lymphatic circulation and resection during operation. The second is the increased pressure in lymphatics compared to the abdominal cavity and tissue pressure. Malignant invasion

**Table 1** Patient and treatment characteristics

Characteristic	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Mean values
Age	72	73	48	73	62	73	49	31	55	59.5 (31.0–73.0)
Gender	E	K	K	E	K	K	K	E	E	E/K: 4/5
BMI	24	16	18	23	27	24	26	23	25	22.6 (16.0–27.0)
Albumin	Normal	Low	Normal	Normal	Low	Normal	Normal	Normal	Normal	–
Hgb	Normal	Normal	Normal	Normal	Low	Normal	Normal	Low	Normal	–
CRP	Normal	Normal	Normal	Normal	High	Normal	Normal	Normal	Normal	–
Localization	1/3 upper	1/3 distal	1/3 distal	1/3 middle	1/3 upper	Linitis plastica	1/3 distal	1/3 distal	1/3 middle	–
Surgery type	TG + D2-LA + M-LA	STG + D2-LA	STG + D2-LA	TG + D2-LA + SP + DP	TG + D2-LA	TG + D2-LA	STG + D2-LA	TG + D2-LA	TG + D2-LA	–
Peroperatuar LL	No	No	Yes	No	No	No	No	No	No	–
Resected lymph node No.	40	24	30	31	42	27	20	42	48	33.8 (20.0–48.0)
Metastatic lymph node No.	2	0	0	9	2	9	9	21	26	8.7 (0–26.0)
Vascular invasion	No	No	No	Yes	No	Yes	No	Yes	Yes	–
Lymphatic invasion	No	No	No	Yes	No	Yes	No	Yes	Yes	–
Neural invasion	No	No	No	Yes	Yes	Yes	No	Yes	No	–
T stage	T3	T1b	T2	T4a	T3	T4b	T3	T4a	T4a	–
N stage	N1	N0	N0	N3	N1	N3	N3	N3	N3	–
TNM stage	IIB	IA	IB	IIIC	IIB	IIIC	IIIB	IIIC	IIIC	–
Start days of oral feeding	5	4	4	2	4	5	5	3	3	3.9 (2.0–5.0)
Start time of LL (day)	7	6	5	7	5	6	7	5	5	5.9 (5.0–7.0)
Flow of LL (cc/day)	600	1,000	1,500	1,000	900	800	700	750	1,200	939 [600–1,500]
Cessation time of oral feeding (day)	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	–
TPN	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	–
PPN	No	No	Yes	No	No	Yes	No	No	No	–
Sandostatin administration	No	No	Yes	No	Yes	No	No	No	Yes	–
Removal of drainage tube	Yes	Yes	Yes	No	No	No	No	No	No	–
Removal of drainage tube + diuretic administration	Yes	No	Yes	No	No	No	No	No	Yes	–
Clamping of drainage tube + diuretic administration	No	No	Yes	No	No	No	No	No	Yes	–
Diet with MCTs	No	No	Yes	No	Yes	No	No	No	Yes	–
Fistula closure duration (day)	15	9	51	20	22	22	15	8	45	23 [8–51]
Hospital stay duration (day)	15	11	40	20	22	30	20	11	45	24 [11–45]

BMI, body mass index; TG, total gastrectomy; LA, lymphadenectomy; D2-LA, D2-lymphadenectomy; M-LA, mediastinal lymphadenectomy; STG, subtotal gastrectomy; SP, splenectomy; DP, distal pancreatectomy; LL, lymphatic leakage; TNM, tumor-node-metastasis; TPN, total parental nutrition; PPN, periferial parental nutrition; MCTs, medium-chain triglycerides.

can causes deterioration and fibrosis of lymphatic system and consequently due to the obstruction occurred in distal segments, lymphatic fluid may extravasate and CA may occur (12).

Clinical presentation of CA includes nonspecific findings such as abdominal distension, indigestion, nausea and vomiting (18,19). An important clinical observation is milky-like fluid in the drainage tube or paracentesis (20). In our series, perioperative high-volume LL was observed in one patient and although the lymphatic ducts were primarily ligated, CA still developed in the postoperative period. A diagnosis was made with the postoperative appearance of a milky appearance lymphatic fluid from the drainage tubes in all other patients.

Grianiatsos *et al.* (16) suggested criteria for CA diagnosis which included aspiration and drainage tube fluids should not be hemorrhagic, should not contain high levels of amylase and bilirubin, but should contain high triglyceride and be milky or creamy in appearances. Our diagnosis was based on the suspicion of the presence of milky/creamy drainage fluid and this was confirmed with biochemical tests.

Kuboki *et al.* (21) reported in their study that dissection of para-aortic area, retroperitoneal invasion and early enteral feeding are independent risk factors for CA. In another study, the number of resected lymph nodes and concomitant vascular resection were presented as independent risk factors for postoperative pancreatic surgery (22). All patients in our series underwent D2-LA according to Japanese gastric cancer treatment guidelines (23). The average number of resected lymph nodes was 33.8. With regard to the extent of retroperitoneal dissection and the number of resected lymph nodes, the results correlate with the literature.

Many patients had high T, N and TNM stages in our series. Also 55.5% of the patients were over the age of 60. The presence and absence of lymphatic, vascular and neural invasion were histopathologically similar. There was no important difference in preoperative hemoglobin and albumin values. In terms of body mass index (BMI), two patients were thin. Most patients (6/9) underwent TG.

First-line treatment of CA usually includes cessation of oral feeding plus TPN (24-26). Diuretic administration, solely or combined with other treatments, is another treatment approach (27). Another treatment modality is the implementation of a diet solely with MCTs (with 6-12 carbon). MCTs might decrease lymphatic flow and provide regular nutrition because it is directly transported to intestinal cells (3). Cárdenas *et al.* recommended a diet with

MCTs as the first-line medical care (1). Except for MCTs in one patient, all of the treatment modalities implemented in our study failed. Moreover during TPN implementation the patient encountered life threatening catheterisation complications and was subsequently treated with diet containing MCTs.

Some authors have presented somatostatin or octreotide administration as an effective treatment but the detailed mechanism of this treatment is not yet understood. Somatostatin might reduce LL within 24-72 hours (2,28-32).

In patients where the conservative treatment remains ineffective, surgical intervention is advised (16,25). Sixty seven percent of patients with CA were cured with conservative treatment, while 33% required surgical intervention in the study of Aalami *et al.* (25). Sometimes a major leakage area cannot be observed even during surgical exploration (27).

In our study, cessation of oral feeding, TPN, PPN, sandostatin analogs administration, removal of the drainage tube (drainage tube was removed while fistula flow between 500-1,000 cc per day), clamping the drainage tube (drainage tube was clamped while fistula flow between 1,000-1,500 cc per day), diuretic administration and diet treatment with MCTs were applied solely or in combination with other treatments as treatment. Removal of the drainage tube was successful in one patient. In this patient stopping of LL was attributed to the increased intra-abdominal pressure from accumulating lymphatic fluid due to the removal of drainage tube and subsequent peritoneal absorption. In another patient diuretic administration in addition to the removal of drainage tube was successful. Oral feeding was not stopped in both patients.

In another patient (case No. 3) clamping the drainage tube was applied. However this failed. TPN was planned for this patient but hemopneumothorax occurred during right subclavian vein catheterization. The treatment continued with cessation of oral feeding, PPN, sandostatin analogs and diuretic administration, clamping of the drainage tube followed by the removal of drainage tube. Although CA regressed, it resumed 2 days after oral feeding and the patient was finally successfully treated with a diet including protein, carbohydrate and MCTs.

Three other patients were treated by cessation of oral feeding and TPN, two patients were treated by cessation of oral feeding in addition to TPN and diet with MCTs and the last one patient was cured by cessation of oral feeding, TPN and sandostatin analogs administration. None of the patients required surgical exploration.

This study has some shortcomings. The most important is limited number of cases. However, the studies including high volume CA are limited in the literature. Another; satisfactory statistical analysis couldn't done accordingly limited number of cases.

## Conclusions

All our results suggest that CA is an important complication after D2-LA although it is rarely seen. Surgeons should be aware of abnormalities in lymphatic system and operate carefully and meticulously in order to avoid these complications. Injured lymphatic ducts should be ligated. Usually, first-line treatment of CA usually includes cessation of oral feeding plus TPN. But TPN has own complications and it no harmless. We suggest, diet with MCTs and/or removal of drainage tube might be used as first-line medical treatment for reduce side effects and length of hospital stay because of they are noninvasive and more convenient treatment options for treatment of CA.

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## Footnote

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## Does the lymphadenectomy have no significant impact on gastric cancer patients with negative nodes?

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Recently, Jin *et al.* (1) reported that tumor invasion (T stage), lymphovascular invasion, and signet ring histology were significantly associated with the recurrence of gastric cancer patients with negative nodes after surgery. Although this paper has been published, several profound issues should be discussed for the correct guidance to readers.

Authors adopted the clinicopathological data from seven hospitals to set up the negative-node patient database for further statistical analysis. However, 54 of 317 negative-node patients were identified to experience disease recurrence after surgery. It is really incredible that only 54 cases of negative-node disease were statistically analyzed for about 30 variables in that study, which cannot guarantee the accuracy of results and conclusions in that study.

A total of 86 patients underwent the neoadjuvant therapy, in which those patients should be excluded in the study because of postoperative stage migration. We took notice of 30 cases underwent neoadjuvant therapy presented the recurrence after surgery. Authors should figure out which patients were diagnosed as advanced stage disease with the high risk of lymph node metastases.

Many articles have demonstrated that lymph node metastasis was positively related to the depth of tumor invasion in gastric cancer (2). The median number of nodes examined was 15 for T3 tumors and 18 for T4 tumors, which is much lower than that in Asian. More than half of negative-node patients experienced recurrence presented T3 or T4 tumor invasion, which indicated that the false negative rate of lymph node metastasis in those patients

was underestimated inevitably. In my opinion, it is still controversial that whether the micrometastasis in negative nodes has impact on the survival of patients with gastric cancer.

Authors stated that all included patients had a range of lymph nodes retrieved from 1 to 54, and the median number of examined nodes for 317 negative-node disease patients was 16 (range, 9–22). Notably, the median number of examined nodes for 54 negative-node disease patients presented the recurrence was only 14 (range, 6–22), which is absolutely cannot be deemed as the basic guarantee of node dissection for gastric cancer in the current AJCC/UICC TNM classification (3). How did authors explain the lymphovascular invasion, the most intensive factor related to lymph node metastasis, has the intensive effect on the survival in that study?

Therefore, we think that Jin and colleagues cannot elucidate the elaborately potential factor in relation to the recurrence of gastric cancer. The patients included should be guaranteed with the radical lymphadenectomy (D2 and number of examined nodes more than 15). The patients who underwent neoadjuvant therapy should be excluded, owing to initial advanced stage of disease. Lastly, the quantity of patients experienced recurrence of gastric cancer need to be enlarged for accurately statistical calculation.

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## Footnote

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# Results of the REGATTA trial on surgical therapy of limited metastatic gastric cancer: open issues and future perspectives

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Gastric cancer (GC) is the third leading cause of cancer-related death worldwide (723,000 deaths, 8.8% of cancer associated mortality), with regional, etiological differences and the highest prevalence in Asia (1-3). In Western countries most of the patients are diagnosed in advanced stages (up to 80% stage IV) as the cancer remains often asymptomatic or presents with unspecific symptoms (4). Patients with stage III and IV GC have a poor prognosis with 5-year overall survival (OS) rates of 9.2–19.8% and 4.0%, respectively. Treatment in these stages is mainly in palliative intent (5). However, in Eastern countries active screening programs proved to be beneficial and higher percentages of patients are diagnosed in early stages, when treatment can be curative (6). The current standard therapy for early GC is gastrectomy and DII-lymphadenectomy, whereas locally advanced stages require a multimodality treatment approach including surgery combined with perioperative chemotherapy or chemo-radiotherapy (CRT) (5). The cornerstone of the treatment of advanced/metastatic GC remains chemotherapy; in addition, combinational strategies or monotherapy with targeted therapies against Her2 (ERBB2) or VEGFR2 (KDR) were recently introduced and proved to prolong OS (2,7,8). Furthermore molecular analysis of GC has led to new molecularly based GC classifications based on mutation status, gene copy-number changes, gene expression, and DNA methylation data (9,10). Of note, patient stratification

to targeted agents or combinational therapies based on molecular signatures will become important as new therapies like immunotherapy evolve but only subgroups of patients benefit from these novel treatment approaches. The prevalence of Her2 overexpression is only about 10% to 25% (11,12); thus, in the majority of patients chemotherapy and inhibition of angiogenesis or maybe in the future immunotherapeutic approaches are their only options. Therefore, identification of predictive biomarkers for patients' stratification is of utmost importance and should be the aim of future upcoming trials combining molecular testing and targeted therapy approaches.

Advanced stage GC patients experience often side effects from the local tumor growth. Major complications are bleeding, gastrointestinal obstruction or perforation (5). Therefore, palliative surgical approaches such as gastric resection and other non-resectional procedures for stage IV disease have been controversially discussed over the last years (5,13). Gastric resection or non-resectional approaches (e.g., gastric bypass) improved dramatically over time due to advances in peri- and postoperative management of patients and also improvements in patient selection (14). Another open question is the value of metastatic resection in very limited metastatic disease.

Improvements of oncological therapies and close interdisciplinary collaboration led in the recent years to an extension of surgical indications for metastatic disease in

different entities. Currently, for esophageal and GC there is still an ongoing discussion on broadening of surgical indications. Mönig *et al.* emphasize the need to reevaluate the value of surgical resection in the frame of multimodal therapeutic strategies even though the recent guidelines do not recommend surgery for local metastatic GC (15). Overall, different retrospective trials support the hypothesis that certain subgroups may benefit from surgical treatment of metastatic disease in addition to systemic treatment. Potentially systemic treatment can stratify patients into different prognostic groups according to response to systemic chemotherapy. In addition, the FLOT-3-trial could identify a subgroup of patients with metastatic disease with an intermediate prognosis (between localized and diffuse metastatic disease) that may potentially have a benefit from additional surgery. However the data have to be interpreted carefully as the trial is powered to identify a prognostic model for selecting patients treated with systemic chemotherapy and who may also be candidates for surgical intervention. The bi-modal concept has then to be validated in a future randomized trial identifying the optimal candidates for this interventional strategy (16). Prospective controlled trials have to proof if patients with limited metastatic GC benefit from metastasectomy.

The recent study by Fujitani *et al.* published in *Lancet Oncology* (17) addresses the highly relevant question whether gastrectomy in addition to chemotherapy improves survival for patients with advanced GC with a single non-curable factor. This question was addressed for the first time within a prospective randomized phase III clinical trial. This so-called reductive gastrectomy for advanced tumor in three Asian countries (REGATTA) trial was an open-label trial conducted at 44 sites in Japan, South Korea, and Singapore and included 175 patients aged 20 to 75 years, which were randomized between February 2008 and September 2013 to receive chemotherapy alone (n=86) or gastrectomy followed by chemotherapy (n=89). The single noncurable factor was defined as liver, peritoneal, or para-aortic lymph node metastasis. Chemotherapy consisted of oral S-1 at 80 mg/m<sup>2</sup>/d on days 1 to 21 and cisplatin at 60 mg/m<sup>2</sup> on day 8 of 5-week cycles. Gastrectomy was limited to D1 lymphadenectomy without resection of metastatic lesions. The primary endpoint was OS. Treatment groups were balanced with regard to baseline characteristics except for primary tumor location; middle-third tumors were more common in the chemotherapy group (57% *vs.* 34%), and upper-third tumors were more common in the surgery-plus-chemotherapy

group (34% *vs.* 19%). Peritoneal metastasis was the most common non-curable factor in 75% of all patients. The study was closed for futility in September 2013. OS at 2 years was 31.7% [95% confidence interval (CI), 21.7–42.2%] in the chemotherapy group *vs.* 25.1% (95% CI, 16.2–34.9%) in the gastrectomy-plus-chemotherapy group. Median OS was 16.6 months (95% CI, 13.7–19.8 months) *vs.* 14.3 months (95% CI, 11.8–16.3 months; hazard ratio =1.09, P=0.70). Grade 3 or 4 chemotherapy-related adverse events occurred more frequently in the gastrectomy-plus-chemotherapy group, including leukopenia (18% *vs.* 3%), anorexia (29% *vs.* 12%), nausea (15% *vs.* 5%), and hyponatremia (9% *vs.* 5%). One death considered related to treatment occurred in each group. The authors conclude that palliative surgery did not improve the OS of the included patients and that according to the REGATTA trial chemotherapy alone remains the standard of care for these patients (17). However some interesting finding could be observed and should be further investigated. Five patients were assigned to chemotherapy and showed during chemotherapy a disappearance of all noncurable factors and could afterwards undergo gastrectomy in curative attempt. These observations raise the question if conversion surgery could be a better strategy to identify patients more likely to benefit from surgery. In general this would necessitate a trial assessing patients receiving chemotherapy in the metastatic setting stratified to continuation chemotherapy versus surgery after achieving therapy response to chemotherapy.

Another ongoing clinical trial that will shed light on these open questions is the gastrectomy with metastasectomy plus systemic chemotherapy (GYMS) *vs.* systemic chemotherapy alone (SA) (GYMSSA) trial (18). The trial design includes a randomization to gastrectomy plus metastasectomy followed by systemic treatment versus systemic therapy alone; patient recruitment has been completed. The endpoint analysis is expected to show the effectiveness of tumor and metastases resection on OS and treatment associated adverse events. In contrast to the REGATTA trial the GYMSSA study aimed a complete resection including all metastatic sites and may therefore show a different result from REGATTA. Results are eagerly awaited.

Important prerequisites for the indication of surgical resection for oligometastatic GC in a multimodal setting are certainly an adequate clinical performance status, limited metastatic disease, that can be completely resected (or in the case of liver metastases ablated) and good response to chemotherapy. The ongoing RENAISSANCE/FLOT-5-trial (19) will clarify whether surgical resection in the

frame of a perioperative chemotherapy concept can be superior for patients with oligometastatic GC compared to chemotherapy alone.

Analysis of debulking surgery for GC was unsuccessful, except when it aimed for R0 resection (20) and therefore the concept of cytoreductive surgery (CRS) receives more attention. Thereby CRS attempts to reduce the neoplastic mass in a manner that other therapeutic strategies can be added such as hyperthermic intraperitoneal chemotherapy (HIPEC) (21). Further advantages of CRS are the reduction of the tumor mass (reduction of resistant cell clones, immunosuppression and metastatic spread), which leads to a better perfusion of the remaining malignant tissue and offers the chance for a better and more complete response to chemotherapy (22). Patient selection is crucial for these highly experimental multimodality therapy approaches which should be carried out by a multidisciplinary group of specialists (anesthesiologists, surgeons, and oncologists) in order to achieve better results and to reduce the high costs related to these procedures and relevant complications.

The results of the REGATTA trial show that the biological behavior of GC is unpredictable and that even oligo-metastatic disease cannot be generalized to one therapy concept. In summary, REGATTA does not completely exclude the possibility of gastrectomy in oligometastatic stages of GC but highlights the necessity of the optimal timing in the setting of a combined treatment approach. Furthermore a better characterization of the patient's prognosis and response to systemic treatment has to be established to identify the subgroups of patients with less aggressive tumor behavior and more likelihood to benefit from surgery. At the moment the GC population clinically still looks very heterogeneous and the probably to benefit from combined approaches including CRS and HIPEC cannot be easily predicted, if at all. This has to be investigated in future trials that will hopefully help to answer some of the unsolved issues. Furthermore, guidelines for treatment of patients with oligometastatic GC should be developed to improve and individualize therapy for this group of patients.

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# Minimally invasive function-preserving surgery based on sentinel node concept in early gastric cancer

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**Abstract:** Recent meta-analyses and a prospective multicenter trial of sentinel node (SN) mapping for early gastric cancer have shown acceptable SN detection rates and accuracy of determination of lymph node status. A dual-tracer method that employs radioactive colloids and blue dyes is currently considered the most reliable method for the stable detection of SNs in patients with early gastric cancer. However the new technologies such as indocyanine green (ICG) infrared or fluorescence imaging may revolutionize the SN mapping procedures in gastric cancer. For early stage gastric cancer, the establishment of individualized, minimally invasive treatments based on SN concept can retain the patients' quality of life (QOL). The combination of non-exposed endoscopic wall-inversion surgery (NEWS) with SN biopsy is expected to become a promising, ideal minimally invasive, function-preserving surgery to cure cases of cN0 early gastric cancer.

**Keywords:** Sentinel nodes; gastric cancer; laparoscopic; function-preserving

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## Introduction

Many patients with early gastric cancer are currently treated with advanced laparoscopic gastrectomy procedures, such as laparoscopy-assisted distal gastrectomy (LADG) and laparoscopy-assisted total gastrectomy with standard lymph node dissection in Asian countries (1-4). Advanced laparoscopic gastrectomy contributes to both better esthetics and early postoperative recovery (5). However, patients' quality of life (QOL) is mainly affected by late phase complications including dumping syndrome and body weight loss resulting from oral intake disturbance. Therefore, both minimal invasiveness for early phase recovery by laparoscopic surgery and additional late phase function-preserving gastric cancer surgery should

be carefully considered in patients indicated for these procedures.

Function-preserving gastrectomy such as partial gastrectomy, segmental gastrectomy, and proximal gastrectomy with limited lymph node dissection is known to improve postoperative late phase function. However, a certain incidence of skip metastasis in the 2<sup>nd</sup> or 3<sup>rd</sup> compartment of regional lymph nodes remains an obstacle to the wider application of these procedures. To overcome these issues, the concept of sentinel node (SN) mapping may become a novel diagnostic tool for the identification of clinically undetectable lymph node metastasis in patients with early gastric cancer.

The clinical application of SN mapping for early gastric cancer has been controversial for years. However, single

institutional results, including ours and those from a recent multicenter trial of SN mapping for early gastric cancer, are considered acceptable in terms of the SN detection rate and accuracy of determination of lymph node status (6,7). On the basis of these results, we are developing a novel, minimally invasive function-preserving gastrectomy technique combined with SN mapping.

### Laparoscopic SN mapping procedures

A dual-tracer method that utilizes radioactive colloids and blue dyes is currently considered the most reliable method for the stable detection of SNs in patients with early gastric cancer (7,8). An accumulation of radioactive colloids facilitates the identification of SNs even in resected specimens by using a hand-held gamma probe, and the blue dye is effective for intraoperative visualization of lymphatic flow, even during laparoscopic surgery. Technetium-99m tin colloid, technetium-99m sulfur colloid, and technetium-99m antimony sulfur colloid are preferentially used as radioactive tracers. Isosulfan blue and indocyanine green (ICG) are the currently preferred choices as dye tracers.

In our institution, patients with clinical T1 (or T2) tumors, primary lesions less than 4 cm in diameter, and clinical N0 gastric cancer, undergo SN mapping and biopsy. In our procedures, 2.0 mL (150 MBq) of technetium-99m tin colloid solution is injected the day before surgery into four quadrants of the submucosal layer of the primary tumor site using an endoscopic puncture needle. Endoscopic injections facilitate accurate tracer injection. Technetium-99m tin colloid with relatively large particle size accumulates in the SNs after local administration.

The blue dye is injected into four quadrants of the submucosal layer of the primary site using an endoscopic puncture needle at the beginning of surgery. Blue lymphatic vessels and blue-stained nodes can be identified by laparoscopy within 15 min after the injection of the blue dye. Simultaneously, a hand-held gamma probe is used to locate the radioactive SN, similar to esophageal SN mapping. Intraoperative gamma probing is feasible in laparoscopic gastrectomy using a special gamma detector introducer from trocar ports.

For intraoperative SN sampling, the pick-up method is well established for the detection of melanoma and breast cancer. However, it is recommended that the clinical application of intraoperative SN sampling for gastric

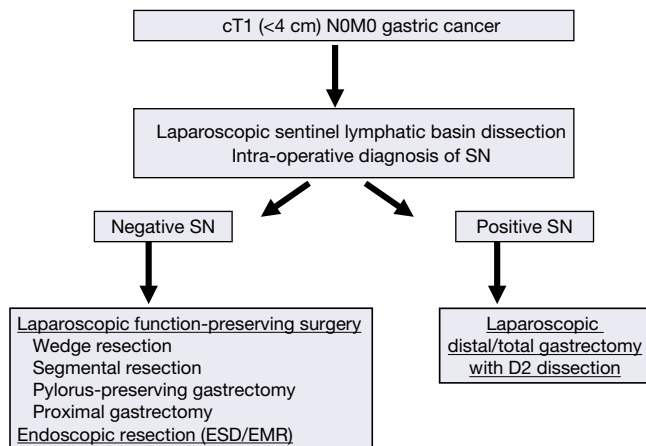
cancer should include sentinel lymphatic basin dissection, which is a sort of focused lymph node dissection involving hot and blue nodes (7,8). The gastric lymphatic basins were considered to be divided in the following five directions along the main arteries: left gastric artery area, right gastric artery area, left gastroepiploic artery area, right gastroepiploic artery area, and posterior gastric artery area (9).

ICG is known to have excitation and fluorescence wavelengths in the near-infrared range (10). Till date, some investigators have used infrared ray electronic endoscopy (IREE) to demonstrate the clinical utility of intraoperative ICG infrared imaging as a new tracer for laparoscopic SN biopsy (11,12). IREE might be a useful tool to improve visualization of ICG-stained lymphatic vessels and SNs even in the fat tissues. More recently, ICG fluorescence imaging has been developed as another promising novel technique for SN mapping (13,14). SN could be clearly visualized by ICG fluorescence imaging compared to the naked eye. Further studies would be needed to evaluate the clinical efficacy of ICG infrared or fluorescence imaging and to compare those with radio-guided methods in prospective studies. However these new technologies might revolutionize the SN mapping procedures not only in gastric cancer but also in many other solid tumors.

### Results of SN mapping for gastric cancer

To date, more than 50 single institutional studies have demonstrated acceptable outcomes of SN mapping for early gastric cancer in terms of the SN detection rate (90–100%) and accuracy (85–100%) of determination of lymph node status; these outcomes are comparable to those of SN mapping for melanoma and breast cancer (8). Recently, Wang *et al.* reported a systematic review that evaluated the diagnostic value of SN biopsy for gastric cancer (14). The results of their large-scale meta-analysis, which included 38 relevant studies with 2,128 patients, demonstrated that the SN detection rate and accuracy of prediction of lymph node metastasis based on SN status were 94% and 92%, respectively (14). They concluded that the SN concept is technically feasible for gastric cancer, especially cases with early T stage (T1), with the use of combined tracers and submucosal injection methods during the SN biopsy procedures.

Our group in the Japan recently conducted a multicenter



**Figure 1** Individualized function-preserving approaches for cT1N0M0 gastric cancer based on sentinel node mapping. SN, sentinel node; ESD, endoscopic submucosal dissection; EMR, endoscopic mucosal resection.

prospective trial of SN mapping using a dual-tracer method with a radioactive colloid and blue dye (7). In the trial, SN mapping was performed between 2004 and 2008 for approximately 400 patients with early gastric cancer at 12 comprehensive hospitals, including our institution. Eligibility criteria were that patients had cT1N0M0 or cT2N0M0 single tumor with diameter of primary lesion less than 4 cm, without any previous treatments. As results, the SN detection rate was 98% and the accuracy of determination of metastatic status was 99% (7). The results of that clinical trial are expected to provide us with perspectives on the future of SN navigation surgery for early gastric cancer.

### Clinical application of laparoscopic SN mapping for early gastric cancer

The distribution of sentinel lymphatic basins and the pathological status of SNs would be useful in deciding on the minimized extent of gastric resection and in avoiding the universal application of distal or total gastrectomy with D2 dissection. Appropriate indications for laparoscopic surgeries such as partial (wedge) resection, segmental gastrectomy, pylorus-preserving gastrectomy, and proximal gastrectomy (LAPG) for cT1N0 gastric cancer could be individually determined on the basis of SN status (Figures 1,2) (15,16).

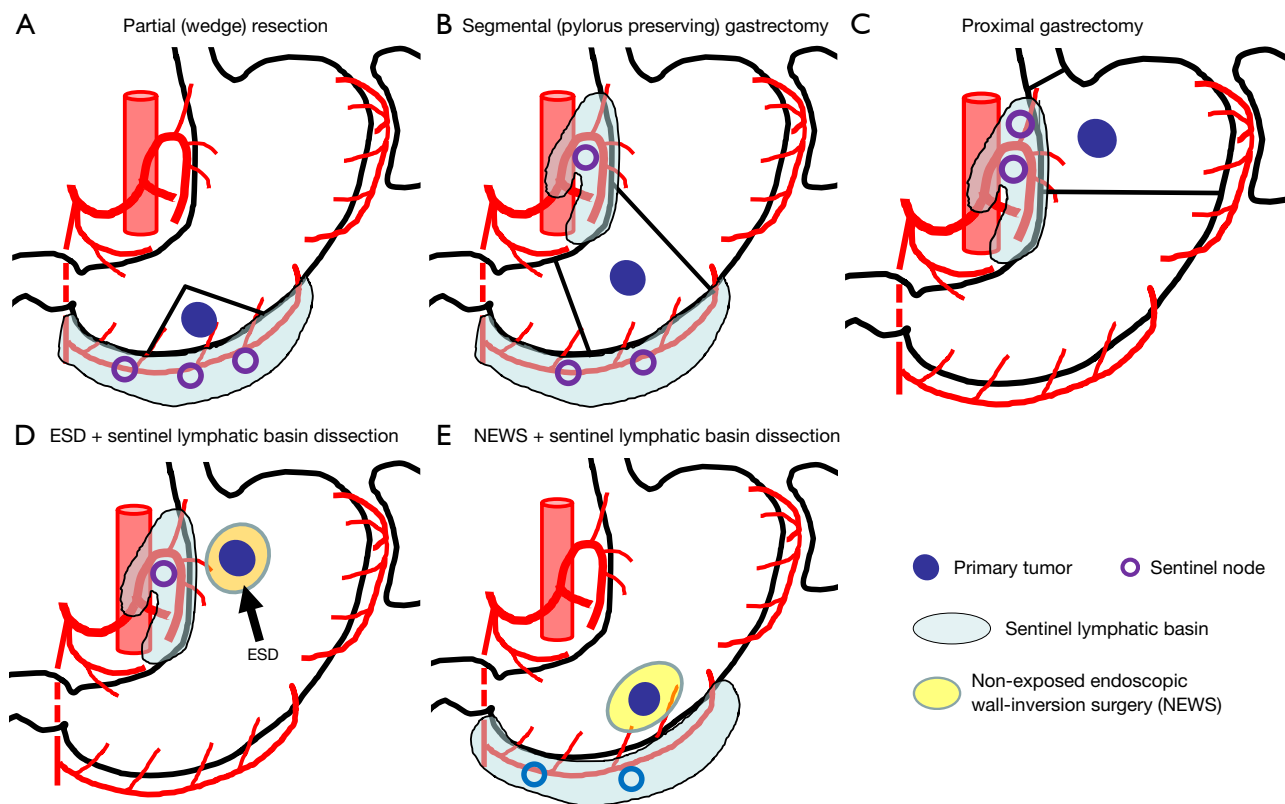
Earlier recovery after surgery and preservation of QOL in the late phase can be achieved by laparoscopic limited gastrectomy with SN navigation. Our study group in Japan currently started the multicenter prospective trial which will evaluate the function-preserving gastrectomy with SN mapping in terms of long-term survival and patients' QOL as the next step.

A combination of laparoscopic SN biopsy and endoscopic mucosal resection (EMR)/endoscopic submucosal dissection (ESD) for early gastric cancer is another attractive option as a novel, whole stomach-preserved, minimally invasive approach. If all SNs are pathologically negative for cancer metastasis, theoretically, EMR/ESD instead of gastrectomy may be sufficient for the curative resection of cT1 gastric cancer beyond the EMR criteria (Figure 2E) (17,18). However, further studies are required to verify the safety and effectiveness of combined treatments involving laparoscopic SN biopsy and EMR/ESD.

Nowadays, LADG or LAPG are frequently applied to the patients with early gastric cancer according to the results of pathological assessment of primary tumor resected by EMR/ESD in clinical practices. To date, it has not been clarified whether the SN mapping is feasible even after EMR/ESD. One of the most important issues is whether lymphatic flow from the primary tumor to the original SNs may change after EMR/ESD. In our preliminary study, however, at least the sentinel lymphatic basin is not markedly affected by previous EMR/ESD (17,18). Modified gastrectomy according to SN distribution and metastatic status might be feasible even for the patients who underwent EMR/ESD prior to surgery.

### Non-exposed endoscopic wall-inversion surgery (NEWS) plus SN mapping

In current function-preserving surgeries such as laparoscopic local resection or segmental gastrectomy, the approach of gastrectomy is only from the outside of the stomach, in which the demarcation line of the tumor cannot be visualized at the phase of resection. Therefore, the surgeons cannot avoid a wider resection of the stomach than is desired to prevent a positive surgical margin. The recent appearance of a new technique, referred to as NEWS is a technique of full thickness partial resection, which can minimize the extent of gastric resection using endoscopic and laparoscopic surgery without transluminal access mainly



**Figure 2** Laparoscopic function-preserving gastrectomy with sentinel lymphatic basin dissection. (A) Partial (wedge) resection; (B) segmental (pylorus preserving) gastrectomy; (C) proximal gastrectomy; (D) sentinel lymphatic basin dissection plus ESD; (E) NEWS with SN biopsy and sentinel lymphatic basin dissection. ESD, endoscopic submucosal dissection; NEWS, non-exposed endoscopic wall-inversion surgery; SN, sentinel node.

designed to treat gastric cancer. We have been accumulating cases of NEWS with SN biopsy for early gastric cancer with the risk of lymph node metastasis in the clinical trial (19,20).

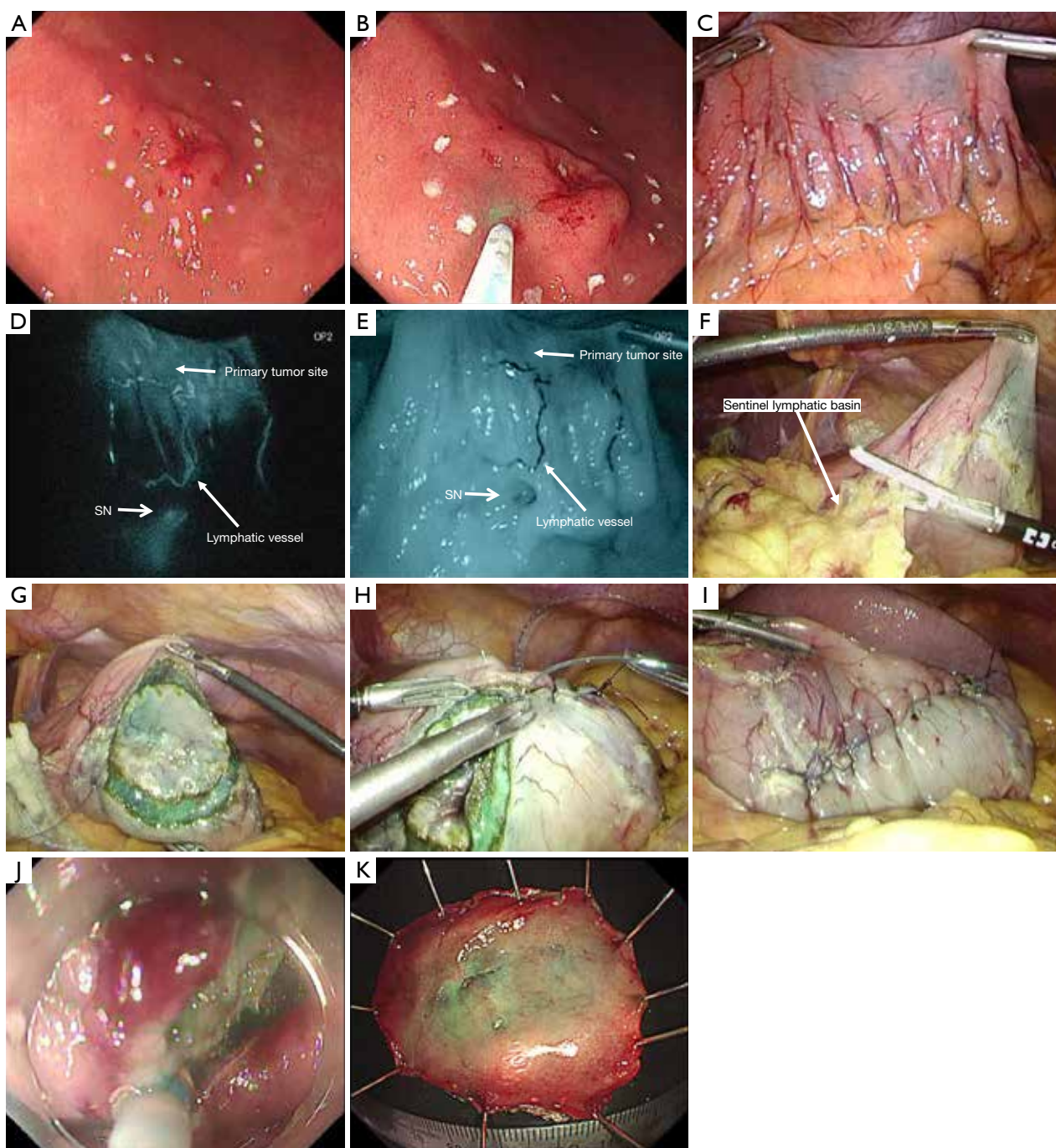
In briefly, after placing mucosal markings, ICG was injected endoscopically into the submucosa around the lesion to examine SNs (*Figure 3*) (19). The SN basin including hot or stained SNs was dissected, and an intraoperative pathological diagnosis confirmed that no metastasis had occurred. Subsequently, NEWS was performed for the primary lesion. Serosal markings were placed laparoscopically, submucosal injection was added endoscopically, and circumferential sero-muscular incision and suturing were performed laparoscopically, with the lesion inverted toward the inside of the stomach. Finally, the circumferential mucosal incision was performed, and the lesion was retrieved perorally.

The NEWS combined with the SN biopsy can minimize

not only the area of lymphadenectomy, but also the extent of gastric resection as partial gastrectomy for patients with SN-negative for metastasis (19). Furthermore, NEWS does not need intentional perforation, which enables us to apply this technique to cancers without a risk of iatrogenic dissemination. The combination of NEWS with SN biopsy is expected to become a promising, ideal minimally invasive, function-preserving surgery to cure cases of cN0 early gastric cancer.

For early stage gastric cancer, for which a better prognosis can be achieved through conventional surgical approaches, the establishment of individualized, minimally invasive treatments that may retain the patients' QOL should be the next surgical challenge. Although further studies are needed for careful validation, function preserving gastrectomy based on SN navigation could be a promising strategy to achieve this goal.





**Figure 3** NEWS with SN biopsy and sentinel lymphatic basin dissection. (A) Early gastric cancer was located at the anterior side of the greater curvature in the lower gastric body. Mucosal markings were placed after precise observation of a demarcation line; (B) ICG was injected to the gastric submucosal layer surrounding the primary tumor; (C) laparoscopic observation of ICG with normal light; (D,E) observation of ICG with infrared ray electronic endoscopy. Infrared ray electronic endoscopy can visualize SNs and lymphatics clearly; (F) resection of sentinel lymphatic basin; (G) laparoscopic circumferential sero-muscular incision; (H,I) laparoscopic sero-muscular suturing and inversion of the primary lesion; (J) endoscopic circumferential mucosal and remnant submucosal tissue incision was performed. Finally the detached primary lesion was retrieved perorally; (K) retrieved primary tumor. NEWS, non-exposed endoscopic wall-inversion surgery; SN, sentinel node; ICG, indocyanine green.



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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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# Endoscopic resection of early gastric cancer: current status and new approaches

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**Abstract:** Endoscopic resection (ER) of early gastric cancer (EGC) has been an optimal treatment for selected patients. As endoscopic submucosal dissection (ESD) has been widely used for treatment of EGC, concerns have been asked to achieve curative resection for EGC while guaranteeing precise prediction of lymph node metastasis (LNM). Moreover, a new microscopic imaging for precise endoscopic diagnosis of EGC is introduced. This review covers the current status and new approaches of ER of EGC.

**Keywords:** Endoscopic resection (ER); early gastric cancer (EGC); confocal laser endomicroscopy; sentinel node navigation

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Early gastric cancer (EGC) is defined when the cancer invasion is limited to the mucosa or submucosa, regardless of the presence of lymph node metastasis (LNM). Advances in endoscopic technology were achieved minimal invasive surgery for EGC. Recently, endoscopic resection (ER) is becoming accepted as one of the standard treatments together with surgical resection (1). Still, the major obstacle to ER for EGC has been its limitations of predicting LNM. Considering reductions of quality of life and low risk of LNM, surgical removal of EGC might be excessive for the majority of patients. Therefore, new approaches to the next level of endoscopic treatment have been evolved. In this review, we will keep track of the progress of ER in two time periods and suggest the prospect of the therapeutic strategy for EGC in the future.

## Expanding indication of endoscopic resection (ER)

### *Endoscopic mucosal resection (EMR)*

EMR for EGC was first described in 1974, which is to lift

and remove the lesion after submucosal injection. This technique was learned from the polypectomy for colon polyp (2). "Strip biopsy" which was introduced in 1984 could be resected small gastric lesion easily (3). After submucosal injection, lesion was lifted by a grasper and removed using a snare. In 1988, EMR after circumferential precutting (EMR-P) was introduced (4). It helped the precise *en bloc* resection by resecting with a snare after peripheral cutting of the lesion. However, this technique has a higher perforation and bleeding risk. Since then, EMR with a cap-fitted endoscope (EMR-C) was developed in 1992 and used to treat relatively small EGC (5). Another technique is EMR with ligation (EMR-L), which was started as a standard endoscopic variceal ligation (6). These techniques helped to remove the lesion more safely and quickly. Currently, EMR was accepted to be a minimally invasive and safe technique and became an axis of treatment for EGC (7). The following is the absolute indication of EMR for EGC which was declared by Japanese Gastric Cancer Association in 1998: (I) elevated cancers less than 2 cm in diameter; and (II) small (<1 cm) depressed cancers

without ulceration. The lesion must also be differentiated cancer confined to the mucosa. EMR showed excellent outcome compared to surgery. The 5-year overall survival rates and recurrence rates did not differ between the EMR and surgery groups (93.6% vs. 94.2% and 1.2% vs. 1.1%) (8). Although the risk of metachronous gastric cancer was higher in the EMR group than in the surgery group (5.8% vs. 1.1%), another lesions were also successfully retreated by EMR or surgery. A major limitation of EMR was incomplete resection for lesions larger than 2 cm in diameter due to the size limitations of accessories. Piecemeal resection caused a high risk of local recurrence (2.3–36.5%) (9). So, the size limitations for *en bloc* resection of EGC kept demanding improvement in techniques.

### **Endoscopic submucosal dissection (ESD)**

ESD was introduced for complete removal of EGC regardless of its size. It could remove *en bloc* EGC which is limited mucosa by dissecting the submucosal layer (10). ESD is superior to EMR because it enables precise pathologic staging for large EGC. It has become one of the standard treatments and is being used to achieve *en bloc* resection for EGCs that would otherwise require piecemeal or surgical resection (9). As the development of ESD technique, indications of ER for EGC were expanded. In a study involving 5,265 patients who had undergone gastrectomy with D2 level lymph node dissection, the risks of LNM can be clustered to a number of pathological findings of the involved mucosa and submucosa: macroscopic appearance, size, depth, differentiation of cancer, lymphatic and vascular involvement (11). The current expanded indication of ER for patients with EGC is differentiated type cancers without evidence of lymphovascular invasion, including: (I) mucosal cancer without ulceration, irrespective of tumor size; (II) mucosal cancer with ulceration, less than 3 cm in diameter; and (III) minimal (500  $\mu\text{m}$  from the muscularis mucosa) submucosal invasive cancer less than 3 cm in size.

Recent meta-analyses to compare the efficacy and safety of ESD and EMR for EGC showed that ESD had advantages in *en bloc* resection rate, histologically complete resection rate and local recurrence rate even for small lesions (9). The 5-year overall survival rates and recurrence-free rates of ESD have been reported to 93.6–100% and 98.7–100%. For complications, delayed bleeding occurs more during ESD, with an incidence rate of up to 7–15.6%. Perforation is higher during ESD (3.6–4.5% vs. 1.0–1.2%), which was endoscopically managed in most cases. To demonstrate the

efficacy and safety of ESD especially for EGCs in expanded indication, well-controlled, prospective randomized trials with a large population and long-term follow-up periods are needed.

### **Challenges to endoscopic submucosal dissection (ESD)**

To guarantee the curative ER or stratify the risk of LNM for EGC, several key points should be checked for the pathologic diagnosis of ESD specimen (12). Complete resection should be confirmed by the precise lateral and vertical margin status. The distance from the lateral margin of the tumor to the margin of the specimen should be described. In case of positive lateral margin, the number of sections and the extent showing positive tumor cells should be documented. If ESD specimen shows a positive vertical margin, the positive tumor site and the distance from the lower edge of muscularis mucosae to the positive margin should be demonstrated. In addition, depth of invasion, histologic type, lymphovascular invasion of the tumor should be evaluated. If the undifferentiated type is mixed within the differentiated type cancer, the proportion of undifferentiated type should be evaluated to predict the risk of vascular invasion and LNM. In case of submucosal invasive cancer, the extent of submucosal invasion and histologic type should be described to determine additional surgery. It is important to identify the muscularis mucosae by using the immunohistochemistry of desmin, because the risk of LNM is higher when the tumor depth is 500  $\mu\text{m}$  or more from the lower edge of muscularis mucosae ( $\geq \text{sm}2$ ) than  $\text{sm}1$ . For careful microscopic examination of vascular invasion, Victoria blue staining is helpful, and immunohistochemistry of D2-40 is useful for evaluation of lymphatic invasion.

### **Non-curative resection or high-risk of recurrence**

Non-curative resection is defined as the presence of positive lateral or vertical resection margins. Submucosal and lymphovascular invasion, or undifferentiated histology means high-risks of recurrence or LNM. Conceptually, the patients with incomplete resection after ESD can be managed with gastrectomy with lymph node dissection. However, when only a small portion of positive lateral margins or unclear lateral margins are found on the post-ESD specimen, this may suggest a lower risk of LNM in the cases having no other factor of non-curative resection (9). The rate of residual cancer in the positive lateral margin group (25.0%) was

reported to be significantly lower than that in the positive vertical margin group (33.3%) or in the positive lateral and vertical margin group (66.7%) among the patients who underwent curative gastrectomy due to non-curative ER for EGC (13). The patients having mucosal cancer with lateral cut-end-positive status with no LNM can be recommended to have close follow-up or endoscopic treatment (14). Another report demonstrated that neither residual cancer nor LNM was found in the patients with less than 500  $\mu\text{m}$  submucosal invasion without margin involvement in endoscopically resected specimens among 43 patients who were operated on due to residual mucosal cancer, a mucosal cancer larger than 3 cm, or a submucosal cancer regardless of size or margin involvement (15). Lymphatic involvement and tumor size have been reported to be independent risk factors for LNM in EGC with submucosal invasion (16,17). Based on the results of the studies, ER may be feasible for highly selective submucosal cancers with no lymphovascular invasion. Gastrectomy with lymph node dissection should be recommended to patients with positive vertical margins, submucosal involvement having high risk features or lymphovascular invasion.

### *Undifferentiated adenocarcinoma*

Traditionally, poorly differentiated adenocarcinomas were candidates for surgery. However, in a retrospective study, 1,362 patients with EGC of signet ring cell histology who underwent gastrectomy showed the similar rate of LNM compared with the patients with differentiated EGC (18). A recent report showed that LNM was significantly associated with female sex, tumor size, depth of tumor invasion and lymphatic involvement in poorly differentiated EGC (19). Although endoscopic management for the patients with undifferentiated adenocarcinoma is still controversial, small studies have reported successful ESD for lesions smaller than 20 mm without lymphovascular invasion (9). Another study showed that poorly differentiated EGC confined to the mucosa or with minimal submucosal infiltration ( $\leq 500 \mu\text{m}$ ) could be considered for curative EMR due to the low risk of LNM (20). Moreover, a study showed that EGC with signet ring cell histology can be treated by EMR, if it is smaller than 25 mm, limited to the sm2 layer, and does not involve the lymphatic-vascular structure (21). However, larger lesions showing submucosal invasion and ulceration lower the possibility of curative resection with ESD. A recent report showed that ESD for undifferentiated

EGC can achieve curative resection with an excellent 5-year mortality rate (22). *En bloc* and R0 resection were achieved in 99.0% and 90.7%. Curative resection was achieved in 63.9%. Among the patients who had additional surgery, the rate of local residual tumor and LNM was 4.8% and 9.5%. None had local recurrence or lymph node or distant metastasis in the patients with curative resection during a median follow-up of 76.4 months.

### *Complications related to gastric endoscopic submucosal dissection (ESD)*

Intraoperative bleeding occurs insignificantly in almost all gastric ESDs and postoperative bleeding needed to endoscopic intervention can occur in around 5% for gastric ESD. The risk factor for intraoperative bleeding complication is reported to be tumor location, in which the submucosal layer is vascular-rich with some large vessels penetrating from the muscle layer. In order to prevent intraoperative bleeding complication, it is necessary to perform submucosal dissection with clear endoscopic view, appropriate traction and water irrigation. It is important to find out vessels in the submucosal layer before cutting (23). Delayed bleeding occurs usually within 24 h and possibly within 2 weeks. The risk factors are reported to be tumor location, resection sized, patient age, use of antithrombotic agents, procedure time, and so on (24,25).

Intraoperative and delayed perforations occur in around 5% and 0.5% for gastric ESD, respectively. The risk analyses showed that the tumor location, tumor size, ulcerative findings, resection piece, and so on were independent risk factors for intraoperative perforation (25,26). In order to prevent intraoperative perforation, it is necessary to make a sufficient space in the submucosal layer by using hyaluronic acid solution for easier maneuverability. Appropriate sedation without body movement or gag reflex for longer procedure and carbon oxide insufflation are also desirable to prevent perforation and lessen the subsequent deterioration (27).

### **Advances in diagnostic and therapeutic endoscopy**

To expand ESD criteria, instrumental and technical advances in diagnostic and therapeutic endoscopy have been challenged. Early detection of gastric cancer or precancerous lesion as well as precise staging is integral to curative ER. Over the past decades, several advances

in diagnostic endoscopy including magnifying endoscopy, narrow-band imaging, and virtual chromoendoscopy have allowed improvement in tissue characterization by detailed imaging of the mucosal pit pattern and microvascular structures. However, these techniques could not provide microscopic visualization of histology. Microscopic imaging is aimed not only to predict histology, but to visualize actual microscopic mucosal architectures in real time, high resolution and high magnification. Moreover, it is useful in microscopically guided target biopsy for EGC because it can avoid sampling errors caused by conventional biopsies in ill-defined, large mucosal cancers. Lastly, it helps to determine the margin of EGC before ESD.

### *Image enhanced endoscopy*

The advanced imaging modalities create the opportunity to make a real time *in vivo* histological prediction, a so-called 'optical biopsy.' This may eventually allow for dispensation with random non-targeted biopsies, possibly with cost savings, but more importantly offering greater accuracy in endoscopic diagnosis.

NBI uses two discrete bands of light: one blue at 415 nm and one green at 540 nm. Narrow band blue light displays superficial capillary networks, while green light displays subepithelial vessels and when combined offer an extremely high contrast image of the tissue surface (28). Capillaries on the surface are displayed in brown and veins in the sub surface are displayed in cyan. NBI is perhaps the most widely studied of the non-dye-based chromoendoscopy techniques. This modality, available on Olympus endoscopy systems, utilises an electronically activated filter placed in front of the endoscope light source. White light is filtered in order to allow only the limited wavelengths of 415 and 540 nm to reach the mucosa. This technique exploits the principle that the depth of light penetration is proportional to wavelength. By restricting the spectrum to visible blue and green light, penetration is limited to the superficial mucosal layers. Additionally these wavelengths coincide with the optimal light absorption peaks of haemoglobin, causing haem-rich structures such as capillaries to appear darker. Mucosal blood vessels appear brown due to the reflection of blue light while submucosal vessels have a green discolouration. Given that angiogenesis is an early feature in premalignant lesions, NBI creates sharp contrast with the background normal mucosa.

FICE, also known as optimal band imaging, selects specific wavelengths before reassigning these to either the

red, blue or green elements of the light spectrum. Sixty possible permutations of potential color combinations are created, ten of which can be stored as presets and are activated by the use of endoscopy system keyboard. Three of these presets can be assigned to a button on the endoscope, allowing for rapid alternation between the white light image and the most commonly used FICE settings (29).

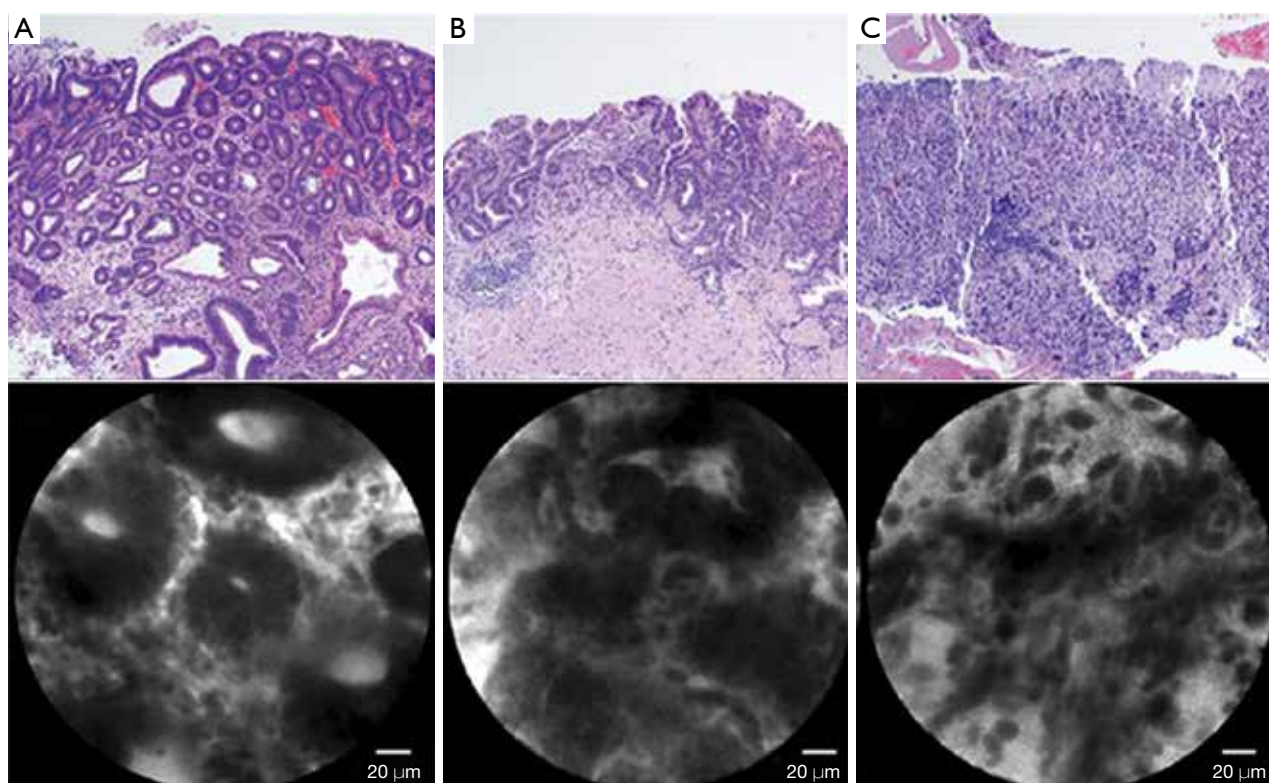
I-Scan is able to create three different imaging options by using different processing algorithms; tone enhancement, surface enhancement and contrast enhancement, with an appropriate setting selected based on lesion characteristics.

The features of the BLI endoscope system include a laser illumination technology that combines two kinds of laser light with phosphor. Laser illumination is brighter than that obtained with the xenon light source and filter. One light source is the white-light mode laser (peak wavelength 450 nm), which excites phosphor to produce white illumination with a broad spectrum suitable for normal observation. The other is the short wavelength narrow-band light laser (peak wavelength 410 nm), which produces a clear image of superficial microvessels and the microstructure of the mucous membrane.

The IMAGE 1 SPIES is the newly developed color spectrum shifting technology from Karl Storz. SPIES SPECTRA allows recognition of the finest tissue structures. The bright red portions of the visible spectrum are filtered out and the remaining color portions are expanded. This makes it easier to differentiate between tissue types, enhancing light/dark contrast by obtaining luminance intensity data for each pixel and applying an algorithm that allows for the detailed observation of mucosal surface structure. SPIES CLARA image features a clear display of details in both light and dark areas. This supports proper illumination in each part of the endoscopic image. SPIES CHROMA intensifies the color contrast in the image. Clearly visible structure surfaces are given added emphasis while retaining the natural color perception in the image (30).

Autofluorescence imaging (AFI) is based on the detection of natural tissue fluorescence emitted by endogenous molecules (fluorophores) such as collagen, flavins, and porphyrins. After excitation by a short-wavelength light source, these fluorophores emit light of longer wavelengths (fluorescence). The overall fluorescence emission differs among various tissue types due to corresponding differences in fluorophore concentration, metabolic state, and/or spatial distribution. AFI may be useful for defining the location and border of gastric lesions because of the autofluorescence of abnormal tissue (31).





**Figure 1** Features of confocal endomicroscopy. (A) Dysplasia, dark epithelium with irregular and varying thickness is observed; (B) differentiated adenocarcinoma, disorganized epithelium with dark and irregular glands is observed; (C) undifferentiated adenocarcinoma, dark and irregular cells with no identifiable glandular structures are observed. (H&E,  $\times 100$ ).

### *Confocal laser endomicroscopy*

Confocal laser endomicroscopy (32) is a system using laser light (currently blue laser light of 488 nm) for excitation and capture of laser-induced fluorescence from the defined lesion. Usually, exogenous fluorophores (intravenous fluorescein, 2.5 mL, 10%) are used to enhance the optical contrast (9). There are 2 types of confocal laser endomicroscopy (CLE), endoscopy-based CLE (eCLE) (33), which is integrated into an endoscope, and through-the-scope probe-based CLE (pCLE) (34) that can be inserted through the working channel of endoscopes. Compared with eCLE, pCLE shows somewhat lower resolution, but faster image acquisition. It also provides microscopic video sequences and can be used into the bile duct or through ultrasonography-guided needles. For accurate interpretation of microscopic images, adequate training in the endoscopic technique and knowledge about histopathology of EGC is required. In 2004, the first study on CLE was reported in patients who performed screening colonoscopy (35). In the stomach, several studies have been

reported CLE imaging for *Helicobacter pylori* infection and gastritis (36), intestinal metaplasia (37) and hyperplastic and adenomatous polyps (38). From the Miami classification (39), the key features used to distinguish non-neoplastic tissue, dysplasia, and adenocarcinoma are as follows: (I) normal or non-neoplastic mucosa, round regular crypts, cobblestone appearance of normal glands; (II) dysplasia, irregular crypt lumen, dark irregular thickened epithelium; and (III) gastric adenocarcinoma, completely disorganized epithelium, fluorescein leakage, dark irregular epithelium. Differentiated and undifferentiated adenocarcinoma can be distinguished based on the presence of discriminable glandular structures (33) (*Figure 1*). In the studies to evaluate efficacy in pre-ESD pathologic diagnosis or post-ESD surveillance for high-grade neoplasia and superficial gastric cancer, CLE showed high accuracy (91.7–99%) and decreased biopsies. Moreover, CLE would have directed 10% of the patients to surgery instead of ESD by correctly showing undifferentiated carcinoma. CLE is a promising technology for identifying EGC and has potential to decrease



the rate of discrepancy pre- and post-ESD histopathology.

### ***Beyond endoscopic submucosal dissection (ESD)***

As mentioned above, a major limitation of ESD for curative treatment of EGC is inaccuracy in lymph node status. Ultimately, ESD is a curative treatment modality only if EGCs do not have regional LNM. N staging for EGC is mostly performed by CT or EUS, but diagnostic yields were not so satisfactory. EUS has a limitation not only to evaluate of regional LNM but to predict depth of invasion. It takes a lot out of the patients and endoscopists to decide and follow up after ESD. Finally, it is most important to decide what could be a minimally invasive treatment for EGC patients with a potential to escape the expanded ESD indication. Some patients who underwent surgical operation are diagnosed as mucosal cancer without LNM on the final pathology. In contrast, it is not unusual that some patients are required to have additional surgery or to give careful consideration of additional surgery after ESD. Because of these important problems, a paradigm shift has been emerged.

### ***Endoscopic submucosal dissection (ESD) with sentinel node navigation***

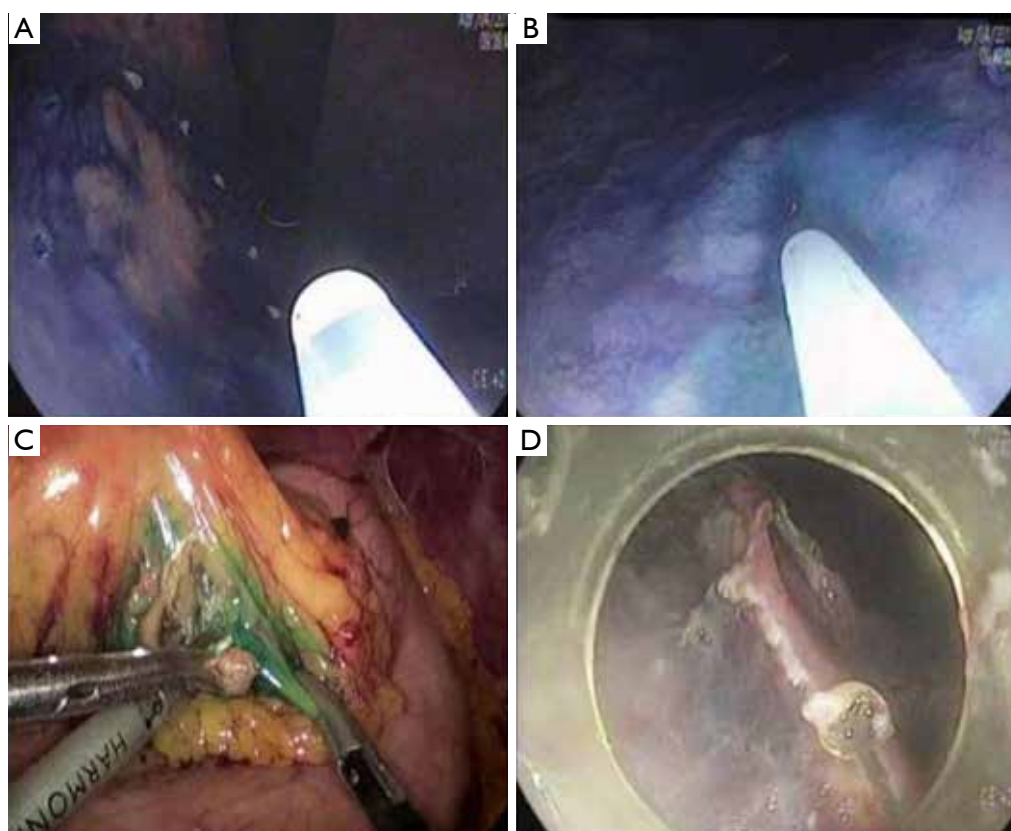
Sentinel lymph node is the hypothetical first lymph node or group of nodes draining a cancer and is considered the first site of micrometastasis along the route of lymphatic drainage. Sentinel node navigation is defined as a novel, minimally invasive surgery based on sentinel node mapping and the sentinel node-targeted diagnosis of nodal metastasis. The concept of sentinel node has evolved from the surgical staging of both breast cancer and melanoma. It avoided unnecessary prophylactic radical lymphadenectomy such as axillary lymph node dissection in breast cancer patients with negative sentinel node for cancer metastasis. Although the clinical application of sentinel node mapping for EGC has been controversial for years, sentinel node mapping, using a dual-tracer method that utilizes radioactive colloids and blue dyes, is currently considered the most reliable method for the stable detection of sentinel nodes in patients with EGC (9). An accumulation of radioactive colloids facilitates the identification of sentinel nodes even in resected specimens, and the blue dye is effective for intraoperative visualization of lymphatic flow, even during laparoscopic surgery. Usually, technetium-99m tin colloid, technetium-99m sulfur colloid, and technetium-99m antimony sulfur colloid are used as radioactive tracers. Isosulfan blue,

patent blue, and indocyanine green (ICG) are currently the preferred dye tracers. The patients with clinical T1N0 (<4 cm) gastric cancer can undergo sentinel node mapping and biopsy without limitation of tumor location. Radioactive colloids and blue dyes are injected the day before surgery and just before the procedure into four quadrants of the submucosal layer around the primary tumor using an endoscopic puncture needle. Studies are investigating sentinel lymph node navigation using endoscopic injection of radiocolloids dye or ICG, or CT lymphography using nanoscale iodized oil emulsion to increase the accuracy of detecting LNM. A recent meta-analysis showed that the sentinel node detection rate, sensitivity, negative predictive value, and accuracy were 93.7%, 76.9%, 90.3%, and 90.2%, respectively (40). When considering laparoscopic procedure, sentinel node identification rate, sensitivity, false negative rate, and accuracy were 89.3%, 68.6%, 31.4%, and 92.6%, respectively. Combined ESD and sentinel node navigation surgery might be a feasible, minimally invasive procedure that allows *en bloc* tumor resection to be achieved while assessing the pathological status of the regional lymph nodes (Figure 2). A case series reported that combined ESD and sentinel node navigation was conducted for 13 patients with clinical T1N0 (20) EGC, and was completed in 12 patients (41). One patient was converted to gastrectomy after sentinel node navigation surgery. *En bloc* resection was achieved in all other cases.

### ***Hybrid natural orifice transluminal endoscopic surgery (NOTES)***

The risk of LNM in EGC exceeding the indication has known to 5.7–20% (42). In other words, at least 80% of patients might potentially save their stomach with curative endoscopic treatment if depth of invasion of the tumor is within the submucosa and microscopic vertical margin is secured after ESD.

NOTES may be applied as a modified treatment for EGC. NOTES means that abdominal operations are performed with an endoscope passed through a natural orifice (e.g., mouth, urethra, anus) and then through an internal incision in the stomach, vagina or colon (43). This procedure allows flexible endoscope to reach organs outside the lumen of the bowel. NOTES is minimally invasive compared to open surgery is exposed to fewer risks. Hybrid NOTES enables minimal tumor resection using the ESD technique, and laparoscopic lymphadenectomy can be performed simultaneously in cases of EGC with high risk



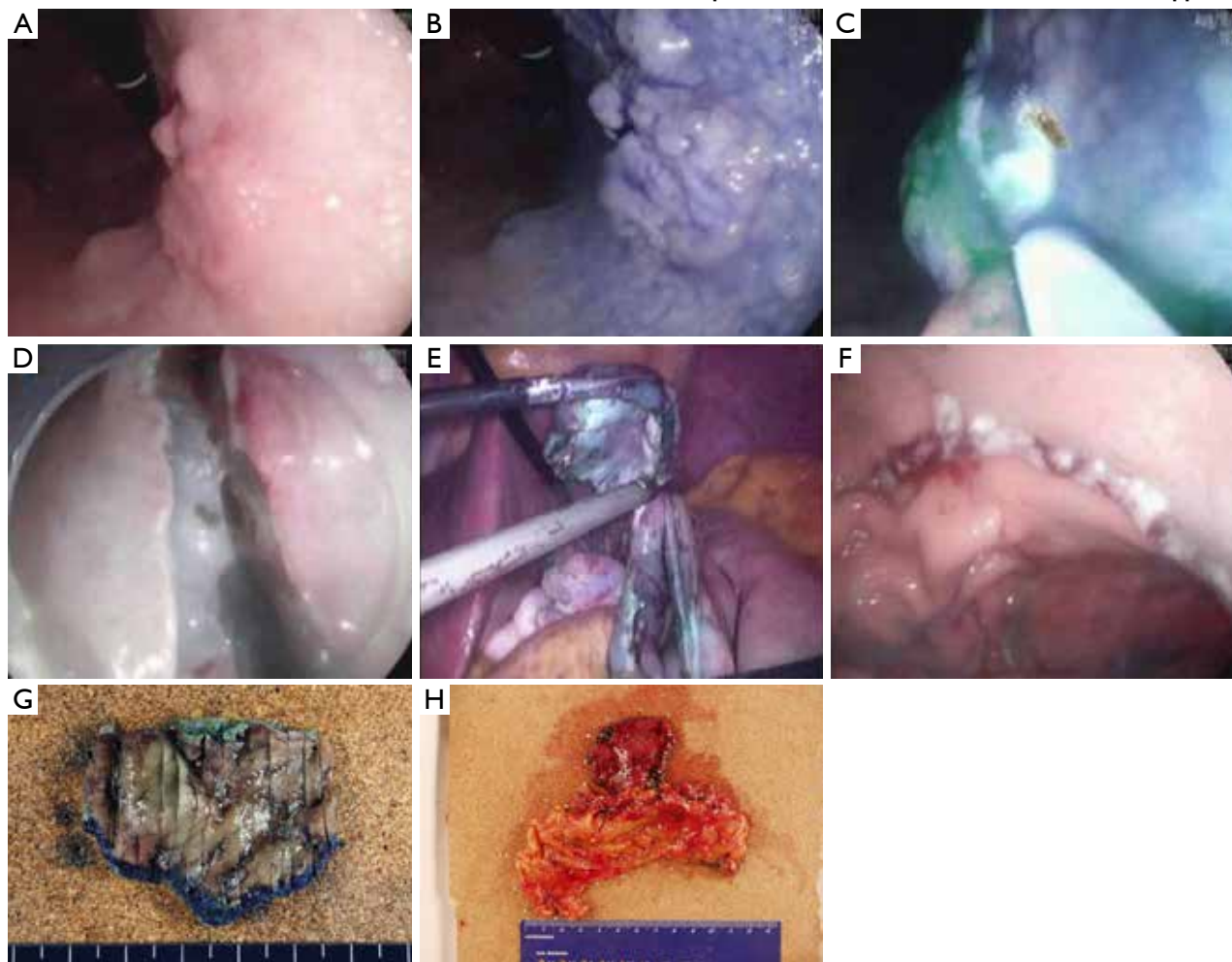
**Figure 2** Endoscopic submucosal dissection with sentinel node navigation. (A) Marking for endoscopic submucosal dissection is performed around the tumor; (B) indocyanine green is injected into the submucosal layer around the tumor for sentinel node navigation; (C) sentinel node harvest is performed by laparoscopic pick-up biopsy; (D) endoscopic submucosal dissection is performed.

for LNM. Hybrid NOTES for EGC means endoscopic full-thickness gastric resection (EFTGR) with laparoscopic regional lymph node dissection. It consists of EFTGR and laparoscopic lymphadenectomy after sentinel node navigation. EFTGR consists of five major procedures: (I) marking around the lesion safety margin confirmed by margin biopsies; (II) a circumferential incision as deep as the submucosal layer around the lesion; (III) circumferential endoscopic full-thickness resection around the lesion through the submucosal incision line under the laparoscopic guidance; (IV) laparoscopic full-thickness resection around the remaining lesion through the EFTGR incision line inside the peritoneal cavity; and (V) laparoscopic closure of the resection margin (44) (*Figure 3*). The lymph node dissection is performed before the full-thickness resection. Depending on the location of the lesion, the regional lymph nodes are dissected after sentinel lymph node navigation. The first prospective, pilot study for 14 patients with EGC was published in Korea (45). The case series concluded

that hybrid NOTES could be a bridge between ER and laparoscopic surgery and may prevent extensive gastrectomy with lymphadenectomy in patients with EGC. EFTGR has a limited indication because of the potential for tumor dissemination into the abdominal space during the procedure and vagus nerve injury. Until now, several studies have been published, and techniques are being developed to accomplish non-exposed endoscopic wall-inversion surgery (9). This new method may be an alternative to surgery in patients with submucosal cancer with or without ulceration, or mucosal cancer technically difficult to resect with ESD.

#### *Upcoming challenges in the new era*

The key to improving therapeutic outcomes for EGC is early detection and accurate diagnosis. In spite of many advantages, endomicroscopy including CLE is still limited to some tertiary centers throughout the world. Clinical use of CLE before ESD will provide more accurate diagnosis



**Figure 3** Endoscopic full-thickness gastric resection. (A) An elevated lesion is noted at the lesser curvature of upper body; (B) the lesion becomes distinct by chromoendoscopy using acetic acid and indigo carmine; (C) for sentinel node navigation, indocyanine green is injected into the submucosal layer after marking around the tumor; (D) endoscopic full-thickness resection is performed after sentinel node harvest and regional lymph node dissection; (E) final resection is performed with laparoscopy; (F) gastric closure is achieved with laparoscopy; (G) resected specimen; (H) resected lymph node.

of EGC compared with biopsies. Moreover, advance in endoscopic instruments, techniques and training is essential to improve outcomes of patients with EGC. Recently, novel laser system for ESD was introduced. ESD was completed using only the thulium laser, instead of endoscopy knives, without significant complications in all 10 patients (46). Moreover the concept of endoscopic surgery including ESD or EFTGR with sentinel node navigation could be a bridge between ER and laparoscopic surgery in respect to therapeutic efficacy, and preserving function and quality of life in patients with EGC. However, selected location, size of the tumor, long-term clinical outcomes, and occurrence of metachronous cancer should be carefully evaluated.

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None.

### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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# Single incision gastrectomy for gastric cancer

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**Contributions:** (I) Conception and design: YS Suh; (II) Administrative support: HJ Lee, HK Yang; (III) Provision of study materials or patients: YS Suh; (IV) Collection and assembly of data: YS Suh; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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**Abstract:** Based on rapid development of laparoscopic techniques and instruments, single-incision laparoscopic surgery (SILS) is expected to be the next step of “more” minimally invasive surgery. A few institutions gradually started to report their experience of single incision gastrectomy (SIG) for gastric cancer, but it is still difficult to accept that SIG can be performed as a popular procedure because of its technical difficulty. For wide adoption of SIG, the simplicity, safety and reproducibility of not only lymph node dissection but also reconstruction should be evaluated compared to a conventional procedure. With a thorough understanding of unique characteristics of SILS, single incision distal gastrectomy (SIDG) for early gastric cancer performed by laparoscopic surgeons with advanced technique is expected to have promising potential about excellent cosmesis, comparable morbidity and mortality in carefully selected patients. For appropriate adoption and steady progress of this state-of-the art surgery, scientific evaluation with healthy critics is necessary with new generation of SILS instrument platform.

**Keywords:** Single-incision laparoscopic surgery (SILS); gastric cancer; single incision distal gastrectomy (SIDG); minimally invasive surgery

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## Introduction for single-incision laparoscopic surgery (SILS)

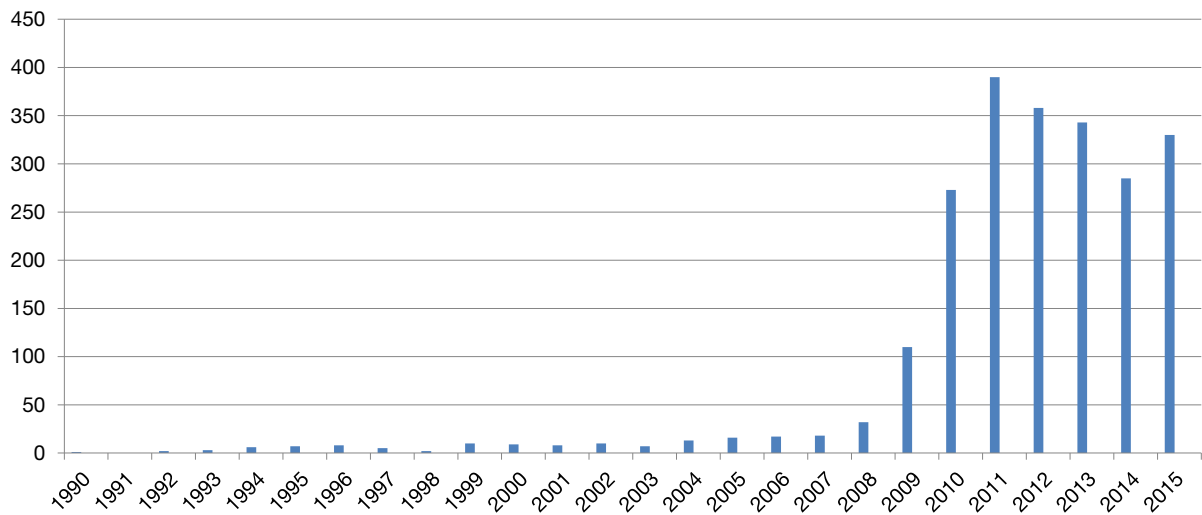
Laparoscopic gastrectomy has been known to have several advantages, including less postoperative pain, better cosmesis, less inflammatory reaction, rapid recovery of bowel function, and fast recovery compared to conventional open surgery (1). For early gastric cancer, laparoscopic gastrectomy and lymph node dissection is considered safe and comparable procedure in terms of postoperative outcome even in large scale randomized clinical trial, and also expected to show promising long-term survival outcome (2-4). Technically, laparoscopic gastrectomy may be feasible and gradually standardized even for advanced gastric cancer (5).

Owing to rapid development of laparoscopic instruments and techniques, SILS could be expected to be the next step of “more” minimally invasive surgery and also becoming an academic issue recently (*Figure 1*).

The first adoption of SILS starts from the early 1990's (6). However, it took long time for this novel approach using single umbilical incision to be generalized because of technical difficulties with unstandardized surgical procedures and limitation of laparoscopic instruments. Especially, SILS has typical disadvantage including the lack of “triangulation” among instruments and camera scope, and extremely narrow range of motion around a single port, which may lead to collision among each instrument, uncomfortable or limited surgical view, unnecessarily larger umbilical incision and lack of assistance.

In terms of general surgery including appendectomy or cholecystectomy, recent several studies have reported that SILS is feasible and has similar surgical outcome without increasing significant complication (7-10). In terms of malignancy of digestive tract, SILS has been eagerly investigated in colorectal cancer and showed comparable outcome in a few studies including randomized clinical trial





**Figure 1** Time trends of the number of searched reports using keyword of “single incision laparoscopic” from 1990 to 2015 using PubMed as of January, 2016.

or matched retrospective study, even though the number of sample size was limited (11-14).

### Single incision distal gastrectomy (SIDG)

For gastric cancer, SIDG with lymph node dissection was firstly reported in 2011 (15). Nowadays a few institutions gradually started to report their experience, but it is still difficult to accept that SIDG can be performed as more popular procedure (*Table 1*).

Gastric cancer surgeries consist of three major parts including lymph node dissection, gastrectomy, and reconstruction. Compared to other surgeries in gastrointestinal tract, there are more complicated guidelines for lymph node dissection around major nominated vessels and various ways of laparoscopic reconstruction in laparoscopic gastric cancer surgery which are continuously investigated and modified (26-28). To evaluate feasibility of SIDG for gastric cancer, we should consider these troublesome characteristics and its adequate solution in advance.

### Prerequisites

Usually SILS requires at least 2.5 or 3 cm sized umbilical incision which is significantly much larger incision than conventional laparoscopic surgery. Therefore, many surgeons concerned that single wound complication including incisional hernia. However, resected stomach, several stations of lymph nodes and omentum consists of

bulky specimen compared to relatively small appendix or gallbladder, or uniformly tubular structure of colon or rectum. To retrieve that bulky specimen without squeezing, current multiport laparoscopic gastric cancer surgery usually requires at least 2.5–3 cm sized incision, which means single incision laparoscopic gastric surgery does not require any extension of periumbilical wound and only omits other multi ports. Therefore, it may be more favorable situation for gastric surgery to adopt SILS compared to other intestinal surgeries. According to previous studies, there are several prerequisites to adopt SIDG as of now.

Firstly, in case of conventional rigid 30-degree laparoscope, energy device and camera scope almost always parallel to the surgical “point of interest” and very close between each other, which may lead to frequent collision and hinder the safe surgical view. To avoid this collision among grasper, energy device, stapler and camera system, the tip (camera) of the laparoscope should be located as much as far from other devices. Therefore, flexible laparoscope seems to be a nearly mandatory instrument. During the SILS, frequent movement of camera scope is more limited compared to conventional multiport laparoscopic surgery because of collision of instruments. Recently developed 3D scope system could be useful in terms of superior task efficiency because it can show more effective perspective and depth of field to operator, which means the decreased number of “air-catching” and less position change of camera scope (29-31). Secondly, the length and shape of instrument can be chosen depending

**Table 1** Previous historical reports of single incision distal gastrectomy for gastric cancer

Year	Publication	Author	Country	Pure or additional	Anastomosis	n	Analysis
2015	<i>J Gastric Cancer</i> (16)	Suh <i>et al.</i>	Korea	Pure	11 for Billroth I (uDelta); 5 for Roux-en Y	16	Comparative study (Billroth I vs. Roux-en Y)
2015	<i>Surg Endosc</i> (17)	Kim <i>et al.</i>	Korea	Pure	Billroth I	48	Comparative study (vs. 46 reduced ports)
2014	<i>J Am Coll Surg</i> (18)	Ahn <i>et al.</i>	Korea	Pure	42 for Roux-en Y; 8 for Billroth I	50	Comparative study (vs. 50 multiports laparoscopic distal gastrectomy)
2014	<i>J Am Coll Surg</i> (19)	Ahn <i>et al.</i>	Korea	Pure	Roux-en Y	22	Single arm, feasibility
2014	<i>J Gastrointest Surg</i> (20)	Omori <i>et al.</i>	Japan	With assistance	Billroth I, linear (intact)	45	Single arm, feasibility
2014	<i>Ann Surg Treat Res</i> (21)	Ahn <i>et al.</i>	Korea	Pure	Roux-en Y	14	Single arm, D2 LND with mid pancreas mobilization
2013	<i>J Laparoendosc Adv Surg Tech A</i> (22)	Kong <i>et al.</i>	China	Pure	Billroth II	4	Case report with D2 LND
2012	<i>Surg Laparosc Endosc Percutan Tech</i> (23)	Park <i>et al.</i>	Korea	2 mm additional	Billroth I (delta anastomosis)	2	Case report with D1 + $\beta$ LND
2012	<i>Surg Endosc</i> (24)	Omori <i>et al.</i>	Japan	2 mm additional	Billroth I (efficient purse string)	20	Single arm, feasibility
2011	<i>Surg Innov</i> (25)	Ozdemir <i>et al.</i>	UK	Pure	Billroth II	1	Case report with D1 + $\alpha$ LND
2011	<i>Surg Endosc</i> (15)	Omori <i>et al.</i>	Japan	2 mm additional	1 for Roux-en Y and 6 for Billroth I; (efficient purse string)	7	Single arm, feasibility

LND indicates lymphadenectomy.

on the situation. “Collision” is always problematic issue not only inside the peritoneal cavity but also outside the port in SILS. If possible, longer devices including energy device are much more useful to avoid collision among devices outside the port, because instruments longer than 40 cm makes wider gap between two hands of operator compared to conventional instruments. During the SILS, conventional linear grasper sometimes cannot effectively reach small lymph nodes around suprapancreatic area due to collision of energy device or protruded pancreas body with low lying umbilicus. For such cases, bending graspers are occasionally helpful to perform meticulous dissection of those lymph nodes. However, operator should be competent to perform “cross-handed manipulation” of instruments which is sometimes obviously required and also offers more various way of approach under limited surgical field. Lastly, operator should accustom himself to surgical procedure with minimal assistant, especially making good surgical field. To make good surgical field without any special assistant, frequent position change and subsequent

traction using gravity should be utilized, and skillful usage of one left-handed grasper is important to make critical surgical field. However, obese patients who have much visceral fat are still not be a recommendable indication for SIDG because huge amount fat including possible metastatic lymph nodes is big hurdle to make clear surgical field without effective assistance.

### *Lymphadenectomy*

For early gastric cancer located in lower one-third of the stomach, D1 or D1+ lymph node dissection is required according the Japanese gastric cancer treatment guideline (26). One of the most important stations is station #6 around right gastroepiploic vessels. Because the root of right gastroepiploic vessels is slightly right side from the midline, the approach to the station #6 is usually performed using left side approach which is preferred by some Japanese surgeons (32,33). Using the gravity with right side upward position, dissection of station #6 including soft tissue at

the anterior surface of pancreas head can be performed safely. However, regarding the dissection of suprapancreatic lymph nodes, the neck and body of pancreas is sometimes significantly protruded, which make it difficult to approach the lymph nodes behind that pancreas using a straight energy based device from down the umbilicus. Especially, station #11p is troublesome area for complete dissection if the proximal part of splenic artery is tortuous. In our early experience, one patient was readmitted after discharge because of splenic artery pseudoaneurysm, and underwent reoperation with intensive care. This type of unique complication that might result from thermal damage by the various energy device was already reported even in a previous large scale study of laparoscopic distal gastrectomy with lymph node dissection (34,35). In particular, during SIDG, use of an energy-based device should be minded with much more caution because there is no effective assistance to avoid possible thermal injury to adjacent tissues, including major vessels. Because dissection of #11p is not mandatory for complete dissection in distal third early gastric cancer, strict indication for early gastric cancer and rather incomplete, safe exploration around station #11p with careful usage of energy device might be more safe approach to adopt SIDG for gastric cancer as of now (26). As an alternative, mid-pancreas mobilization, somewhat aggressive mobilization for early gastric cancer, was recently introduced for complete dissection of #11p LN (21).

### **Reconstruction**

For the generalization of a new procedure such as SIDG, the simplicity, safety and reproducibility of not only lymph node dissection but also reconstruction should be evaluated compared to a conventional procedure (17). Regarding reconstruction, to consider procedure generalization, gastroduodenostomy or gastrojejunostomy should be equivocally evaluated after SIDG. Compared to Billroth II or Roux-en Y anastomosis using gastrojejunostomy, Billroth I anastomosis using gastroduodenostomy has been known to offer such advantages as more simple, less anatomical change after anastomosis, more physiological food passage and a lower incidence of internal hernia or adhesion and is consequently the most common anastomosis technique after distal gastrectomy in Korea and Japan, even in expert groups (33,36).

Compared to gastroduodenostomy, gastrojejunostomy can be relatively simple procedure, and most of studies on the initial experience with SIDG preferred BII or Roux-en Y reconstruction using gastrojejunostomy (19,22,25). In

laparoscopic surgery, gastroduodenostomy has been usually considered as a more difficult technique because of the limitation of the intracorporeal approach with a circular stapler as well as the narrow working space around the duodenal stump. One of the well-established intracorporeal gastroduodenostomy, Delta-shaped anastomosis still requires advanced assistance because that assistant usually manipulates remnant stomach as well as staplers for reconstruction itself (37-39). In addition, it is more difficult to expect such advanced-assistance dependent procedure in SIDG, and one more small assistance grasper is likely to result in more collision because it makes narrow port space more crowded. Therefore, there have been limited number of original experience or modification of Billroth I anastomosis after SIDG, and reproducibility of gastroduodenostomy in pure SIDG still seems to be doubtful (20,23,24). We reported our novel technique for gastroduodenostomy, "unaided delta-shaped anastomosis", without any additional port or intracorporeal assistance for pure SIDG, and also hope this technique will contribute to reproducible establishment of gastroduodenostomy in SIDG after validation (17).

### **Outcome and understanding**

Regarding the outcomes of SIDG for gastric cancer, there have been only a few comparative studies (16-18). Two studies comparing SIDG and multi (three or more) port totally laparoscopic distal gastrectomy (TLDG) reported similar operation time and comparable complication rate (16,18). Regarding the oncologic outcome, the numbers of retrieved lymph nodes were similar between SIDG and TLDG in both studies. Interestingly these two studies showed similar operation time of SIDG ( $144.5 \pm 35.4$  and  $135.3 \pm 18.8$  minutes) compared to TLDG ( $140.3 \pm 36.3$  and  $132.8 \pm 27.0$  minutes). However previous report of large scale randomized clinical trial performed by a "master class" group reported mean operation time of LADG as  $184.7 \pm 55.0$  minutes, which is much longer than that of SIDG studies (2,40). Considering standard deviation of 55.0 minutes, only limited population with shortest operation time in that trial may have similar operation time to SIDG studies. Therefore, recent limited reports of SIDG may have been understood as those results could be achieved only after the limited surgeons who have advanced skill for laparoscopic surgery carefully selected "surgeon-friendly" patients, and not be easily generalized for laparoscopic surgeons with insufficient

experience as of now. In addition, even though previous studies of SIDG reported comparable morbidity and absence of open/multiport conversion, low competency for unexpected intraoperative accident in pure single port surgery still cannot be ignored. Single incision gastrectomy (SIG) usually requires least number of personnel, only one scopist and scrub nurse, in operating theatre. This procedure might receive any attention as “economically-efficient” surgery for a while (41,42). However, low competency for intraoperative accidents including critical bleeding in SIDG is inevitable which is similar or more serious situation to that in transition period from open surgery to early laparoscopic surgery. In addition, considering the first step of standardization of surgical procedures are education and consensus, this dramatic advances in laparoscopic surgery has a tendency to longer distance trainees from the patient and especially assistant has none or least participatory role in SIG, which may result in much steeper learning curve for laparoscopic surgery in the future (43,44).

To evaluate outcome of surgical procedure, the measurement of quality of life (QOL) is one of the most important issues, which will guide us from the comfort of previous medicine into a world that is less concrete and less controllable, but more human (45,46). However, the objective and reproducible evaluation of QOL is not easy, especially in minimally invasive surgery or simple basic surgical procedure. Recently, for cholecystectomy, double-blinded RCT evaluating QOL between single-port cholecystectomy and conventional laparoscopic cholecystectomy was firstly reported (10). Using previously validated cosmesis and body image scores, and short form 36 health survey questionnaire SF-36, this study reported the statistical advantage of cosmesis and body image, higher QOL regarding emotional wellbeing, physical pain, physical health and mental health after postoperative 1 year, and less postoperative pain in single port cholecystectomy (47-49). However, quality of life in SIDG compared to TLGDG was not comprehensively evaluated until now. Only regarding postoperative pain, previous two studies reported inconsistent results and difference of VAS score is less than 1 point in even significant result (16,18). In the future, scientific evaluation of QOL will guide us to more reasonable assessment of outcome of this state-of-the-art procedure.

### Single incision total gastrectomy

The case report of pure single incision total gastrectomy

for proximal early gastric cancer was firstly reported in 2014 (50). Collision of each instrument is expected to be more serious and making good surgical field also more difficult, however authors reported similar operation outcome compared to conventional multiport laparoscopic total gastrectomy. Obviously total gastrectomy has been known as a surgical technique with more significant morbidity and mortality compared to distal gastrectomy. Because this report is the only study based on single institution’s early experience as of now, hasty adoption with distorted attraction to new technique should be postponed if it were not for enough experience of SIDG or other pure SILS.

### Conclusions

As of now, SILS is one of the closest approaches to the ideal concept of “scarless” surgery. With a thorough understanding of unique characteristics of SILS, SIDG for gastric cancer performed by laparoscopic surgeons with advanced technique is expected to have promising positive potential about excellent cosmesis, comparable morbidity and mortality in carefully selected patients. For appropriate adoption and steady progress of this state-of-the-art surgery, scientific evaluation with healthy critics is necessary with new generation of SILS instrument platform. Lastly, we have to keep in mind that the long term outcome of a large scale randomized clinical trial comparing “conventional” multiport laparoscopic distal gastrectomy and open distal gastrectomy for early gastric cancer is still waiting for us before SIDG (2).

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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# Reduced port laparoscopic gastrectomy for gastric cancer

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**Abstract:** The use of reduced port laparoscopic surgery (RPS) has become increasingly popular. The concept of RPS includes all procedures derived from various efforts minimizing the invasiveness of surgery, with single-incision laparoscopic surgery (SILS) being the ultimate reduced port technique. Reduced-port laparoscopic gastrectomy (RPLG) for gastric cancer has not yet been fully established and still has issues such as feasibility, oncological validity, training, and education. The short-term results of reported studies are acceptable. However, long-term results that verify positive results or radical cure even in cases of cancer have not yet been published. Patients for whom RPLG is indicated should be selected carefully. Prospective multicenter studies should be conducted to establish RPS as a truly evidence-based practice that addresses not only cosmesis but also the appropriate balance between minimal invasiveness and radical cure.

**Keywords:** Laparoscopic gastrectomy; reduced port surgery; single incision

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## Introduction

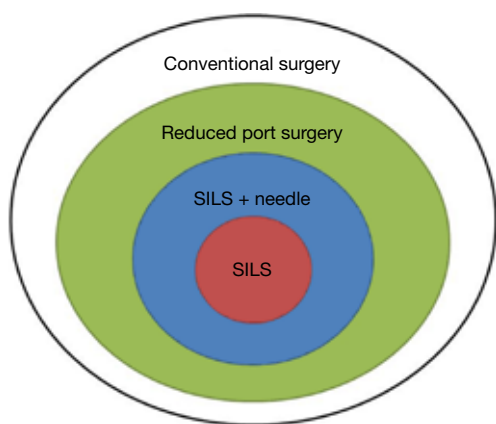
The use of reduced port laparoscopic surgery (RPS) has been increasing recently (1). RPS involves fewer ports than standard laparoscopic surgery and can allow for needlescopic surgery through narrower ports (2) by involving single-incision laparoscopic surgery (SILS). SILS, which is performed from a single incision at the umbilicus, can be considered the ultimate reduced-port technique. Needlescopic surgery and SILS were introduced almost simultaneously in the 1990s (3,4). Although they were originally used for surgical treatment of benign diseases, with the advances in techniques and devices, their applications have expanded to include malignant diseases such as colorectal and gastric cancers (5-8). Now, the concepts of SILS, RPS, and needlescopic surgery have been combined and are difficult to distinguish from each other (*Figure 1*). The term RPS integrates these concepts and is considered to be derived from the various efforts aimed at minimally

invasive surgery.

The history of RPS use for malignant diseases such as gastric cancer is short, and its usefulness has not yet been fully established. This review describes the present concept, situations, and challenges of RPS for gastric resection of gastric cancer, and these issues are presented in light of the existing literature.

## Concept and history of reduced-port laparoscopic gastrectomy for gastric cancer

Laparoscopic surgery is a minimally invasive treatment, and its widely known advantages include reduced bleeding and its contribution to minute lymph node dissection (9,10). In the reduced-port laparoscopic gastrectomy (RPLG) concept, when laparoscopic surgery is performed for gastric cancer, the resected specimen and retrieved lymph nodes are usually extracted in a plastic bag through the umbilicus or another incision. In general, the incision must be at



**Figure 1** Concept of reduced-port surgery. SILS, single-incision laparoscopic surgery.

least around 3 cm. Therefore, gastric resection performed through an incision no larger than 3 cm can be the ultimate single-incision laparoscopic gastrectomy (SILG).

The application of RPS to gastric cancer was first reported by Omori *et al.* (7). Since then, many RPLG techniques have been reported (11-18). Reports have described the feasibility of RPLG and the techniques in detail. The minimal invasiveness, associated postoperative pain, and cosmetic outcomes of RPLG are reported to be similar to those of conventional laparoscopic gastrectomy (CLG). Interestingly, Kawamura *et al.* (16) reported that the amount of oral intake during the early postoperative period in RPLG exceeds that in CLG.

Many reports have indicated that the grade of lymph node dissection in RPLG also does not differ from that in CLG. Although the prospect for radical cure is thought to be not inferior, no long-term studies have confirmed this prediction. Lee *et al.* (18) verified the non-inferiority of RPLG to CLG in an animal study; the incidences of inflammatory reactions and complications were similar to those in CLG. We anticipate that such results will soon be verified in clinical studies.

The application of RPLG to gastric cancer remains controversial, and critical comments have been made regarding this (19). The fourth edition of the Japanese gastric cancer guidelines (20) states that laparoscopic surgery for gastric cancer is an option for patients with stage I disease, although the long-term results of the JCOG0912 phase III and KLASS-01 trials are awaited (21-23). In such a situation, consensus is difficult to reach on the usefulness of RPS, which is technically more challenging. Moreover,

the benefit and effect of RPLG in comparison with those of CLG and open surgery should be discussed. Whether performing RPS requires special training and can be established as a standard operation remains to be elucidated.

The educational issue should also be considered for junior surgeons. Naturally, such an operation is technically difficult to perform from a single incision. Laparoscopic surgery requires the use of forceps, which restricts the view on the two-dimensional monitor and thus requires its own particular skill set. The degree of restriction is increased in RPS. Therefore, skilled surgeons who can perform laparoscopic surgery are needed (24). Generally, it is desirable that surgeons with adequate experience in ordinary laparoscopic gastric resection perform RPS as the next step.

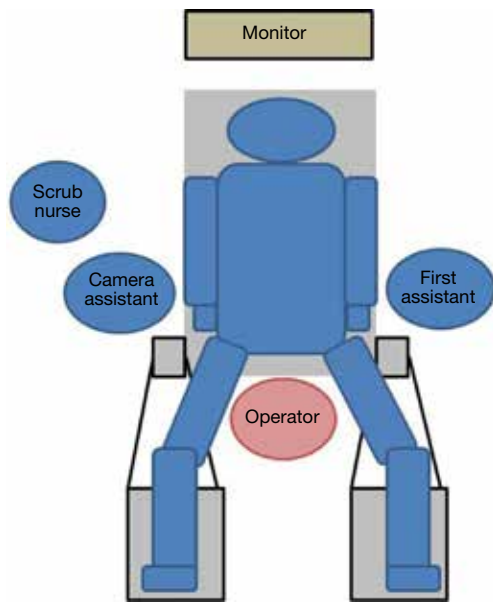
One of the technical solutions for the oncological and educational problems described earlier is the use of thinner forceps such as needle forceps, which are generally 3 mm or less in diameter (25,26). These needle forceps are useful for establishing the working angle in each procedure, which contributes to maintaining the quality of lymphadenectomy and reconstruction. They also keep the assistant motivated to participate in the operation by holding the needle forceps, which can contribute to the education of junior surgeons. Moreover, the cosmetic outcome and degree of invasiveness could be maintained even if these needle forceps are added.

Authors have also ranked RPS from standpoints other than the cosmetic outcome and degree of invasiveness. In physically small patients, the area of the abdominal cavity that receives the ports is small. If ports of conventional size and number are used, forceps interfere with each other; and as a result, the target angle needed to reach an organ is difficult to achieve.

In this case, if forceps are centralized in a single incision at the umbilicus, we have to resolve the problem of interference, but the target angle is easy to achieve. We overcome the problem by inserting a total of three needle forceps, one held in the operator's left hand, and two held in the assistant's two hands, from incisions other than those at the umbilicus. We have adopted the concept of needle-assisted surgery. The mobilization of internal organs and the procedure of lymph node dissection and reconstruction in gastric resection are performed as in CLG. Thus, the introduction of RPS seems to be relatively easy for the surgeon who is used to CLG.

## Indications

The indications for RPLG include early gastric cancer in patients who are slim and have little visceral fat. Patients



**Figure 2** Set-up and position in SILG: the surgeon stands between the patient's legs. SILG, single-incision laparoscopic gastrectomy.

with a belly wall area are also in this category. Specifically, the distance from the umbilicus to the xiphoid process of 15 cm or less and a BMI of 20 kg/m<sup>2</sup> or less are preferable. RPLG is also particularly appropriate for young women because of its cosmetic benefit (27). Some institutions consider advanced gastric cancer as an indication or do not take sex or physical condition into consideration when deciding whether RPLG should be indicated (28).

### Variation of the reduced-port laparoscopic gastrectomy (RPLG) procedure

RPLG includes SILG and various RPLG procedures, as it requires fewer ports or introducing a smaller port incision than that in CLG. The SILG and RPLG procedures that were introduced in the authors' institute are described herein by referring to published articles.

### Single-incision laparoscopic gastrectomy

SILG in this chapter refers to the procedure where only one small incision is made without any additional port, which we call "pure SILG." Reports on pure SILG (7,12-15,17,28-34) described its feasibility, cosmetic results, and minimal invasiveness. The feature of SILG is based on the concept of standardizing SILG in each institute.

### Set-up

The patient is placed supine in the dorsosacral position. The surgeon stands between the patient's legs, the camera assistant stands at the patient's right side, and the first assistant stands at the patient's left side. A monitor is placed above the patient's head (Figure 2). A 10-mm endoscope with a high-definition camera is preferred. A flexible endoscope is preferable than a rigid endoscope because its flexibility can prevent conflict between the forceps.

### Access device

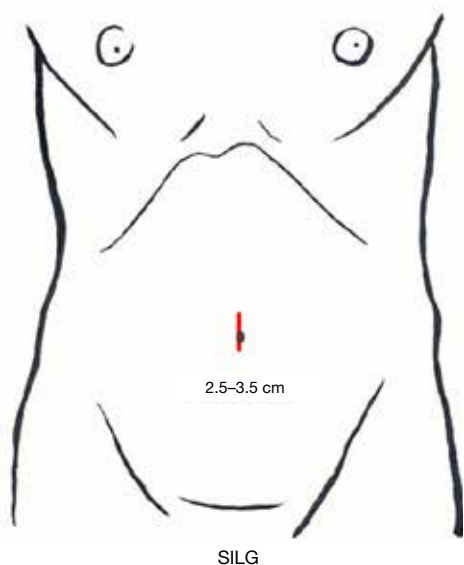
A 2.5- to 3.5-cm incision is made in the umbilicus (Figure 3). Different kinds of access device have been developed and commercialized, and are chosen according to the discretion of the surgeons' in each institute. The present authors use Lap-Protector (Hakko Co., Ltd., Nagano, Japan) for wound protection and EZ Access (Hakko Co., Ltd., Nagano, Japan), which can be assembled as an umbilical access device. Two 12- and 5-mm trocars each are inserted through the EZ Access device. By using a 10-mm, 30-degree endoscope, both the surgeon's and assistant's forceps are inserted through the respective trocars. The energy device, stapler, and gauze are inserted and removed through the 12-mm trocar (Figure 4). Four trocars are also generally inserted in previous reports.

### Liver retraction

Retraction of the left lobe of the liver is important for gastrectomy. It is simply performed with percutaneous stitching nylon thread or by using a penrose drain. The present authors use a 2-0 nylon thread and a medium-sized Silicon-disc (Hakko Co., Ltd., Nagano, Japan).

### Single-incision laparoscopic gastrectomy (SILG) procedure

Almost all procedures are performed in the same manner as those in CLG. The unique tips of the SILG are as follows: (I) the operating table is more tilted into the head-up position to gain the benefit of counter traction by gravity; (II) a curved instrument is frequently used to prevent the conflict between forceps; (III) an innovation that uses small clips, which are hanged with percutaneous thread and then retracted. Instead of organ traction by using forceps, each clip is used to grasp the tissue of the organ and create the working field. Thus, the technical quality of SILG is maintained so



**Figure 3** Skin incision in SILG: a 2.5 to 3.5-cm incision is made at the umbilicus. SILG, single-incision laparoscopic gastrectomy.



**Figure 4** Set-up of umbilical access device: two 12-mm trocars and two 5-mm trocars are inserted through the EZ access device.

as not to be inferior to RPLG or CLG. Reconstruction is also performed through a single incision. In this situation, stapling should be carefully executed. A 10-mm stapler is rather large for the access device, and assist forceps should be appropriately inserted. The present authors perform Roux-en-Y reconstruction after gastrectomy with the use of a linear stapler. The Y limb is created extracorporeally to shorten the execution time. Gastrojejunostomy is performed intracorporeally. We always choose side-to-side anastomosis by using a 60-mm linear stapler. The stapler entry hole is sutured intracorporeally. The 15-cm 3-0 V-Loc 180 (Covidien, Mansfield, MA, USA), a barbed suture material, is used for the suturing. This material prevents line slack during the suturing and does not require knotting, which facilitates

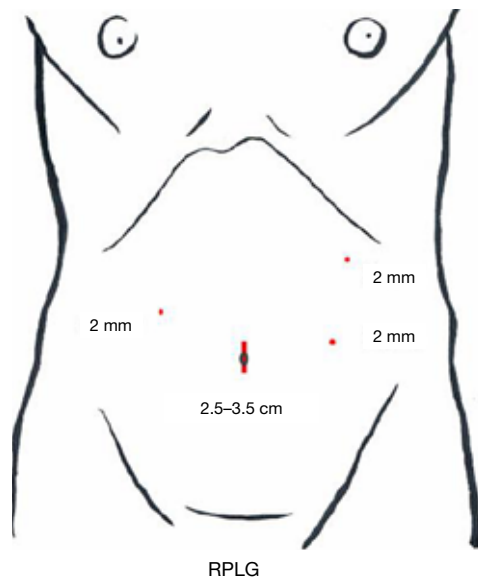


**Figure 5** Postoperative scar of SILG. SILG, single-incision laparoscopic gastrectomy.

laparoscopic suturing especially for SILG. Petersen's defect and the mesenteric space around the Y limb are also closed with a continuous barbed suture. Finally, the single umbilical opening is cosmetically closed with an appropriate buried suture, and the scar is generally invisible after 3 months (*Figure 5*).

### Reduced-port laparoscopic gastrectomy

The term RPLG can be applied to various procedures with various efforts to achieve minimal invasiveness. Many literatures indicated that RPLG procedures are comparable with CLG procedures (11,35-41). The present authors' concept of RPLG was derived from SILG. Sometimes, we encounter instrument conflicts at SILG and cannot maintain an adequate working angle. Additional ports should be inserted if necessary, but in a minimally invasive manner. We prefer to use the 2.1-mm-diameter BJ Needle forceps (NITTI-ON Co., Ltd., Chiba, Japan), not through an additional port, but via a dedicated puncture port (*Figure 6*). The tiny wound made by the BJ needle does not cause postoperative pain or an unsatisfactory cosmetic outcome (*Figure 7*). Even one additional BJ Needle in the surgeon's left hand is useful for obtaining the proper manipulation angle in the laparoscopic view. According to the authors' experience, a maximum of three additional BJ Needles, one in the surgeon's left hand and one each in the assistant's right and left hands, will create almost the same tissue traction as in conventional laparoscopic surgery. The authors named this standardized



**Figure 6** Skin incision in RPLG: a 3-cm incision is made at umbilicus and three puncture for needle forceps are made at lateral side. RPLG, reduced-port laparoscopic gastrectomy.

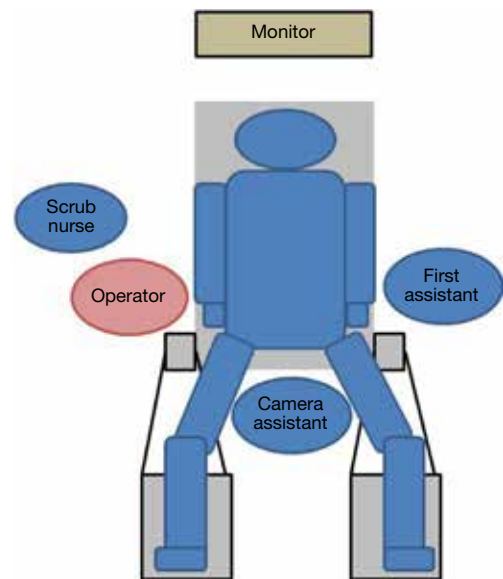


**Figure 7** Postoperative scar of RPLG. RPLG, reduced-port laparoscopic gastrectomy.

procedure “needle device-assisted single-incision laparoscopic gastrectomy (NA-SILG).”

#### Set-up

The set-up for NA-SILG is identical to that for SILG. The surgeon stands at the patient’s right side, the camera



**Figure 8** Set-up and position in RPLG: the surgeon stands at the patient’s right side. RPLG, reduced-port laparoscopic gastrectomy.

assistant stands between the patient’s legs, and the first assistant stands at the patient’s left side (*Figure 8*). The other equipment is placed as it is for SILG.

#### Access device

A 3-cm incision (a little smaller than the incision for SILG) is made at the umbilicus, and the Lap-Protector is used, with only two 12-mm trocars inserted through the EZ Access device. A 10-mm 30-degree endoscope and the surgeon’s right forceps are inserted through the respective trocars. The energy device, stapler, and gauze are inserted and removed through the 12-mm trocar. As additional punctures, a puncture for the 2.1-diameter BJ Needle forceps is made at the right lateral side of the abdomen for the operator’s left hand and two punctures are made at the left side for the assistant’s both hands (*Figure 9*).

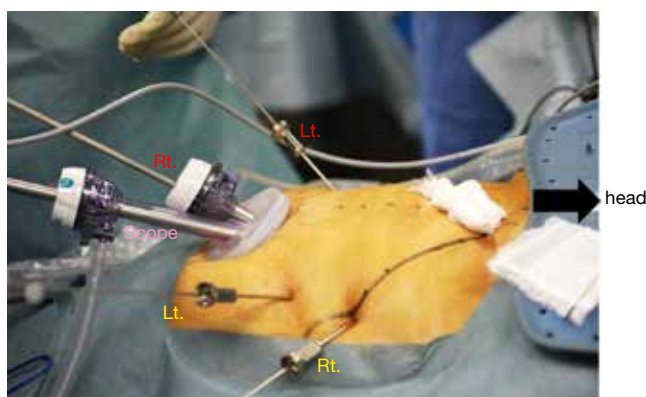
#### Liver retraction

The liver retraction procedure is performed in the same manner as in SILG.

#### Needle device-assisted single-incision laparoscopic gastrectomy (NA-SILG) procedure

Dissection and reconstruction are performed in the same





**Figure 9** Set-up of needle forceps: three needle forceps are added.

manner as in SILG. The difference is that the forceps in the operator's left hand are inserted via the patient's right abdomen, and the two forceps in the assistant's hands are inserted via the left abdomen. The same operative field attained in CLG is thereby attained in NA-SILG. The distance between the operator's two hands becomes comfortably wide, and a comfortable operating angle is obtained. The assistant performs the same procedure as in CLG. Thus, in NA-SILG, operators can easily master their roles, which can solve the educational problem in RPLG. The postoperative incisional pain and the incision required are minimal. The authors believe that the needle instruments are useful not only in single-incision surgery but also in facilitating RPS.

### Results in reduced-port laparoscopic gastrectomy (RPLG)

#### *Feasibility*

The feasibility of RPLG seems to be almost established in previous reports (7,11,14,17,25-43). The median operative time in previous reports was 241.9 minutes (range, 186–302 minutes). The complication rate ranged from 0% to 20.8%. Furthermore, the procedure was not associated with any mortality and conversion to open surgery. However, the operator of the procedure is limited to an elected surgeon and institute where CLG has already been established and standardized. Almost all patients who underwent RPS are also elected according to the surgeon's decision. That is, the possibility of selection bias should be taken into consideration in the interpretation of the results.

#### *Oncological validity*

So far, no report has described the long-term results concerning oncological validity. Predictive parameter may be the number of retrieved lymph nodes. In addition, that of previous reports was 36.5 (range, 24–66), which seemed to be comparable with that of CLG (7,11,14,17,25-43). The long-term results can be expected.

#### *Training and education*

The technical demand in RPLG is high (42). The preferable indications are early-stage cancer and slim patients, as described previously. However, surgeons in training would want to perform CLG for patients under the same indication as in the surgical training. That is, junior surgeons may lose their chance to assuming the role of operator. One solution is to standardize RPLG for many patients, including fat or advanced-stage cancer patients. In fact, introduction of thinner forceps as the needle device facilitates RPS, and junior surgeons can participate and assist during RPLG in the same way as they can in CLG.

### Discussion

As described earlier, the institutions that have reported on RPLG so far, including our facility, are those that have standardized CLG. Therefore, we can argue that RPLG cannot be introduced as easily as CLG. Moreover, because RPLG is regarded mainly for its cosmetic benefit, it will be interesting to determine how effective and ontologically valid the procedure is. Whether RPLG can be taught and mastered as well as CLG should also be investigated.

For future prospect, standardizing the RPLG technique, shortening the learning curve, and reducing the difficulty of the technique are important issues to be addressed. Developing a new device is warranted. Novel devices such as flexible forceps, forceps with flexible tips, and an oval access port (43) have been reported. Single-port devices for robot-assisted surgery have also been developed, and these devices are expected to improve the ease with which SILG is performed. However, the size and cost of the apparatus are still problematic. Certain robot-supporting technology will be indispensable for the breakthrough in RPS (44-48).

### Conclusions

RPLG for gastric cancer has been developed through



advances in technology and devices, and the technical issues have been overcome in the same way. Problems in feasibility, oncological validity, training, and education will be solved with various efforts. The short-term results reported in literatures are acceptable. Long-term results that verify positive results or radical cure even for cases of cancer have not yet been published; thus, patients indicated for RPLG should be selected carefully. Prospective multicenter studies should also be conducted to establish RPS as a truly evidence-based practice that addresses not only cosmesis but also the proper balance between minimal invasiveness and radical cure.

### Acknowledgements

None.

### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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# Laparoscopic splenic hilar lymphadenectomy for advanced gastric cancer

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**Abstract:** Laparoscopic distal gastrectomy has recently become accepted as a surgical option for early gastric cancer in the distal stomach, but laparoscopic total gastrectomy (LTG) has not become widespread because of technical difficulties of esophagojejunal anastomosis and splenic hilar lymphadenectomy. Splenic hilar lymphadenectomy should be employed in the treatment of advanced proximal gastric cancer to complete D2 dissection, but laparoscopically it is technically difficult even for skilled surgeons. Based on the evidence that prophylactic combined resection of spleen in total gastrectomy increased the risk of postoperative morbidity with no survival impact, surgeons have preferred laparoscopic spleen-preserving splenic hilar lymphadenectomy (LSPL) for advanced tumors without metastasis to splenic hilar nodes or invasion to the greater curvature of the stomach, and reports with LSPL have been increasing rather than LTG with splenectomy. In this paper, recent reports with laparoscopic splenic hilar lymphadenectomy were reviewed.

**Keywords:** Laparoscopic total gastrectomy (LTG); splenic hilar lymphadenectomy; advanced gastric cancer; spleen-preserving; splenectomy

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## Introduction

Laparoscopic distal gastrectomy (LDG) has become widespread as a treatment of early gastric cancer in the distal stomach especially in Eastern Asia with the short-term advantages such as less blood loss and prompter postoperative recovery (1). LDG has recently been applied to advanced gastric cancer, and several large-scale randomized controlled trials comparing open and laparoscopic distal gastrectomy for advanced gastric cancer in the distal stomach have been performed in Korea and Japan (2,3) to evaluate feasibility and long-term oncologic outcome of LDG. However, the use of laparoscopic total gastrectomy (LTG) remains limited because of the high technical demands of esophagojejunostomy (4-6) and

the complexity of lymphadenectomy at the splenic hilum (5,7,8-21). Because of the variation of the vascular anatomy in the splenic hilum and with the concern of pancreas-related complications, splenic hilar lymphadenectomy is technically challenging even for skilled surgeons. Based on the evidence that prophylactic combined resection of spleen in total gastrectomy increased the risk of postoperative morbidity (22,23) or had no survival benefit (24,25), surgeons have preferred laparoscopic spleen-preserving splenic hilar lymphadenectomy (LSPL) (8-19) rather than LTG with splenectomy (20,21). Since the first report by Hyung *et al.* (8) in 2008, the number of studies with acceptable feasibility of LSPL has increased (8-19). For further advanced cases, such as with metastasis to splenic hilar nodes or invasion to the greater curvature

of the stomach, or with direct invasion to distal pancreas, LTG with splenectomy, sometimes with combined resection of distal pancreas has been performed (19-21). In this paper, the recent reports of LTG with splenic hilar lymphadenectomy were reviewed.

### **Inclusion/exclusion criteria for the review**

For the review of laparoscopic splenic hilar lymphadenectomy, an English literature search was performed on the PubMed database using the terms “gastric cancer” AND “laparoscopic” AND “splenic hilar lymphadenectomy” along with their synonyms or abbreviations on December 23, 2015. Case series including less than 10 patients, or technical reports without surgical outcomes were excluded to keep the quality of the review. The endpoints were clinical indication, the length of the operation, blood loss, conversion, overall morbidity, mortality, length of the hospital stay, and number of harvested lymph nodes (in total and in the splenic hilum). As a result, 15 studies were included in this review. Tumor stage was classified according to the 7<sup>th</sup> edition of TNM classification (26). Postoperative complications were classified according to the Clavien-Dindo classification system (27).

### **Laparoscopic spleen-preserving splenic hilar lymphadenectomy (LSPL) (Table 1)**

Since Hyung *et al.* (8) firstly reported the initial case series of LSPL with the acceptable feasibility, the number of patients included in the following studies has increased. Some technical reports provided better anatomical understandings. We have proposed efficient lymphadenectomy technique with ‘medial approach’ (5) by identifying the membranous border between the perigastric tissue and the surface of the retroperitoneum. The concept following the perigastric fascias and the intrafascial space based on embryological and anatomical background was also helpful (11). Together with the technical progress, comparative study of laparoscopy-assisted total gastrectomy (LATG) with LSPL and open total gastrectomy for clinical T1-T2 tumors (9) was performed. Longer operation time, less blood loss, and earlier postoperative recovery were found in LATG with LSPL, which was consistent with the previous results of LDG (1). Gradually this operative procedure was applied to more advanced tumors (10-12,14-19), unless they had definite lymph node enlargement in the

splenic hilum or direct tumor invasion of the gastrosplenic ligament. Among the 13 studies with LSPL, the indication was up to T2 in three studies, and up to T3 in five and T4a in five studies, respectively. The overall morbidity rate was 6–19%, which was acceptable, but Lu *et al.* (15) revealed in the study with 325 cases, that BMI exceeding 25 kg/m<sup>2</sup>, tumor location in the greater curvature, and No.10 LN metastases were significantly associated with increased rates of major perioperative complications, and further consideration of optimal indication seemed required. Because there are anatomical variations in the splenic hilum, preoperative evaluation by three-dimensional (3D) CT angiography was helpful to accomplish LSPL safely (12,14,16,18). Kinoshita *et al.* (16) used integrated 3D anatomic simulation software, which was also helpful in enhancing the quality of surgery. Robotic approach might be also helpful in completing technically-demanding LSPL procedure with current laparoscopic instruments (13).

Regarding the surgical outcomes of LSPL among the 13 studies, the operation time and blood loss ranged from 162 to 359 minutes, and 18 to 201 g, respectively. The length of hospital stay ranged from 7 to 13 days. The mortality rate was extremely low, and with the low overall morbidity rate (6–19%), LSPL seemed technically feasible with acceptable short-term surgical outcome.

### **LTG with splenectomy (Tables 2,3)**

Because prophylactic combined resection of spleen increased the risk of postoperative morbidity (22,23) with no survival benefit (24,25) in open total gastrectomy, the reports on LTG with splenectomy were limited (19-21). There were only small case series so far. The indication was for advanced tumors such as T3-T4aN1-2 (19), or tumors invading the greater curvature of the upper third of the stomach, pancreatic parenchyma, or spleen (20), in which splenectomy was mandatory to accomplish R0 resection. These reports showed technical feasibility of this procedure, but the number of the patients included in the studies were limited. Further larger study is required for precise evaluation of this procedure.

### **Discussion**

Splenic hilar lymphadenectomy should be employed in the treatment of advanced proximal gastric cancer to complete D2 dissection, and LTG with LSPL or splenectomy are selected. Because combined splenectomy increased

Table 1 Laparoscopic spleen-preserving splenic hilar lymphadenectomy												
Author (ref)	Year	n	Clinical indication	Operation time (min)	Blood loss (g)	Conversion (%)	Morbidity <sup>b</sup> (%)	Mortality (%)	Hospital stay (days)	Harvested LNs (n)	Splenic hilar LNs (n)	Novelty
Hyung et al., (8)	2008	15	cT1–2, cN0–1	211	68	0	13.0 <sup>c</sup>	0	7.0	57.0	2.7	Novel technical report
Okabe et al., (7)	2010	53 <sup>a</sup>	Stage IA–IIIB	359	187	1.9	19.0	0	13.0	51.0	2.6	Laparoscopic medial approach technique
Guan et al., (9)	2013	41	cT1–2	236	104	2.4	4.9 <sup>c</sup>	0	9.7	23.0	1.1	Earlier recovery than open total gastrectomy
Mou et al., (10)	2013	12	Stage IIA–IIIC	268	150	0	0	0	9.4	24.0	4.8	Technically feasible for advanced cancer
Huang et al., (11)	2014	54	T2–3	162	42	0	9.3 <sup>c</sup>	0	10.3	40.0	3.0	Technically feasible following the perigastric fascia
Li et al., (12)	2014	108	T2–3	169	46	0	12.0 <sup>c</sup>	0	11.9	44.0	3.0	With multi-slice spiral CT angiography
Son et al., (13)	2014	58	T1b–T2	210	201	0	8.6	0	7.9	43.0	0.8	Robotic versus laparoscopic
Wang et al., (14)	2014	312	T2–T4a	174	50	NE	15.0 <sup>c</sup>	0	12.3	43.0	2.9	With 3-dimensional CT
Lu et al., (15)	2015	325	T2–T3	174 <sup>d</sup> , 224 <sup>e</sup>	NE	0	2.5 <sup>f</sup>	0.6	12.0 <sup>d</sup> , 20.0 <sup>e</sup>	NE	NE	Risk factors of perioperative complications

Table 1 (continued)

**Table 1** (continued)

Author (ref)	Year	n	Clinical indication	Operation time (min)	Blood loss (g)	Conversion (%)	Morbidity <sup>b</sup> (%)	Mortality (%)	Hospital stay (days)	Harvested LNs (n)	Splenic hilar LNs (n)	Novelty
Kinoshita et al., (16)	2015	20	Up to T3N1M0	318	18	0	0	0	8.0	43.0	2.0	With 3-dimensional anatomic simulation software
Wang et al., (17)	2015	16	T2-T4a	329	136	0	6.0	0	9.6	28.0	4.3	Technically feasible with omnibearing method
Zheng et al., (18)	2015	317	Up to T4a	175	54	NE	6.9 <sup>c</sup>	NE	12.0-13.0 <sup>g</sup>	40.0-44.0 <sup>g</sup>	2.5-3.0 <sup>g</sup>	Analysis of splenic hilar vascular anatomy
Usui et al., (19)	2015	159	T2-3, N0	339	106	0	0	0	8.4	40	1.3	In comparison with combined splenectomy

<sup>a</sup>, including cases with D1+ LN dissection; <sup>b</sup>, grade II or more by Clavien-Dindo classification; <sup>c</sup>, grade not mentioned; <sup>d</sup>, without major perioperative complications (n=310); <sup>e</sup>, with major perioperative complications (n=15); <sup>f</sup>, grade IIIa or higher; <sup>g</sup>, with subgroup analysis by variation of vascular anatomy; LN, lymph node; NE, not evaluated.

**Table 2** Laparoscopic total gastrectomy with splenectomy

Author (ref)	Year	n	Clinical indication	Operation time (min)	Blood loss (g)	Conversion (%)	Morbidity <sup>a</sup> (%)	Mortality (%)	Hospital stay (days)	Harvested LNs (n)	Splenic hilar, LNs (n)	Novelty
Nakata et al., (20)	2015	18	T1bN1-	388	45	0	33	0	12	51	NE	Technically feasible
Usui et al., (19)	2016	19 <sup>h</sup>	T3-T4a, N1-2	357	210	NE	0	0	14	41	2.4	Technically feasible

<sup>a</sup>, including cases with D1+ LN dissection; <sup>h</sup>, 12 cases were hand-assisted; LN, lymph node; NE, not evaluated.



**Table 3** Laparoscopic total gastrectomy with D2 lymphadenectomy

Author (ref)	Year	n	Clinical indication	Operation time (min)	Blood loss (g)	Conversion (%)	Morbidity <sup>a</sup> (%)	Mortality (%)	Hospital stay (days)	Harvested LNs (n)	Splenic hilar, LNs (n)	Novelty
Lee et al., (21)	2012	94 <sup>i</sup>	Up to T4aN1	230	150	0	18	0	7.4	61	NE	D2 lymphadenectomy feasible

<sup>a</sup>, including cases with D1+ LN dissection; <sup>i</sup>, 46 cases with spleen-preserving, and 48 cases with splenectomy; LN, lymph node; NE, not evaluated.

the risk of postoperative morbidity and mortality in randomized clinical trials and could not show survival benefit compared with spleen preservation (22-25), routine or prophylactic splenectomy is not recommended by National Comprehensive Cancer Network guidelines (28). Recently, a large, multicenter, randomized controlled trial with 505 patients comparing splenectomy with spleen preservation on the proximal gastric cancer was performed (29,30). Proximal gastric adenocarcinoma of T2-4/N0-2/M0 not invading the greater curvature was eligible, and splenectomy resulted in higher morbidity, larger blood loss, and no survival advantage. The 5-year overall survivals were 75.1% and 76.4% in the splenectomy and spleen-preserving arms respectively, and the non-inferiority of spleen preservation was confirmed. They concluded that prophylactic splenectomy should be avoided not only for operative safety but also for survival benefit.

Even with the evidence described above, further advanced tumors such as those with direct invasion of the gastrosplenic ligament, pancreatic parenchyma, or spleen need to be resected by total gastrectomy with splenectomy, sometimes with combined resection of distal pancreas. Laparoscopic resection of such advanced tumors is technically demanding because huge tumor prevents laparoscopic view, or handling of the tumor is sometimes difficult, and care must be taken not to manipulate the tumor. Technical improvement for better short-term outcomes and validation of oncological outcomes with longer follow-up data would be required.

LTG with LSPL has gradually become popular with acceptable surgical outcomes, but careful interpretation is required. These excellent surgical results were provided by laparoscopic expert surgeons. Even if prophylactic splenectomy was denied, D2 lymphadenectomy for advanced gastric cancer is still a standard (31) for advanced gastric cancer. LTG with LSPL is still technically difficult for many surgeons and cannot be a standard at this moment. Further technical progress or acceptance of more simplified concept of lymphadenectomy, such as 'D2-No.10' lymphadenectomy for some limited cases might be required for LTG to be a first choice for advanced gastric cancer.

## Conclusions

With the short-term advantage over open gastrectomy, laparoscopic gastrectomy has been applied not only in early but also advanced gastric cancer, or more complicated procedures such as LTG with LSPL or splenectomy.

With the development of laparoscopic devices, advanced knowledge of laparoscopic view, and accumulated technical experiences, such laparoscopic advanced surgery could be feasible in near future. And by overcoming a critical validation of oncological outcomes, it still has a chance to be a procedure of choice as a treatment for advanced gastric cancer.

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### Footnote

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# Laparoscopic D2 distal gastrectomy for advanced gastric cancer: a myth or a reality?

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Dr. Hu and associates (1) have published a randomized controlled trial (RCT) analyzing the safety and efficacy of radical laparoscopic and open distal gastrectomy (LG) with D2 lymphadenectomy for the treatment of advanced gastric cancer (AGC). The trial was conducted between September 2012 and December 2014 recruiting 1,056 patients with clinical stage T2-4N0-3M0. There were 528 patients in both groups. There were 15 experienced Chinese surgeons who participated in the RCT. The primary end points were morbidity and mortality within 30 postoperative days. The only complication that almost reached statistical significance in favor of open procedure was that of anastomotic leakage. Based on Clavien-Dindo classification, both groups were equivalent in their outcome. If one looks at the operating time, this was significantly longer in the laparoscopic group; however the blood loss was significantly less in the laparoscopic group. Postoperative variables such as time to first liquid intake and hospital stay favored the laparoscopic group but not by a large margin. The authors concluded that these results attest to the safety of LG with D2 lymphadenectomy for AGC by experienced gastric surgeons at high volume tertiary referral centers.

Like the above trial, a vast majority of gastric cancer surgeries in Japan and South Korea are performed at high-volume institutions, where at least 200 gastric cancer surgeries per annum are undertaken. In this

RCT, the eligibility criteria for surgeons performing either open or laparoscopic D2 gastrectomies were (I) surgeons selected from the members of the Chinese Laparoscopic Gastrointestinal Surgery Study (CLASS) group who have performed at least 50 distal gastrectomies with D2 lymphadenectomy; (II) have performed at least 300 gastrectomies for patients with AGC annually at each institute; and (III) were determined to be qualified surgeons by the CLASS academic committee on the basis of the evaluation of unedited videos of both their open and laparoscopic gastrectomy with D2 lymphadenectomy procedures. In contrast, the majority of gastric cancer surgeries in the United States are not necessarily performed in high volume centers and such stringent criteria for performing gastric resection in routine clinical settings are never applied. A “high volume” institution in the United States has been defined in some studies as an institution performing more than 15–20 gastrectomies per year (2,3). So the questions remain, (I) will Western surgeons ever be able to attain this sort of experience in gastric resection in their life time even if they are based at high volume tertiary centers; (II) is their training as thorough for performing gastric resection; and (III) will they be able to achieve the same results as their counterparts in the east in a short period of time? The answer to these questions is obviously no. This is evident by the fact, that despite the performance

of less extensive lymphadenectomies (i.e., either D1 or D1+) in the United States, surgical morbidity and mortality rates for gastric adenocarcinoma are generally much higher in the United States than in the east. Seoul National University Hospital performs almost 1,000 gastric cancer operations per year, and recently reported a morbidity rate of 18% and mortality rate of 0.5% (4). In a prospective, randomized trial from 24 Japanese institutions of D2 versus extended para-aortic lymphadenectomy, the morbidity rate was 20.9–28.1%, and the mortality rate was only 0.8% (5). In the United States, single institution series have reported morbidity rates following gastrectomy of up to 40% (6). A recent review of Medicare records found that over 80% of patients were operated on at centers that performed 20 or less gastrectomies per year, with inpatient mortality rates from 4.1–9.5% depending on comorbidities (3). One needs to remember that these statistics are for open and not for laparoscopic resection which is technically far more demanding. Therefore, one has to applaud the postoperative morbidity rates of this RCT (1) which is 15.2% in the LG group and 12.9% in open gastrectomy (OG) group. The mortality rate was 0.4% for LG and zero for the OG. These statistics will be very difficult to replicate by Western surgeons simply because of the far lower incidence of gastric cancer and therefore lack of experience with laparoscopic gastric surgery and D2 lymphadenectomy for AGC in their part of the world. Additionally, the incidence of gastric cancer has been steadily decreasing in the last 4 decades in most Western countries, Japan and USA which will further hamper gaining surgical experience in gastric surgery in the future (7). The lack of surgical experience has an important implication in gastric surgery because Wu *et al.* (8) have found that surgical morbidity and mortality rates decrease only after 200 radical gastric resections.

The second important issue is that of lymphadenectomy in particular D2 dissection. The two terminologies which are commonly used in gastric lymph node dissection are (I) non-compliance i.e., performance of less dissection than specified; and (II) contamination i.e., performance of more extensive dissection than specified. The compliance rates of D2 lymphadenectomy in the present RCT were very high; 99.4% for LG and 99.6% for OG. Therefore, there was hardly any violation of the set protocol. If we look at some of the statistics from the Netherland's RCT (9) for open D1 vs. D2 lymphadenectomy, non-compliance occurred in 84% of D1 and D2 cases. Furthermore, contamination occurred in 48% of the D1 and 52% of D2 cases. The results showed

substantial protocol violations by the surgical-pathologic teams due to extending or limiting lymphadenectomy; leading either to under treatment or over treatment in both the D1 and D2 groups and impacting both the short and long-term results. A recent Korean study (10) has suggested that at least 42 gastrectomies are required to improve lymphadenectomy skills and reduction in complications. This implies that the superior surgical results reported in this RCT for D2 gastrectomy are achieved as a result of a greater degree of technical expertise in gastric surgery through increased exposure over a prolonged period of time, a task which may not be attainable by the western surgeon even in high volume centers where the limited case load is shared by a number of gastric surgeons. To put this in perspective, most of the high volume centers in Japan, China and Korea are performing at least 200+ D2 gastrectomies per annum on a conservative estimate. It will take a western surgeon at least 10 years or even more to accumulate that sort of experience.

The foregoing discussion begs the questions: should the western surgeons continue to undertake laparoscopic D2 gastrectomy with limited training and expertise in this area? The answer to the above question is yes, provided (I) all the cases of AGC are referred to well established high volume gastric surgical centers; (II) the cases should be performed by a limited number of well-trained gastric surgeons who are proficient in both open and laparoscopic D2 gastric resections; (III) the surgeons with gastric surgery should undertake at least 6 months sabbatical to some well reputed high volume eastern gastric centers to undertake extensive training in gastric surgery followed by an objective evaluation of their skills akin to that expected of CLASS surgeons and (IV) lastly on their return to their home country, these surgeons should operate with a more senior gastric surgeon, with their results audited at monthly intervals to access their morbidity and mortality data. Certainly there is now ample evidence that D2 gastrectomy prolongs the survival of AGC and that laparoscopic surgery produces equivalent if not better results to open resection.

In the 21<sup>st</sup> century, it is hoped that national guidelines will be devised and implemented to improve the care of AGC patients. It is no longer acceptable, based on the data produced in the east, that a practicing general surgeon in a low volume "gastric resection center" should be permitted to continue to undertake occasional gastrectomy and less than D2 lymphadenectomy; even going so far as to say, that to do so, falls below a safe standard of care.

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## Footnote

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# Laparoscopic gastric cancer surgery results in reduced wound complication and overall morbidity

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Laparoscopy-assisted distal gastrectomy (LADG) was first introduced in 1994 by Dr. Kitano, and was rapidly adopted in Japan, Korea, and China, where gastric cancer remains an endemic disease. However, in other parts of the world, laparoscopic gastrectomy has been relatively unpopular as compared to laparoscopic surgery for other organs, such as colorectal cancer surgery, because lymph node dissection and reconstruction method are more complicated than other organ cancer surgery.

Recently, Kim and colleagues (1) of the Korean Laparoscopic Gastrointestinal Surgery Study (KLASS) Group reported the results of a multicenter randomized trial comparing short-term outcomes for patients with stage I gastric cancer that had LADG *vs.* open distal gastrectomy (ODG). It is the first large scale multicenter randomized controlled study, although its indications are limited to earlier staged (stage I) gastric cancer.

The current report by Kim *et al.* reports a different operative morbidity of 13.0% and 19.9% and similar mortality of 0.6% and 0.3% between laparoscopic and ODG, respectively. The overall complication rate was significantly lower in the LADG group; in particular, the wound complication rate of LADG group was lower than that of the ODG group (3.1% *vs.* 7.7%). On the other hand, the major local and systemic complication rates were similar between the two groups. LADG was also associated with a longer operation time, less blood loss, and a shorter length of hospital stay. Reoperations were required in eight (1.2%) and nine (1.5%) cases in LADG and ODG group, respectively, and 6 out of 612 (0.9%) cases of LADG

were converted to ODG during surgery. The multivariate risk factor analysis identified the operative approach and the number of comorbidities as independent risk factors for postoperative morbidity, whereas the pathologic stage and the extent of lymph node dissection had no significant influences on the development of postoperative complication.

The authors described well how they had ensured surgical quality control between investigator surgeons and institutions before patient enrollment. The eligible surgeons had to have performed over 50 cases each of LADG and ODG and each institution had to conduct over 80 cases annually. Two expert surgeons visited each site and assessed the surgeon's eligibility for participation. In addition, all of the participating surgeons thoroughly peer reviewed each other's unedited videos for the standardization and the quality control of the study. This study group realized that standardization of surgery is of utmost importance in the beginning of surgical clinical trial. However, the rate of the surgeons passing the assessment and whether the evaluators were few of the participating surgeons or an external expert are valuable information that was not mentioned in the report. Additionally, it would have been helpful to address the frequency of the unedited video reviews and whether they were solely for the standardization or for the improvement of surgical techniques. Moreover, since postoperative morbidity decreases with high-volume centers, details about the distribution of the recruited patients per surgeon/institution would have allowed for predictions about how the results would hold in community-based

surgical practices. The impressively low conversion rate of 0.9%, especially when compared to randomized controlled trials for colon cancers (2), seems to be attributable to the efforts dedicated to surgical quality control and the concentration of participating surgeons in few centralized hospitals.

Because this study is based on non-inferiority hypothesis of long-term survival; postoperative morbidity and mortality should be set as one of secondary endpoints as in other clinical laparoscopic surgery trials. However, the comparison of morbidity and mortality offers a valuable practical insight, especially if the long-term survival of the treatment group is similar to that of the control group (3). Myriads of minimally invasive gastric surgeons have been anticipating the report on this project, and the positive results are encouraging to many of us, despite the fact that the short-term results from a study that completed its patient recruitment in 2010 are a little overdue. As the authors mentioned, it is difficult to draw conclusions about whether a sufficient number of patients were included for the comparison of morbidity, as the statistical focus of this research was on the comparison of the long-term survival. Nevertheless, the rate of overall complication rate was significantly lower in the LADG group as compared to the ODG group. Although LADG did not decrease the rate of major abdominal and systemic complications, it significantly decreased the rate of wound related complications, as expected. The reduction in the rate of wound complications would presumably give rise to desirable secondary effects, such as cosmesis, less postoperative pain, earlier recovery, and enhanced quality of life, which are the primary advantages of LADG over ODG.

Although the study reports many positive results that were expected, it gives no conclusive answers about the safety of LADG, since most of the patients included in the study were of stage I gastric cancer. With the exception of South Korea and Japan, which has the national screening system established; 70% to 80% of the gastric cancer patients in the other parts of the world are diagnosed at advanced stages. Most surgical oncologists from China and from the Western world must employ the laparoscopic surgical tools for advanced cancer patients. Advanced gastric cancer surgery involves many unique technical implications: (I) the handling of bulky tumor exposed to serosa; (II) dissection of metastatic lymph nodes; (III) deep sitting nodes, such as 12a and 11p lymph node stations; (IV) total omentectomy; and (V) bleeding tendency. Nevertheless, the greatest advantage

of laparoscopic surgery—securing a magnified visual perspective for meticulous tissue dissection and vessel sealing of all sizes—still holds true for advanced gastric cancer surgery. Also, the technical advances in company-based laparoscope video system and the laparoscopic instrument (e.g., stapler or energy based device) has been gaining more and more momentum. Backed by the general advantages of laparoscopic surgery and the technical advances, a number of pioneer surgeons have been safely performing laparoscopic surgery in advanced gastric cancer patients. Fortunately, the KLASS group has launched and completed patient enrollment of a follow-up clinical trial (KLASS 02), which compares the short- and long-term results of laparoscopic cancer surgery in a set of advanced gastric cancer patients. The short-term results from KLASS 02 should shed light on most of the questions regarding the safety of laparoscopic surgery on advanced stage gastric cancer, and could furthermore elucidate benefits for complications that are not typically associated with stage I gastric cancer.

In conclusion, based on the high priority of this KLASS 01 RCT result, laparoscopic distal gastrectomy proves itself to be an evidence-based practice at least in stage I gastric cancer patients. The morbidity results from this study could provide a standard based on which future studies could evaluate their surgical qualities. Furthermore, it behooves all surgeons in the KLASS group to organize formalized education processes with the instrument companies and the study groups from other countries to train the new physicians all across the globe.

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### Footnote

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# Perspective of new techniques overcoming laparoscopic sentinel node biopsy for early gastric cancer

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*Comment on:* Lee CM, Park S, Park SH, *et al.* Sentinel Node Mapping Using a Fluorescent Dye and Visible Light During Laparoscopic Gastrectomy for Early Gastric Cancer: Result of a Prospective Study From a Single Institute. *Ann Surg* 2016. [Epub ahead of print].

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The modern standard curative procedure for early gastric cancers falling outside the indication parameters for endoscopic resection is laparoscope-assisted gastrectomy with lymph node dissection. Patients undergoing standard gastrectomy with lymph node dissection experience postgastrectomy symptoms. These symptoms often pose life-long problems for patients. Thus, lymph node dissection should be avoided to preserve the stomach, alleviate the aforementioned symptoms, and improve postoperative quality of life. At present, sentinel lymph node (SN) biopsy is the most reliable method for identification of node-negative cases.

A standard method of SN biopsy for early gastric cancer is combination mapping with technetium-99m-tin colloid and isosulfhan blue (1). However, blue dye deteriorates quickly, and radioactive colloids exhibit a shine through effect during gamma probe detection of hot nodes in the surgical field. We believe that combination mapping is not suitable for laparoscopic gastrectomy.

Lee *et al.* developed a new technique for SN mapping using a fluorescent dye and visible light for early gastric cancer that was published in *Annals of Surgery* (2). This fluorescein method is a totally new technique and is superior because of its low cost and because it is suitable for laparoscopic surgery. I am favorably inclined towards this paper because they described the decision process of the optimal setting of the mapping to the last detail. We developed the optimal setting for ICG fluorescent mapping

and also struggled through the decision process (3).

Unfortunately, this paper contains a regrettable point, that is the optimal timing of the judgment about the lymphatic basins and SNs. Lee *et al.* stated that the number of lymphatic basins was only one in all patients, but I think this was a false conclusion. This error may be caused by a misunderstanding of the SN concept, and the setting of the timing of judgment. Sentinel nodes are defined as the first draining nodes from the primary tumor. The definition of the “first node” is the node directly receiving the lymphatics from the tumor, not the node dyeing the fastest. The lymphatic flow of the stomach is complicated, and the direction of the lymphatics from the tumor is not the sole direction; often there are two or three directions. As a result, the number of SNs in early gastric cancer is generally five to eight nodes (1,3,4). The lymphatic basins are thought to be the primary lymphatic drainage area in each patient, and patients with gastric cancer often have two or three basins (1,3-5). The authors need to take sufficient time for detection of and decisions about the SNs and lymphatic basins, while dyeing all of the direct nodes. I am one of the individuals involved in the development of blue dye mapping for gastric cancer, and the optimal timing for the decision about the SNs in blue dye mapping was about 20 minutes after intraoperative endoscopic injection (4).

In recent years, one of the topics under discussion on SN mapping for gastric cancer has been ICG fluorescent mapping. We concluded that ICG fluorescent mapping is

feasible in both, open and laparoscopic surgery for early gastric cancer (3). The weaknesses of ICG fluorescent mapping are the need for laparoscopic equipment that can detect the ICG fluorescence, and the subjectivity of SN evaluation and potential secondary node contamination (3). In comparison with ICG fluorescent mapping, the advantage of the Fluorescein method developed by Lee *et al.* is that it does not need special expensive equipment. Nevertheless, the weakness of the subjectivity of SN evaluation is the same in both methods. This is a common problem in dye mapping. In ICG fluorescent mapping, one attempt to overcome this weakness is adopting new fluorescent agents with both, ICG fluorescence and colloid particle characteristics, such as liposomal ICG or nano-colloidal ICG (6,7). These agents detect only fluorescent SNs and not secondary nodes, and could potentially be useful in laparoscopic SN biopsy in cases of gastric cancer. For the fluorescein method, it will be necessary to develop a new agent having fluorescing equal to Fluorescein and exhibiting nano-colloidal performance. If such an agent is successfully developed, it may be used alone as a standard tracer instead of in combination with other SN mapping tracers.

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# Survival impact of the number of lymph node dissection on stage I–III node-negative gastric cancer

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It is well known that lymph node (LN) status is the most important prognostic factor in localized gastric adenocarcinoma (GC) (1–4). Curative resection including adequate lymphadenectomy provided the chance of a cure for stage I–III disease (1,4,5). Unfortunately, a subgroup of patients with node-negative GC who underwent radical surgery including extensive LN dissection still experiences tumor recurrence, distant metastasis and subsequently died from the disease (6,7). In the issue of *Annals of Surgery*, Jin *et al.* indicated that in node-negative GC patients undergoing curative intent surgery, T3/T4 tumors, presence of lymphovascular invasion and signet ring histology independently affected overall survival suggesting that these patients may benefit from more aggressive adjuvant therapies (8). However, it should be noted that recurrence rates were 8.4% and 10.5% in T1 and stage I GC, respectively and 35.0% and 37.5% in T4 and stage III cancer, respectively in their study. The median number of nodes examined for patients with recurrence was 14 (range, 6–22), which might result in the possibility of underestimation of nodal involvement and understaging. In addition, tumor recurrence rates did not differ regardless of the extent of lymphadenectomy or the total nodes examined. The overall 5-year survival rate was 53% for the whole cohort.

Our previous study has shown that there was no survival benefit of >15 nodes retrieved for patients with T1 node-negative GC; however, patients with T2–4 node-negative GC with extensive lymphadenectomy (>25 nodal dissection) had longer survival time than those with nodes retrieved <25 (6). The GC-specific 5-year survival rates

were 96.2%, 94.6%, and 97.9% in T1 tumor with the number of examined LN <15, 16–25 and >25, respectively (P=0.468). The overall 5-year survival rates were 74.0%, 81.9% and 84.4% for patients with T2, T3 and T4 node-negative GC, respectively. In contrast to the results of Jin *et al.*, our large-scale study (n=1,030) indicated that tumor size, tumor location, the number of nodal retrieval, T4 status, and presence of perineural invasion were prognostic factors for T1–T4 node-negative GC based on multivariate analysis (7). The extent of lymphadenectomy and the number of LNs retrieved might explain the great survival discrepancy between Jin's and our studies (7,8).

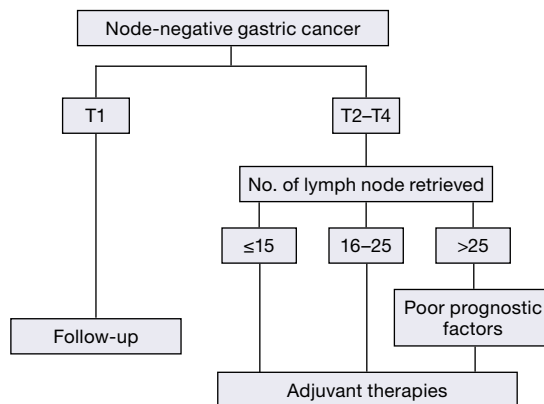
As T1 node-negative GC patients undergoing R0 resection had an excellent 5-year survival period and extremely low recurrence rates (7), we enrolled 448 T2–4 node-negative GC patients, who underwent radical resection (>10 nodes retrieved) without receiving neoadjuvant chemotherapy or postoperative irradiation therapy to identify determinants of tumor recurrence and to analyze the prognostic factors (6). Our results show that there was no significant difference in mean number of LN retrieved between GC patients without recurrence and with recurrence (26 *vs.* 24). The median follow-up time was 78.7 months. Recurrence was found in 85 patients (18.9%) in the whole cohort. Patients with T2, T3 and T4 tumor had recurrence rates of 8.6%, 12.5% and 26.5%. Tumor location, size, tumor invasion depth, and perineural invasion were associated with tumor recurrence and outcome. In contrast to our published article (6), Jin *et al.* included only 148 patients with T2–4 node-negative GC (n=148) and found that tumor recurrence



**Table 1** Comparison of studies by Hsu, Jin and Chou for node-negative gastric cancer patients undergoing surgery

Study	No. of patients	No. of T2–T4	Median No. of LN examined	Median follow-up time	5-year overall survival rates	Predictive factors for survival or recurrence
Hsu <i>et al.</i> (7)	1,030	T2: 149; T3: 71; T4: 307	G1: 11; G2: 20; G3: 32	78.0 months	T1: 96.3%; T2: 91.9%; T3: 92.2%; T4: 72.8%	Tumor size, location, No. of LN examined, T4 lesion, perineural invasion
Jin <i>et al.</i> (8)	317	T2: 44; T3: 64; T4: 40	No recurrence: 16; recurrence: 14	68.0 months	T1–T4: 53%	T-stage $\geq 3$ , lymphovascular invasion, signet ring cell subtype, >15 LN examined
Chou <i>et al.</i> (6)	448	T2: 139; T3: 64; T4: 225	No recurrence: 26*; recurrence: 24*	78.7 months	T2–T4: 84.3%	Tumor size, location, tumor invasion depth, perineural invasion

\*, mean; LN, lymph node; G1, No. of LN examined <15; G2, No. of LN examined, 16–25; G3, No. of LN examined >25.



**Figure 1** Treatment strategies for stage I–III node-negative gastric cancer patients after surgery.

rates were 9.1%, 29.7% and 35.0% in T2, T3 and T4 disease, respectively (8). The mean number of examined LN was 16 in patients with recurrence, which might result in inadequate lymphadenectomy in T2–T4 tumor and subsequently led to higher recurrence rates and worse survival time compared to our previous research (6). Furthermore, a limited sample size in Jin's study might make the statistical difference insignificant between T2–T4 GC patients with less (< D2) and extensive (> D2) lymphadenectomy. *Table 1* summarizes the key messages of node-negative GC studies by Hsu, Jin and Chou.

*Figure 1* showed treatment strategies for stage I–III node-negative GC patients who underwent gastrectomy plus D1/D2 lymphadenectomy. For patients with poor prognostic factors for recurrence, such as a large tumor size, tumor involving the whole stomach, T4 lesion,

presence of perineural invasion, and those with inadequate lymphadenectomy (<25 nodes retrieved for T2–T4 lesion), adjuvant therapies including chemotherapy and/or radiotherapy should be considered to improve patient outcome.

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### Footnote

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# Hybrid surgery for early gastric cancer

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**Abstract:** Endoscopic submucosal dissection (ESD) is the most suitable treatment option in terms of minimally invasive treatment for potential node-negative early gastric cancers (EGCs). Furthermore, making the resection area of the primary lesion as small as possible is ideal for the patient's quality of life, even for potential node-positive EGC. An endoluminal approach is a reasonable option with which to minimize stomach resection area, because this procedure can be accurately demarcated from the inside. From this point of view, endoscopic full-thickness resection (EFTR) may be optimal, while laparoscopic assistance would be more desirable to create a more secure procedure. However, hybrid EFTR for EGCs has two limitations, which must be solved. First, concerns regarding iatrogenic tumor seeding via transluminal communication between the inside and outside of the tract exist. The second limitation relates to the determination of lymphadenectomy. Conventional lymphadenectomy, which involves the removal of the majority of feeding arteries, can lead to necrosis of the remaining gastric wall. Therefore, the resection area of lymphadenectomy should also be carefully determined. To address these two problems, a non-exposed hybrid EFTR combined with sentinel node navigation surgery (SNNS) would be the most ideal method of minimally invasive surgery for EGCs.

**Keywords:** Minimally invasive gastrectomy; endoscopic full-thickness resection (EFTR); non-exposure method; hybrid surgery; sentinel node navigation surgery (SNNS)

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## Introduction

Surgical resection is the first choice of treatment for gastric cancer with a high likelihood of a successful cure. Local resection is an accepted method for potential node-negative resectable gastric cancers. Potential node-negative gastric cancers are early gastric cancers (EGCs), which have invaded the submucosal layers, and in such cases, an endoluminal approach can be applied. Histologically, intramucosal intestinal-type cancers irrespective of size; intramucosal intestinal-type cancers with ulcerative findings, which are  $\leq 3$  cm in size; submucosal intestinal-type cancers invading up to 500  $\mu$ m below the muscularis

mucosae; and intramucosal diffuse-type cancers, which are  $\leq 2$  cm in size, are considered as node-negative cancers (1,2) as long as the lesion can be resected in an en bloc fashion and has no angiolymphatic infiltration.

Endoscopic submucosal dissection (ESD) is an established endoscopic resection technique for EGCs (3-5), and many studies have demonstrated favorable and comparable outcomes for ESD (6,7). While a randomized controlled trial is yet to be published, which directly compares ESD and surgery; it is clearly evident that ESD, which does not leave scars and can preserve the entire stomach, is likely to be far more superior to surgery in terms of the patient's quality of life.

In contrast, potential node-positive EGCs include cancers that extensively invade the submucosal layer and must be resected in a full-thickness fashion to achieve secure en bloc resection. Furthermore, the treatment of potential node-positive EGCs should involve prophylactic dissection of lymph nodes where cancer cells might have metastasized. In this situation, laparoscopic assistance is required to perform a safe and secure resection. Here, we review of the current use of hybrid gastrectomy for EGCs and local lymphadenectomy and discuss its future perspectives.

### Endoscopic full-thickness resection (EFTR) with laparoscopic assistance

With the emergence of natural orifice transluminal surgery (NOTES), laparoscopy-assisted EFTR became known as hybrid NOTES to differentiate this procedure from pure NOTES, which simply refers to endoscopic surgery without laparoscopic involvement (8-12). As pure NOTES is recognized as an advanced and challenging technique, particularly with regard to a transgastric approach that lacks the accessibility and reliability of an endoscopic closure method, the term hybrid NOTES is also uncommonly used. Nowadays, collaborative surgery, using both flexible endoscopy and rigid laparoscopy, is utilized in laparoscopic and endoscopic cooperative surgery (13) or in combined endoscopic and laparoscopic surgery (14).

EFTR with laparoscopic assistance for EGCs has been applied since the late 2000s. Abe *et al.* (15) reported the use of this procedure for an undifferentiated-type intramucosal cancer using the term laparoscopy-assisted EFTR. During this procedure, demarcation of the lesion and mucosal markings is performed by endoscopic observation, followed by endoscopic circumferential submucosal injection and ultimately, circumferential endoscopic mucosal incision. Subsequently, intentional perforation is executed on the exposed muscular layer and full-thickness resection is endoscopically performed under laparoscopic countertraction. After perorally or percutaneously retrieving the tumor, the full-thickness defect is then laparoscopically sutured. Park *et al.* (16) also demonstrated the feasibility of hybrid NOTES for EGC, which was simultaneously performed with laparoscopic colectomy. Cho *et al.* (17) further reported a case series of hybrid NOTES in which the surrounding lymph nodes were dissected.

Although EFTR with laparoscopic assistance is attractive with respect to organ preservation, avoidance of post-operative complications, and maintenance of the patient's

quality of life, there remains an inevitable concern with regard to iatrogenic tumor seeding. By opening the gastric lumen during endoscopic intentional perforation and successive full-thickness resection, tumor cells floating in the gastric juice might be spread via spillage of the stomach contents or via transportation from the exposed surface of the primary lesion to the peritoneum by contact with laparoscopic instruments. Han *et al.* (18) observed tumor cells floating in approximately 15% of stomachs with EGCs. Hence, EFTR, which requires opening of the stomach, should not be deployed during the resection of epithelial neoplasms, which are exposed on the mucosal surface, or when patients possess subepithelial tumors (SETs) with ulcerative findings. In practice, the indication for EFTR with laparoscopic assistance is limited to SETs without ulceration.

### Non-exposure techniques for full-thickness resection

To expand the indication of EFTR methods for cancers without the concern of iatrogenic dissemination by intentional perforation during the procedure, physicians have explored the use of non-exposure techniques for full-thickness resection. Laparoscopic wedge resection is a simple and reliable method. However, an unexpectedly large area has to be resected to achieve a secure R0 resection because demarcation of the lesion cannot be visualized from the outside of the lumen. Moreover, wedge resection using laparoscopic linear staplers leads to severe deformity of the remaining stomach, which might reduce the patient's quality of life in terms of food intake.

To minimize resection area during laparoscopic wedge resection, Inoue *et al.* (19) proposed the use of non-exposed full-thickness resection after seromuscular incision and referred to this as the combination of laparoscopic and endoscopic approaches to neoplasia with non-exposure technique (CLEAN-NET). In this technique, the full layers, including the lesion, are pulled to the peritoneal side after circumferential seromuscular incision and are resected using a linear stapler in the stretched mucosal or full layers. Prior to seromuscular incision, transluminal markings, which can be visible from the outside, are endoscopically made with the aid of a needle knife. Several transluminal sutures are then placed around the lesion to avoid dissociation of the layers. CLEAN-NET is technically accessible, but might become difficult depending on the location of the target lesion, e.g., the posterior wall of the upper third of the

gastric body or fornix.

An ideal specimen that is resected by full-thickness resection would be an optimally demarcated full-layered resection without dissociation between the mucosal and serosal layers. To develop the non-exposure EFTR method, Goto *et al.* (20-22) proposed the use of non-exposed endoscopic wall-inversion surgery (NEWS). In this procedure, first, the resection area is first endoscopically demarcated with mucosal markings, followed by serosal markings under endoscopic navigation. Second, a circumferential seromuscular incision is laparoscopically performed, followed by endoscopic submucosal injection. Third, seromuscular layers are linearly sutured, with the lesion inverted into the inside. Finally, a muco-submucosal incision is endoscopically made, and the resected lesion is transorally retrieved. Using this technique, both mucosal and serosal planes can be optimally resected under direct visualization by endoscopy or laparoscopy. Although several issues need to be addressed, e.g., the technique requires skillful endoscopists and laparoscopists and is time consuming, this methodology is considered to be promising and is expected to develop as an ideal minimally invasive surgical procedure for EGCs in combination with sentinel node navigation surgery (SNNS) as mentioned later (23,24).

Furthermore, other non-exposure methods have been introduced in animal models. For example, Kim *et al.* (25) demonstrated feasibility of the NEWS technique without seromuscular incision to omit a technically challenging phase in laparoscopy. This method may be simpler compared with NEWS, although the serosal area cannot be optimally demarcated and it is difficult to identify a suitable line to be cut at the phase of endoscopic resection for inverted lesion. It is clear that each procedure has its own pros and cons, and thus, further investigations are required to establish the method that is more accessible and clinically oriented.

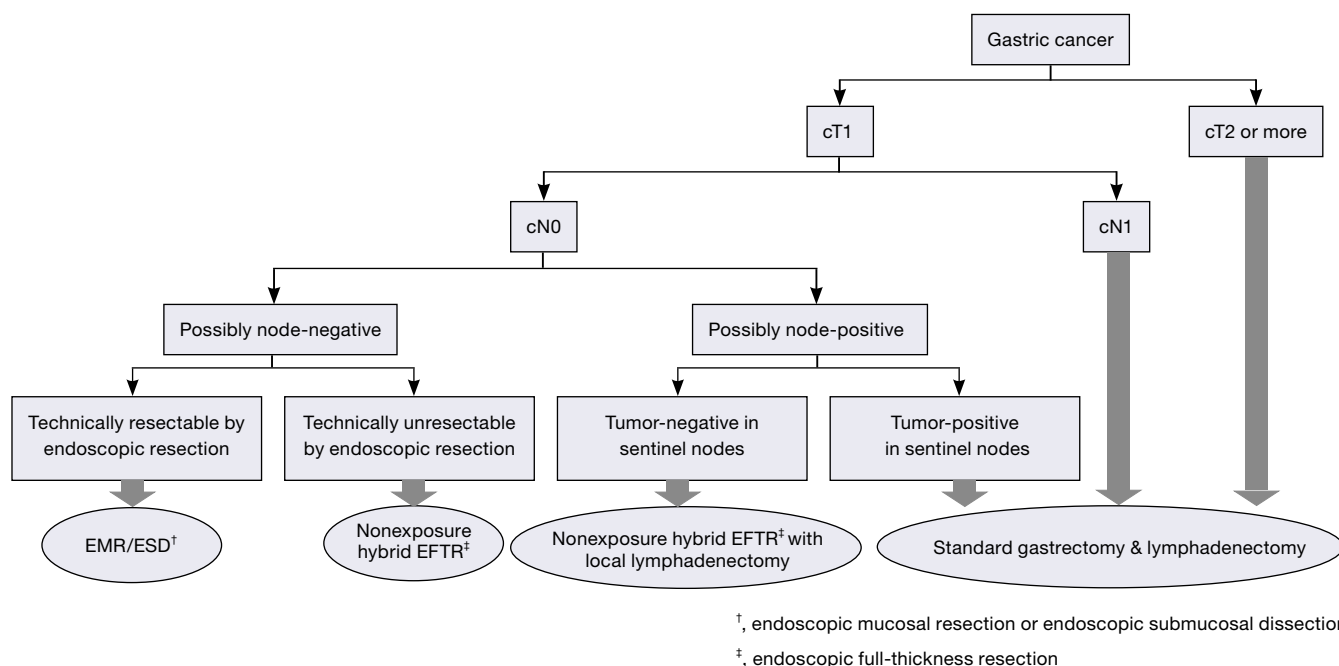
Another advantage of the non-exposure method is that direct thermal damage of the serosal plane can be avoided. In pure EFTR, intentional perforation followed by seromuscular incision requires thermal effects, which can lead to unexpected damage of the organs outside of the stomach. In contrast to non-exposed EFTR, endoscopic intervention by electrocautery devices does not affect the extra-luminal space. From this point of view, non-exposed EFTR without laparoscopic assistance has also been developed. Schmidt *et al.* (26) introduced EFTR after lesion inversion by endoscopic suturing using a specially designed endoscopic suturing device. These authors successfully

demonstrated the feasibility of this method for SETs in a small cases series. Takizawa *et al.* (27) further proposed the use of non-exposed EFTR using a sole flexible endoscope along with some commercially available devices by creating a circler mucosal tunnel around the lesion. Although these procedures are still unestablished, they may still become a promising, safe, and less-invasive method for endoluminal surgery.

### Local lymphadenectomy

For treating cancers, non-exposed EFTR techniques would be appropriate for primary lesions to prevent possible tumor seeding. However, if these techniques are applied to patients, the indication for use is limited to only potential node-negative EGCs because no lymphadenectomy is considered. Because potential node-negative EGCs can be applied to ESD, the indication of EFTR is more restricted to potential node-negative EGCs that are technically difficult to resect by ESD, e.g., EGCs located at the gastric fundus or on the greater curvature at the upper third of the gastric body, or EGCs with severe scarring. To expand the indications for non-exposed EFTR to potential node-positive EGCs, lymphadenectomy should be involved. However, standard lymphadenectomy might cause ischemia and necrosis of the remaining stomach because many lymph nodes lie alongside the major feeder arteries toward the stomach, and standard lymphadenectomy invariably involves the dissection of almost all feeders. Therefore, to perform local resection for potential node-positive cancers, the area of lymphadenectomy should also be localized and as many vessels as possible should be saved.

Regional lymphadenectomy can be an option to minimize the area of lymph node dissection. Seto *et al.* (28) proposed laparoscopic local resection combined with regional lymphadenectomy as a curative treatment option in a previous pilot study. Abe *et al.* (29) further introduced ESD followed by regional lymphadenectomy for EGC in which histological assessment revealed unexpectedly large undifferentiated cancer following ESD. In 2008, these authors proposed the use of hybrid EFTR followed by regional lymphadenectomy for potential node-positive EGCs (15). Cho *et al.* (17) further demonstrated the feasibility of the same method in 2011. Because there were no recurrences in these earlier reports, it appears that regional lymphadenectomy combined with local resection for a primary tumor appears to be acceptable, although large-scale assessments and long-term assessments are



**Figure 1** Advanced surgical approaches for gastric cancers.

urgently required.

However, there is no theoretical or statistical verification for the concept of regional lymphadenectomy. The area of regional lymph nodes for each type of cancer is empirically determined as the neighboring lymph node basin of the primary lesion. However, the precise location of the regional lymph basin receiving lymphatic flow from a tumor is difficult to accurately determine because the lymphatic network surrounding the stomach is complicated. In this regard, the sentinel node (SN) concept is likely to be more useful (30). If SN, which represents the first drainage lymph node from the primary tumor, is found to be negative for cancerous cells, then it can be safely considered that no further metastases exist within the other lymph nodes. Lymphatic flow can be visualized by injecting a stained solution containing indocyanine green into the submucosal layer surrounding the lesion, and subsequently SNs are identified as lymph nodes that have been stained green or have shown radioactive accumulation by preoperatively injecting radioactive materials into the submucosal layer.

By proving that SNs are cancer free, the area of prophylactic lymphadenectomy can be readily minimized. Kitagawa *et al.* (31) aimed to validate the SN concept by investigating the distribution of SNs and tumor-positive lymph nodes in patients undergoing standard gastrectomy and conventional lymphadenectomy after intraoperatively

investigating SNs and demonstrated the favorable diagnostic accuracy of lymph node metastasis using SN investigation.

After this study, we have started SNNS for EGCs, which are cT1N0M0,  $\leq 4$  cm in size, single lesion, and have not received any prior treatment. This technique is now offered by the Japanese government as a highly advanced medical treatment. Future studies will report regarding the clinical outcomes of this procedure.

### Future perspectives

A flowchart depicting the advanced surgical approaches for gastric cancer is shown in *Figure 1*. Hybridization of endoscopy and laparoscopy has become established as less-invasive local resection for primary tumors. Furthermore, the combination of hybrid EFTR and local lymphadenectomy represents a useful curative treatment option for potential node-positive EGCs. In the current situation, the hybridization of non-exposed EFTR, e.g., NEWS and SNNS, would represent an ideal minimally invasive form of gastrectomy that can preserve function (24). However, there is still room for the development of both hybrid EFTR techniques and restricted lymphadenectomy concepts. The confirmation of favorable long-term survival is still required for the use of EFTR for primary lesion as along with the simplification and dissemination of these exciting



procedures. Even in restricted lymphadenectomy navigated by the SN concept, the confirmation of long-term outcome in a large number of cases is still required to promote this new technique. Further investigations are vital if we are to establish the routine use of hybrid surgery for EGCs.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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# Neoadjuvant chemotherapy for locally advanced gastric cancer: the surgeon's role

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**Abstract:** In Western countries gastric cancer is commonly diagnosed in locally advanced stages. Although locally advanced gastric cancer is still a potentially curable disease, the prognosis is poor and surgery as first approach does not represent the best option. In order to improve survival, today the management of locally advanced gastric cancer is based on a multimodal treatment, including surgery with extended lymphadenectomy and effective chemotherapeutic schedules. The multimodal approach in gastric cancer aims to provide successful combination and cooperation between surgery and medical treatment: today there is current evidence supporting the use of systemic chemotherapy in a perioperative setting. The role of chemotherapy in gastric cancer is constantly evolving in order to improve outcomes and to reduce therapy-associated toxicity. In this paper we analyze the multidisciplinary approach in the treatment of locally advanced gastric cancer, particularly focusing on the surgeon's role in this setting.

**Keywords:** Adjuvant therapy; chemotherapy; gastric cancer; multimodal treatment; neoadjuvant therapy

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## Introduction

Despite incidence and mortality are decreasing, gastric cancer is the 5<sup>th</sup> most common malignancy diagnosed worldwide and the second leading cause of cancer related death. In Western countries over the past decades, a decline in the incidence of distal stomach cancers was observed, whereas the incidence of the lower esophagus and the gastroesophageal junction adenocarcinomas is still increasing (1,2). The 5-year relative survival for gastric cancer (all stages) is 20% to 25% with a median survival of about 24 months (3,4).

In most cases early-stage gastric cancer is curable by surgical treatment alone, with a 5-year overall survival (OS) rate of 90%. Unfortunately, in the Western world more than half of patients with gastric cancer are diagnosed in locally advanced stages (T3-4 or N+ gastric cancers) (5) and for these patients surgery as first approach does not represent the best option in the management of their disease. Although locally advanced gastric cancer without

distant metastasis is still a potentially curable disease, the prognosis is poorer than in early stage disease. The survival outcome of locally advanced tumors is decreased by high unresectability rate at presentation and by high recurrence rate even after radical surgery (6,7).

In order to improve these results, two main strategies were diffused in the management of locally advanced gastric cancer: the extended lymphadenectomy (8,9), and the application of new effective postoperative chemotherapeutic schedules (10,11). Despite these “surgical and medical efforts”, prognosis still remains unacceptable for patients with advanced disease (8,10,11). Hence, the rationale of the neoadjuvant approach in gastric cancer aims to provide successful combination and cooperation between surgery and medical treatment. Today there is current evidence supporting the use of systemic chemotherapy in a perioperative setting (before and after surgery), and the role of chemotherapy in gastric cancer is constantly evolving to improve outcomes and to reduce therapy-associated toxicity.

The data used in this review were identified by searches made on MEDLINE, Current Contents, PubMed, and other references taken from relevant original articles (on prospective and retrospective studies) treating about surgery and multimodal treatment for locally advanced gastric cancer.

Only papers published in English until December 2014 were selected. Data from ongoing studies were obtained in December 2014, from the trials registry of the U.S. National Institutes of Health (<http://www.clinicaltrials.gov>). The citations list was presented according to evidence based relevance (i.e., randomized controlled trials, prospective studies, retrospective series).

### Multimodal treatment

In the field of multimodal treatment for gastric cancer there are different possible approaches that vary geographically (12): European clinicians, on the basis of the results of the MAGIC trial (13) and of the French FNCLCC trial (14), are in favor of a perioperative chemotherapy; on the contrary in the U.S., according to the results of the Intergroup 0116 trial (10), patients are treated initially with surgery followed by adjuvant chemoradiotherapy; finally, adjuvant chemotherapy alone after radical surgery is the preferred option in Japan (11).

Historically the first prospective randomized trial demonstrating a survival benefit of postoperative chemoradiation over surgery alone in advanced gastric cancer was the SWOG/Intergroup 0116 trial (10). This study could show an increased 3-year OS with chemoradiation compared to surgery alone from 41% to 50% ( $P=0.005$ ). However, it must be notice that in this trial, 54% of patients underwent a limited lymphadenectomy (less than D1), whereas only 10% of patients received an extended D2 lymphadenectomy. Therefore, the administered chemoradiation seemed to primarily reduce loco-regional recurrence, improving survival, by adjusting an inadequate/incomplete surgery (15). In addition, no survival difference between the two treatment arms was demonstrable if considering only a subgroup of patients with D2 lymphadenectomy. Another trial investigated the role of postoperative chemo-radiotherapy in patients with extended D2 lymphnode dissection: the ARTIST trial (16) showed that the addition of radiotherapy to the adjuvant chemotherapy with capecitabine and cisplatin did not significantly reduce recurrence. A subgroup analysis revealed that the adjunct of radiotherapy increased disease

free survival in gastric cancer patients with lymphnode metastasis, therefore a subsequent trial (ARTIST II) is ongoing for the study of patients with lymphnode-positive gastric cancer (17).

A large randomized trial in Japan (11) compared adjuvant oral chemotherapy with S-1 to surgery alone, and in this case in both treatment arms a D2 lymphadenectomy was performed. Five hundred and twenty-nine patients received an oral chemotherapy (fluoropyrimidine S-1) over 1 year after surgery, and 530 patients were treated only with surgery. With a reduced risk of nodal and peritoneal recurrences, the 3-year survival was significantly higher in the adjuvant chemotherapy group ( $P=0.003$ ). Similar results, even if not so evident, were confirmed in the CLASSIC trial: patients with stage II-III B gastric cancer who underwent curative gastrectomy (D2 lymphadenectomy) were randomized to surgery alone or postoperative chemotherapy with capecitabine and oxaliplatin (XELOX). The 3-year disease free survival rate was 74% in the adjuvant chemotherapy group and 59% in the surgery alone group [hazard ratio (HR)=0.56;  $P<0.0001$ ] (18).

In this variety of results, and even if some questions remain open, in Europe the standard multimodal treatment for locally advanced gastric cancer is the perioperative chemotherapy. All advantages of preoperative neoadjuvant chemotherapy emerged by several European randomized phase-III clinical trials: MAGIC, FFCD9703, EORTC 40954 (13,14,19).

In particular, the effectiveness and the superiority of surgery associated to perioperative chemotherapy, compared to surgery alone, were shown in two randomized phase-III studies (MAGIC and FFCD9703). In the MAGIC trial (13) 503 patients with potentially resectable gastric cancer were randomly assigned to perioperative chemotherapy [both preoperative and postoperative with cisplatin, epirubicin and 5-fluorouracil (5-FU)] *vs.* surgery alone. The results evidenced statistically significant differences in progression free survival [HR=0.66; 95% confidence interval (CI): 0.53-0.81] and in OS (HR=0.75; 95% CI: 0.60-0.93; 5-year OS 36% *vs.* 23%) in favor of the perioperative chemotherapy arm. Moreover, downstaging (documented by low serosal invasion and low nodal involvement rate) and complete surgical resections (R0) were increased after neoadjuvant chemotherapy. In the two groups the incidence of postoperative complications, mortality rates and hospital stay were similar.

In the FFCD9703 trial (14), 224 patients with resectable adenocarcinoma of the lower esophagus, gastroesophageal

junction or stomach were randomized to either perioperative chemotherapy (cisplatin and 5-FU) plus surgery or surgery alone. In the multimodal treatment arm there were significantly increased curative resection (84% *vs.* 74%;  $P=0.04$ ), disease free survival (5-year rate: 34% *vs.* 19%;  $P=0.003$ ) and OS (5-year rate: 38% *vs.* 24%;  $P=0.02$ ) rates.

However, both studies have been criticized: the recruitment period of 8 years each was considered too long, both trials included also esophageal cancers, the preoperative staging was insufficient, the surgical quality was low with suboptimal lymphadenectomy, and there was a low completion rate of the postoperative treatment. Moreover, in both studies neither a clinical, nor a histopathological evaluation of the response to chemotherapy was performed.

A new study, the EORTC 40954 (19), has been designed to overcome the criticism of the previous trials; however, this study was stopped for slow patients recruitment, it could almost confirm the same short-term results as the other two trials, failing to show a survival benefit for the perioperative chemotherapy arm. The low sample size might explain the lack of survival benefit after perioperative chemotherapy observed in this trial.

The topic of a neoadjuvant/perioperative approach in the multimodal treatment of advanced gastric cancer is today still of great interest and many phase-III randomized clinical trials are ongoing focusing on this issue. Aiming to provide further data related to open problems in the management of advanced gastric cancer, following trials are ongoing today: MAGIC B (United Kingdom National Cancer Research Institute ST03 trial—started in 2007) (20), JCOG 0501 (Japan Clinical Oncology Group Study trial—started in 2005) (21) CRITICS (Dutch Colorectal Cancer Group trial—started in 2006) (22) and PRODIGY (Korean trial—started in 2012) (23).

In our institution, we were involved in the multicentric randomized phase III study ITACA-S 2 that compared the efficacy of a perioperative *vs.* a postoperative chemotherapy or chemo-radiotherapy, in patients with resectable gastric cancer (24). However, this study was stopped for low recruitment, and now we are randomizing patients in a new phase II trial [IRST 151.01 trial: study of preoperative or perioperative docetaxel, oxaliplatin, capecitabine (Dox) regimen in patients with locally advanced resectable gastric cancer (Gastro DOC)] (25). This randomized trial compares perioperative chemotherapy (two cycles Dox followed by surgery followed by other two cycles Dox) *vs.* preoperative chemotherapy (four cycles Dox followed by surgery).

Also several meta-analysis aimed to assess the

effectiveness of neoadjuvant chemotherapy in locally advanced gastric cancer analyzing the results of previous clinical trials, but with unclear results. Whereas He (26) failed to show the benefit of neoadjuvant chemotherapy in OS, Li's study (27) demonstrated a minor but significant benefit in patients' survival. This latter result coincided with another meta-analysis by Ge *et al.* (28) that showed that 5-FU-based neoadjuvant chemotherapy has a benefit on the OS of gastroesophageal and gastric cancer patients.

Regardless of the over mentioned published data, a perioperative chemotherapy seems to have many theoretical advantages. This induces European clinicians to prefer this approach in the management of locally advanced gastric cancer.

- (I) Chemotherapeutic regimens administered before surgery can be stronger and more intensive, because of a better general condition of the patient before the surgical intervention;
- (II) Before surgery there is no surgical alteration of blood and lymphatic vessels, that negatively affects the flow of chemotherapeutic molecules toward the tumor region (important for the chemotherapy-induced cell kill);
- (III) The administration of an early chemotherapy could act earlier on micrometastases (29);
- (IV) Neoadjuvant chemotherapy may reduce also the contamination of the abdominal cavity by free tumor cells during surgical manipulation;
- (V) The downsizing and the downstaging of the tumor after neoadjuvant chemotherapy, allow to achieve increased rates of R0 resections (30,31);
- (VI) Neoadjuvant chemotherapy could be seen as an "*in vivo* test" evaluating the applied therapy, and allows consequently to modify the postoperative therapy, according to the individual pathological response (32).

The administration of chemotherapy will be obviously delayed if the first step, in the multimodal approach for advanced gastric cancer, is surgery; this fact has several implication and may affect survival: first of all, micrometastases could evolve to macrometastases if not promptly treated; moreover after surgery the chemotherapeutic dose may be necessarily reduced because the patient is not fit anymore to tolerate a full dose (especially in case of postoperative complications). On the other hand, in the perioperative setting, some surgeon argue that chemotherapy-induced toxicity may lead to increased surgical complications (19,33). In addition, disease progression during neoadjuvant chemotherapy is

another potential trouble for patients who may lose the opportunity for surgery. With respect to point (VI), it must be considered that patients with a good response to chemotherapy, have a significantly improved prognosis, compared to non-responding patients (34). Pathological response is a late assessable parameter, however, an earlier evaluation might be obtained by the analysis of the metabolic response to chemotherapy. The possibility of a reliable early response evaluation and a response prediction seems to represent a very challenging issue (34-39).

### The surgeon's role

Even today, in the era of multimodal approach for locally advanced gastric cancer, the surgeon plays a central role in the management of these diseases. In a real and effective multidisciplinary setting, surgical choices and surgical actions are strongly related to other medical treatments like perioperative chemotherapy. This relation between surgical and medical aspects comes out in all steps of the management of locally advanced gastric cancer: (I) before surgery, (II) during surgery and (III) after surgery.

(I) Often the inaccuracy of pretreatment staging represented a relevant bias for the randomized clinical trials on preoperative treatment, negatively affecting the interpretation of therapy results. During the multimodal treatment for locally advanced gastric cancer the role of the surgeon should not be limited to the time of the tumor resection. For a complete pretreatment evaluation of these patients, a staging laparoscopy should always be performed. Staging laparoscopy may reveal positive cytology or even peritoneal implants undetected by preoperative examination in about 20% of the cases, and in some of them it is possible to prevent an unnecessary laparotomy (40-43). After accurate stratification by staging laparoscopy, appropriate neoadjuvant chemotherapy may offer successful results also in patients with positive peritoneal cytology (M+). Some studies reported the outcomes of potentially curative resections following the clearance of peritoneal cytology (conversion from positive to negative after neoadjuvant chemotherapy), however, benefit on the long-term survival remains to be established (44-46).

Moreover, after neoadjuvant chemotherapy, a second look laparoscopy for restaging is needed, directly involving the surgeon in the evaluation of the efficacy of the neoadjuvant treatment; his findings will guide the subsequent steps in the multimodal approach to locally advanced gastric cancer patients.

(II) During surgery, surgical quality and surgical efficiency must always be the highest possible, obtaining R0 resection and extended lymphadenectomy. A D2 lymphnode dissection is considered today the standard surgical treatment, supported by many data showing that, compared with D1 nodal dissection, D2 dissection offers a survival benefit, if performed by well-trained and experienced surgeons (8,47,48). Inadequate surgery causes reduction in survival and could also lead to misinterpretation of the results of the multimodal treatment. Perioperative chemotherapy should not represent a surrogate of insufficient surgery, in fact, perioperative chemotherapy offers its best results only if associated with an effective radical locoregional surgery, showing once again the centrality of the surgeon's role.

(III) After the resective intervention the role of the surgeon will be obviously focused also on the management of the eventually occurring postoperative complications. Some surgeons complain about the possibility of increasing postoperative complications after neoadjuvant chemotherapy (19,33), however, data from the MAGIC trial (13) showed similar postoperative complications, mortality rates and hospital stay both after surgery alone and after surgery with perioperative chemotherapy for locally advanced gastric cancer. Other reported data show that in patients receiving neoadjuvant chemotherapy followed by gastric resection, postoperative morbidity ranges from 23% to 40% and mortality from 0% to 10% (49-56). These findings are similar to reports of morbidity and mortality in patients undergoing gastric resection without neoadjuvant chemotherapy (57-66).

Finally, the surgeon has a relevant role in the multidisciplinary oncological team also during clinical cases discussion: the surgeon's point of view is of primary importance in the discussion of every single case, in order to obtain the best tailored treatment for patients affected by locally advanced gastric cancer.

### Conclusions

In conclusion, at least in our geographic area, perioperative chemotherapy is a valid option in the multimodal approach for locally advanced gastric cancer. This option is located in a very complex field where different strategies and different physicians are involved to reach a common goal: to improve patients' survival. Today in Europe chemotherapy for locally advanced cancer is administered preferable in a perioperative setting and neoadjuvant chemotherapy has



been shown to be feasible, does not increase postoperative morbidity and mortality, increases the rate of R0 resection, reduces the incidence of systemic metastases and prolongs survival. The surgeon plays a key role in the multidisciplinary multimodal treatment setting, both during surgery with optimal tumor exeresis and extended lymphadenectomy, and also for fundamental evaluations before and after the intervention. Surgical efficiency should be so high to prevent any misleading interpretation of multimodal treatment: perioperative chemotherapy can never be considered a surrogate of inadequate surgery. Finally, we believe that the up-to-date evidence supports the positive effect of perioperative chemotherapy in locally advanced gastric cancers, even if further studies are still required to determine its best regimen and to develop a response-based neoadjuvant concept.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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# Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for gastric cancer and other less common disease histologies: is it time?

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**Abstract:** Gastric cancer is the fourth most commonly diagnosed cancer worldwide, and once spread to the peritoneum, has a 5-year survival of less than 5%. Recent years have demonstrated advances in the use of cytoreductive surgery (CRS) in combination with heated intraperitoneal chemotherapy (HIPEC) for the treatment of peritoneal carcinomatosis due to various malignancies. The frequent desmoplastic stroma and poor vascularization impeding drug delivery particularly in the diffuse form of gastric cancer is thought to provide a sound rationale for a regionalized treatment approach in this disease. Here, we seek to review the available data to define the role of CRS and HIPEC in gastric cancer metastatic to the peritoneal surface, and furthermore, analyze the use of CRS and HIPEC in malignancies less commonly treated with the regionalized perfusion approach.

**Keywords:** Metastatic gastric cancer; peritoneal carcinomatosis; cytoreductive surgery (CRS); heated intraperitoneal chemotherapy (HIPEC); systematic review

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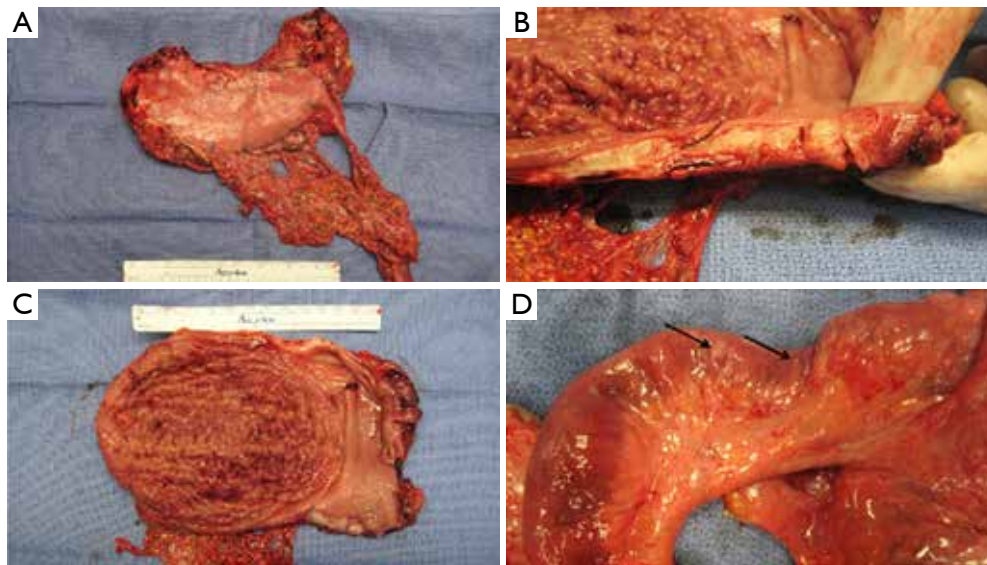
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## Introduction

Gastric cancer, the fourth most common newly diagnosed cancer worldwide, carries an incontrovertible mortality burden with a five-year survival rate of ~25% for all stages (1,2). Up to 40% of gastric cancer patients develop some type of peritoneal spread during the course of their disease, after which their 5-year survival drops to less than 5% (3-5). Those afflicted by peritoneal carcinomatosis from gastric cancer are currently treated as stage IV, receiving systemic chemotherapies with generally bleak results. Indeed, only a minority of patients survive longer than one year and nearly all present challenges to palliation, frequently exacerbated due to common GI failure, in the final weeks of life (6).

The need for therapies addressing peritoneal

carcinomatosis in gastric cancer, combined with an emergence of cytoreductive surgery (CRS) and heated intraperitoneal chemotherapy (HIPEC) in other GI cancers, has led to a number of clinical trials seeking to establish a role for this modality in gastric cancer. This regionally focused approach is built on the concept of maximizing drug delivery to the afflicted surfaces while simultaneously elongating the therapeutic window by reducing systemic toxicity. Indeed, in a large phase III clinical trial in colorectal cancer spread to the peritoneum, HIPEC and CRS extended median survival from 12.6 to 22.3 months (P=0.032) (7). Likewise, small trials and a meta-analysis have indicated an association with prolonged survival when applying this technique to stage IV gastric cancer with



**Figure 1** Diffuse gastric cancer with peritoneal surface involvement. (A) Thickened and ‘rigid’ gastric walls of surgical specimen; (B,C) thickened stomach wall without mucosal involvement; (D) peritoneal implants involving ileum and small bowel mesentery (arrows).

peritoneal carcinomatosis (8-10). High procedure-related morbidity and mortality associated with the CRS-HIPEC approach, however, have sparked a debate on its merit. With the advent of regulatory approval of more effective as well as novel, more personalized treatment options in stage IV gastric cancer, along with advances in tailoring investigational agents specifically for peritoneal delivery, there clearly is a need to outline the appropriate role of CRS-HIPEC in this disease (1,11,12).

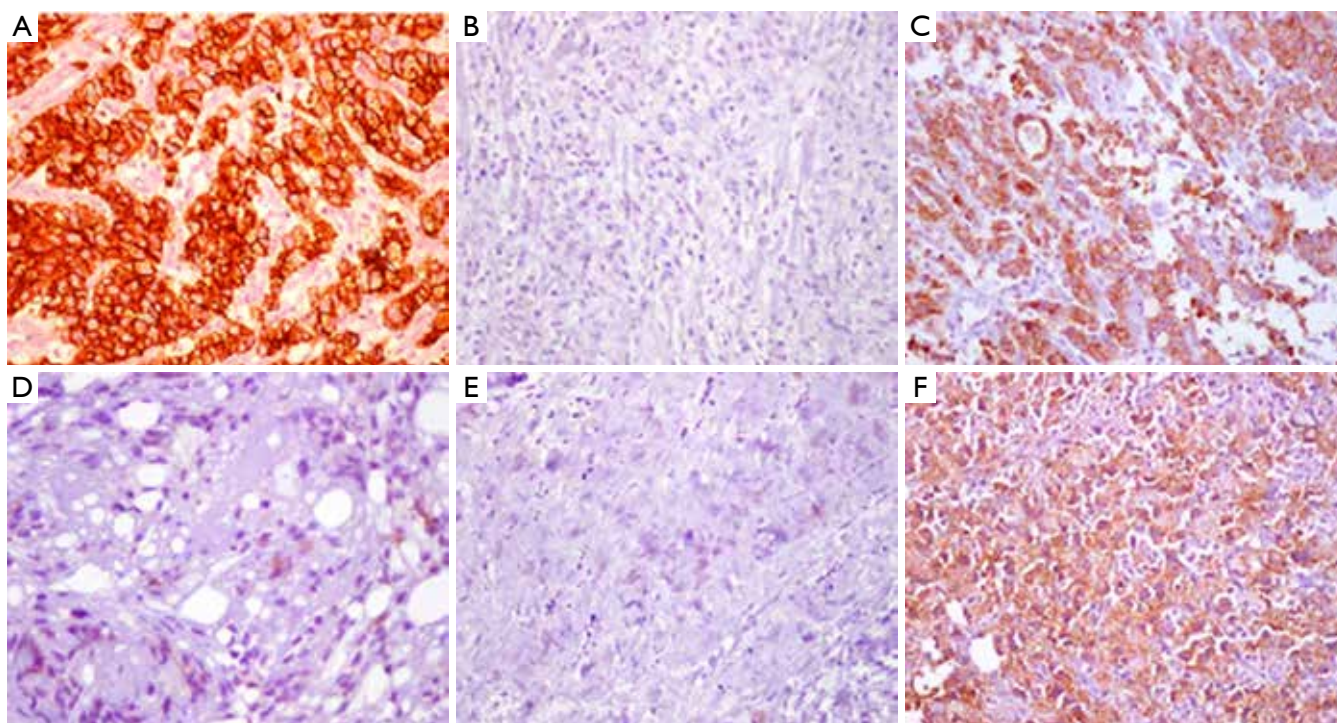
The primary rationale for a regional perfusion approach is the ability to target the tumor burden with up to 20-times higher concentrations of drug measured in the intraperitoneal compartment compared to plasma drug level (13,14). The issue of drug penetration and delivery is particularly important in the diffuse form of gastric cancer, which, together with pancreatic adenocarcinoma, is a prime example of a malignancy with a desmoplastic inflammatory stroma, high interstitial pressures and poor vascularization (15,16). On one hand, pharmacological manipulation has been shown to exploit a tumor’s natural enhanced permeability and retention effect (EPR) by increasing leakage, extravasation, and retention of drug in the tumor tissue via greater permeability due to reduced fibrosis and interstitial pressure (16). On the other hand, direct exposure of tumor deposits to chemotherapy is thought to penetrate superficial cell layers only, and the effect of intraperitoneal chemotherapy may be mediated through rapid systemic absorption and recirculation,

potentially achieving higher intratumoral concentrations than direct drug penetration (16-18).

Additionally, the evolving understanding of the heterogenous landscape of cancer may soon require an approach individualized to metastatic site. Whole genome sequencing (WGS) studies in pancreas and renal cell cancer for example, have sampled multiple metastatic sites and elicited considerable genetic heterogeneity in both somatic mutations as well as chromosomal structural variants at different organ sites within individual patients (19,20). Further recent work has used WGS to identify patients that will have a robust or complete response to platinum-based chemotherapy (21), and it is conceivable that the choice of regional chemotherapy should be guided in the future by unique genotypic signatures of metastatic sites to optimize drug selection. Hence, the merit of individualization based on both histopathology and genotype in the selection of regional drug approaches might be particularly important in metastatic gastric cancer involving the peritoneal surface. *Figure 1* shows an example of the diffuse form of gastric cancer, which is more commonly associated with peritoneal spread than the intestinal subtype of gastric adenocarcinoma. *Figure 2* shows the considerable variability in cytoarchitecture, tumor cellularity, stromal expansion, and E-cadherin expression across a number of peritoneal surface lesions removed from different patients during CRS.

Hence, it is unlikely that a ‘one size fits all’ is the most





**Figure 2** Variability in tumor-stroma ratio, gland formation, stromal and tumor cellularity, and CDH1 expression of peritoneal surface involvement of metastatic gastric cancer. (A-F) Immunohistochemical anti-CDH1 staining of peritoneal deposits of six patients enrolled onto the RECLAP study (22) (magnification, 20 $\times$ ).

effective approach, and the choice of chemotherapeutic regimens, including intraperitoneal therapy for peritoneal involvement, may soon depend on the genetic make-up of both primary and metastatic lesions. Here, we review the currently available data on the use of CRS in combination with HIPEC in gastric cancer, efforts to select patients and reduce morbidity of these procedures, as well as highlight advances of regional chemotherapy approaches in less common histologies, such as adrenocortical cancer (ACC) and abdominal sarcomatosis.

### **Retrospective evaluations of cytoreductive surgery (CRS) and HIPEC versus systemic chemotherapy for peritoneal carcinomatosis from gastric cancer**

Given the rarity and frailty of patients with gastric cancer metastatic to the peritoneum, it is inherently difficult to study such cases clinically. It is thus important to first demonstrate that a new treatment modality can achieve outcomes superior to historical controls receiving standard of care. Indeed, in other GI cancers, retrospective experiences that have to date

not been subjected to randomized controlled have led to accepted standards in treatment. Such was the case with the introduction of surgery for the management of colorectal liver metastases in the 1990s, as well as the use of CRS and HIPEC in the management of appendiceal carcinoma or peritoneal mesothelioma through the pivotal work of Dr. Sugarbaker (23). Accordingly, there are a number of well-conducted retrospective series from high-volume peritoneal surface malignancy centers reporting on outcome of patients with gastric cancer with peritoneal carcinomatosis being treated with CRS and HIPEC. *Table 1* details these reports including number of patients per study, median follow-up, regional chemotherapy used, treatment related complications, and clinical outcome.

Two studies deserve to be highlighted: in the largest study with the most comprehensive follow-up French investigators describe a multi-institutional series of 159 patients treated with CRS and HIPEC and reported 1-, 2-, and 5-year survival rates of 43 %, 18%, and 13%, respectively (26). Also, the study by Hall *et al.* from a high-volume peritoneal surface malignancy center is remarkable as it reported equal 1- and 2-year outcomes between patients with peritoneal



**Table 1** Selected non-randomized studies reporting outcome of patients with peritoneal carcinomatosis due to metastatic gastric cancer

Authors (trial design)	Publication year	Total/HIPEC/other	Agent (dose)	Toxicity	Median follow-up	Clinical outcome
Hultman et al. (24) (Ph II)	2013	18	CRS/HIPEC/EPIC (5 patients CDDP at 50 mg/m <sup>2</sup> , 3 patients oxaliplatin 460 mg/m <sup>2</sup> with IV 5-FU and LV)	62.5% grade II-IV adverse event	14.3 months	8 patients received entire treatment. OS =14.3 months (95% CI, 6.6-20.3)
Wu et al. (25) (RS: ovarian metastasis and peritoneal dissemination)	2013	64, 32	Oxaliplatin 460 mg/m <sup>2</sup>	No difference in grade III/IV AE in HIPEC and non-HIPEC group	11 months	MS CRS + HIPEC vs. CRS only 15.5 and 10.4 months, P=0.018
Glehen et al. (26) (RS, multicenter)	2010	159 (77 CRS + HIPEC closed, 67 CRS + HIPEC open, 12 CRS + HIPEC + EPIC closed)	(I) MMC 30-150 mg/m <sup>2</sup> + CDDP 50-100 mg/m <sup>2</sup> ; (II) OHP 360-460 mg/m <sup>2</sup> ± irinotecan 100-200 mg/m <sup>2</sup> ± IV 5-FU and leucovorin	Post-op mortality 6.5%; grade 3-4 morbidity 27.8%	20.4 months	MS 9.2 months; overall 1-, 3-, 5-year survival of 43%, 18%, 13%
Hall et al. (27) (RS)	2004	60, 34	HIPEC with MMC (10 µg/mL, ~40 mg)	35% HIPEC morbidity vs. 17.5% control	ND	NS, HIPEC 8.0 vs. 7.8 months (P=0.29)
Yonemura et al. (28) (RS)	2005	107	MMC, cisplatin, etoposide at 30, 300, and 150 mg	Not discussed	46 months	MS 11.5 months, 5-year survival 6.7%
Scaringi et al. (29) (RS)	2008	37 (26 with PC, 11 prophylactic)	MMC 120 mg, cisplatin 200 mg/m <sup>2</sup>	10 patients had complications, pulmonary most frequent	ND	MS 23.4 and 6.6 months in prophylactic and PC group, P<0.05
Yonemura et al. (30) (CS)	1996	83	MMC 30 mg, etoposide 150 mg, cisplatin 300 mg	3.6% bowel perforation, 2.4% bone marrow suppression, 1.2% renal dysfunction	46 months	1- and 5-year survival rates of 43% and 11%
Yonemura et al. (31) (CS)	1991	41	MMC 50 mg, cisplatin 300 mg	Renal insufficiency 5%, leukopenia 5%, bowel perforation 2%	41.6 months	MS 14.6 months, 3-year survival rate was 28.5%

Abbreviations: HIPEC, hyperthermic intraperitoneal chemotherapy; CRS, cytoreductive surgery; EPIC, early post-operative intraperitoneal chemotherapy; CDDP, cisplatin; LV, leucovorin; OS, overall survival; RS, retrospective series; MS, median survival; MMC, mitomycin; CDDP, cisplatin; PC, prophylactic; CS, case series.

carcinomatosis that underwent resection with complete CRS followed by HIPEC and patients who underwent radical gastrectomy without peritoneal involvement (27). Both studies reported that outcome was most favorable when a complete surgical cytoreduction could be accomplished.

For the majority of patients listed in *Table 1*, patients had already received at least one line of systemic chemotherapy. The observed results are thus in contrast to those in which the majority of patients treated with systemic chemotherapy only succumb to their disease within the first year. Data from Memorial Sloan Kettering Cancer Center, for example, has shown a median survival of less than 12 months for metastatic gastric cancer treated with chemotherapy only. Furthermore, metastatic disease evidenced by cytology only was not associated with improved survival (32). Other investigators have shown a similarly significant detriment to survival conferred by isolated positive peritoneal cytology (33). Subsequent work from the Memorial group, however, suggests that a multimodality approach of neoadjuvant systemic chemotherapy and surgical resection in patients with M1Cyt+ disease that reverts to negative cytology might be associated with improved disease specific survival (34). Efforts to sterilize the peritoneal compartment in combination with curative resection have been tested in a multicenter randomized trial, which implemented intraperitoneal chemotherapy along with high volume peritoneal lavage in 88 M1Cyt+ patients and is discussed in *Table 2* and the next section “HIPEC as an adjuvant treatment for patients with resectable gastric cancer” (45).

Overall, acknowledging the shortcomings of retrospective series with their inherent selection bias, the data suggests a subset of patients treated with the multimodality approach of CRS combined with HIPEC whose outcome is different from that expected for stage IV patients treated with systemic chemotherapy only.

### **HIPEC as an adjuvant treatment for patients with resectable gastric cancer**

CRS and perfusion of the peritoneal compartment with heated chemotherapy as part of a multimodality approach are likely synergistic therapies. It is well established that smaller tumor burdens aid the efficacy of a sterilizing cytotoxic chemotherapy—a guiding principle of adjuvant chemotherapy (46). Indeed, several studies in *Table 1* support the observation that complete cytoreduction prior to HIPEC is associated with improved survival. Further, several phase II studies looking at HIPEC administered at

time of potentially curative resections for gastric cancer have indicated that regional chemotherapy carries therapeutic activity. *Table 2* lists characteristics and outcomes of patients, without preoperatively confirmed peritoneal disease, that were randomized to peritoneal perfusion at time of gastrectomy (either as hyper- or normothermic regional chemotherapy; and in one series as early post-operative perfusion) versus gastrectomy alone.

In summary, despite the inclusion of some stage IV patients that had peritoneal involvement, the majority of these studies demonstrate improved outcomes including overall survival in patients receiving intraoperative peritoneal chemotherapy. When analyzed in a recent meta-analysis, even patients with limited peritoneal carcinomatosis that randomized to CRS and HIPEC seemed to fare better than those that received curative gastrectomy only (47). The most common morbidity of the addition of peritoneal regional chemotherapy included neutropenia and thrombocytopenia. There were no associated mortalities. This data supports an emerging role for intraoperative peritoneal chemotherapy in gastric cancer, including in patients with both a low and high risk for future peritoneal involvement as well as a limited peritoneal surface disease burden.

### **Cytoreductive surgery (CRS) and HIPEC in patients with known peritoneal carcinomatosis from gastric cancer**

There are now promising results from long term follow-up studies on the outcomes of CRS and HIPEC in patients with peritoneal carcinomatosis from colorectal cancer available (48). These data show improved outcomes in patients treated with the multimodality approach together with the studies on the use of intraperitoneal chemotherapy in the adjuvant setting, provide a solid rationale for a prospective randomized evaluation of CRS and HIPEC for gastric cancer. *Table 3* summarizes clinical studies which randomized gastric cancer patients with stage IV disease to CRS and HIPEC (or early post-operative perfusion) versus standard of care.

Some of these studies, while initially designed to evaluate HIPEC in the adjuvant setting in patients who could undergo a potentially curative resection, include separate analyses of patients that were unexpectedly found to be stage IV at operation but still underwent resection of serosal deposits followed by HIPEC. Some of these stage IV patients only had positive cytology (M1Cyt+). Both 1- and 2-year mortality rates were superior in those who

Authors	Year	Total/HIPEC/ other		Stage		Agent (dose)	Toxicity	Median follow-up	Clinical outcome
		I-III	IV	I-III	IV				
Koga <i>et al.</i> (35)	1988	60	0	24	2	HIPEC: MMC (64-100 mg in 8-12 L)	Anastomotic leak 3.1% HIPEC vs. 7.1% Sx alone; adhesive ileus 3.1% HIPEC vs. 7.1% Sx alone	30 months	NS* OS 83% HIPEC vs. 67.3% Sx alone
Hamazoe <i>et al.</i> (36)	1993	82	0	38	4	HIPEC: MMC (10 µg/mL in 8-12 L)	Thrombocytopenia, transaminitis, anastomotic break 4.8% HIPEC vs. 7.5% surgery alone	6 years	NS 5-year OS 64.2% HIPEC vs. 52.5% Sx alone (P=0.247)
Fujimura <i>et al.</i> (37)	1994	58	0	17	5	HIPEC: MMC (30 mg/kg) & CDDP (300 mg/kg) in 10 L; NIC: MMC (30 mg/kg) & CDDP (300 mg/kg) in 10 L	Decreased BM, renal dysfunction, intestinal perforation	31-37 months	3-year OS 68% HIPEC vs. 51% NIC vs. 23% Sx alone (P<0.001)
Sautner <i>et al.</i> (38)	1994	67	0	40	27	EPIC: treatment between 10 <sup>th</sup> and 28 <sup>th</sup> postop day	Nausea, vomiting, diarrhea present in 24 patients (73%)	72.5 months	NS MS 17.3 months HIPEC vs. 16.0 months control (P=0.6)
Ikeguchi <i>et al.</i> (39)	1995	174	0	78	0	HIPEC: MMC (80-100 mg/m <sup>2</sup> ) in 8-10 L (post-op MMC & UFT)	ND	6 years	NS* 5-year OS 51% HIPEC vs. 46% Sx alone
Rosen <i>et al.</i> (40)	1998	91	0	46	0	Perfusion: MMC (50 mg) & CH (375 mg)	Morbidity: 35% perfusion vs 16% Sx alone (P<0.02); mortality (60 days): 11% vs. 2%	597 days	NS OS 738.9 days HIPEC vs. 515.4 days Sx alone (P=0.44)
Fujimoto <i>et al.</i> (41)	1999	141	0	58	13	HIPEC: MMC (10 µg/mL) in 3-4 L (post-op chemo)	No difference in rate of duodenal stump leak	ND	8-year OS 62% HIPEC vs. 49% Sx alone (P=0.0362)
Shimoyama <i>et al.</i> (42)	1999	29	0	30	0	Perfusion: MMC (10 mg) in 500 mL; regional perfusion: MMC (10 mg) in 500 mL (post op chemo: CDDP, UFT)	No difference in rate of anastomotic leak or pancreatic leak	47 months	OS improved for perfusion vs. regional perfusion vs. Sx alone (P=0.049)
Yonemura <i>et al.</i> (43)	2001	139	0	35	13	HIPEC: MMC (30 mg) & CDDP (300 mg) in 8-10 L; NIC: MMC (30 mg) & CDDP (300 mg) in 8-10 L	No difference in rate of leak, pneumonia, renal dysfunction, mortality	5.5 years	OS* 61% HIPEC vs. 43% NIC & 42% Sx alone (NS btw NIC & surgery alone)
Miyashiro <i>et al.</i> (44)	2011	268	0	ND	ND	Perfusion: CDDP (70 mg/m <sup>2</sup> ) in 1 L (post op chemo: CDDP, 5FU)	Mortality 3 vs. 1 patients; grade 4 AE: 2 vs. 3 patients	6 years	NS OS 62.0% perfusion vs. 60.9% Sx alone (P=0.482)

\*P value not stated. Abbreviations: HIPEC, hyperthermic intraperitoneal chemotherapy; MMC, mitomycin C; Sx, surgery; EPIC, early postoperative intraperitoneal chemotherapy; NS, not significant; OS, overall survival; CDDP, cisplatin; NIC, normothermic intraperitoneal chemotherapy; MS, median survival; UFT, Tegafur/uracil; ND, not declared; CH, activated carbon.

**Table 3** Randomized controlled trials of patients with peritoneal carcinomatosis or serosal involvement from gastric carcinoma

Author	Year	Total/HIPEC/other	Stage	Agent (dose)	Toxicity	Median follow-up	Clinical outcome
Hagiwara <sup>†</sup> <i>et al.</i> (49)	1992	49, 25	Stage IV: 49; S2: 37/19; S3: 12/5	HIPEC: MMC-CH 500 µg/mL	Leukopenia and thrombocytopenia resolved within 1 month	ND	Survival improvement of 34.6% at 1.5 years, and 41.7% at 2, 2.5, and 3.0 years (P<0.01)
Sautner* <i>et al.</i> (38)	1994	67, 33	T3 <sup>†</sup> : 21/21, T4: 13/12, LN-: 10/10, LN+: 24/23	EPIC: treatment between 10 <sup>th</sup> and 28 <sup>th</sup> postop day	Nausea, vomiting, diarrhea present in 24 pts (73%)	72.5 months	T4 vs. T3 RR 2.4 (P=0.001), OS 42%, 13%, 8% vs. 73.8%, 42.8%, 30.0% at 1-, 3-, and 5-years. Local carcinosis present vs. absent NS-RR 0.95 (P=0.89)
Takahashi* <i>et al.</i> (50)	1995	113, 56	Stage IV: 113; S2: 76/39; S3: 37/17	Perfusion: MMC (50 mg) & CH (375 mg) in 100 mL	NS morbidity except 2 colcutaneous fistulas in HIPEC group	3 years	3-year OS 38% perfusion vs. 20% Sx alone (P<0.05)
Kuramoto <i>et al.</i> (46)	2009	88, 29, 30 (EIPL)	Stage IV: 88	NIC: CDDP (100 mg) in 1.5 & 3 L lavage; NIC + EIPL: CDDP (100 mg) in 1.5 & 10 L lavage; adjuvant 5-FU PO x2 years	ND	5 years	5-year OS 43.8% for EIPL-NIC, 4.6% NIC alone, 0% Sx alone (P<0.0001)
Yang <i>et al.</i> (51)	2011	68, 34	Stage IV: 68	HIPEC: CDDP 120 mg and MMC 30 mg	SAE in 4 CRS only, 5 CRS + HIPEC	32 months	MS in CRS + HIPEC vs. CRS was 11 and 6.5 months (P=0.046)
Rudloff <i>et al.</i> (8)	2014	16, 9	Stage IV: 16	HIPEC: oxaliplatin 460 mg/m <sup>2</sup> + IV 5-FU 400 mg/m <sup>2</sup> and IV leucovorin 20 mg/m <sup>2</sup> ; all received adjuvant FOLFOXIRI	1 mortality septic shock POD 49	ND	MS 11.3 in HIPEC vs. 4.3 in chemo alone

<sup>†</sup>, included only patients with S2 or S3 disease; \*, included stage III and stage IV; ^, stage not provided. Abbreviations: HIPEC, hyperthermic intraperitoneal chemotherapy; MMC, mitomycin C; CH, activated carbon; ND, not declared; EPIC, early postoperative intraperitoneal chemotherapy; OS, overall survival; NS, not significant; Sx, surgery; NIC, normothermic intraperitoneal chemotherapy; CDDP, cisplatin; EIPL, extensive intraoperative peritoneal lavage; SAE, serious adverse events; CRS, cytoreductive surgery; MS, median survival.

received intraoperative intraperitoneal chemotherapy while 5-year mortality rates did not differ between the groups (47). These findings are affirmed by the results of the so far largest randomized clinical trial on the subject: Yang and coworkers randomized 68 patients with peritoneal carcinomatosis due to gastric cancer to either CRS alone versus CRS plus HIPEC and showed a small but statistically significant survival improvement in those with peritoneal involvement that received both CRS and HIPEC (51). The design of Yang's and co-workers study was different from the recently presented GYMSSA study where patients were randomized to gastrectomy, CRS, and HIPEC followed by 2<sup>nd</sup> line FOLFOXIRI versus FOLFOXIRI chemotherapy alone (8). These patients had all undergone diagnostic laparoscopy before randomization to assess peritoneal disease burden. While this study did not meet its accrual target and thus remains underpowered, the findings of several patients living beyond one year (one beyond 4 years) in the multimodality arm compared to all patients dying of their disease within one year in the chemotherapy only arm is noteworthy.

### Complications associated with CRS and HIPEC in gastric cancer patients

While the above early, albeit immature, data might point to an emerging role of this approach in the management of metastatic gastric cancer with peritoneal involvement, a concept of clinical equipoise between potentially promising findings and the related risks and burden of the procedure—which are substantial—should be applied. It should also be noted that there is likely a publication bias leading to underreporting of negative findings, however, these reports do exist (52). The main toxicities reported from this approach are neutropenia, particularly in the early post-operative period, as well as GI toxicity, including leaks and fistulas. A number of studies suggest surgical techniques to reduce the likelihood of GI complications. These include (I) complete drainage of the peritoneal chemotherapy effluent followed by extensive washing prior to reestablishing GI continuity or closure; (II) the re-resection of intestinal ends (up to 1 cm) prior to anastomosis in order to join fresh ends which were not exposed to the regional chemotherapy; or (III) avoidance of excessive peritoneal stripping (53).

Despite a relatively common surgical approach there was considerable heterogeneity in the toxicities in these studies. Some reported hardly any leaks or no severe GI toxicity while others, such as the GYMSSA trial, had a high

(≥20 percent) 90-day mortality rate with a limited number of patients receiving the planned adjuvant FOLFOXIRI chemotherapy. The reason for toxicity variation is unknown; potential causes include higher peritoneal disease burden, greater proportion of total gastrectomies compared to partial gastrectomies, or the administration of another 2<sup>nd</sup> line adjuvant chemotherapy regimen (FOLFOXIRI). There was no detectable correlation identifiable between the type of intraperitoneal chemotherapy administered and post-procedure complications. All studies do recommend for these procedures to be performed at high volume peritoneal surface malignancy centers.

### Cytoreductive surgery (CRS) and HIPEC in less common diseases

CRS with HIPEC has been associated with improved outcomes for peritoneal carcinomatosis caused by various histologies such as peritoneal mesothelioma, appendiceal, ovarian, and colorectal cancer (48,51,54-56). However, there are still other histologies, such as those cancers that tend to have confined peritoneal disease without signs of systemic metastasis, which may benefit from HIPEC and warrant further study.

#### CRS and HIPEC in abdominal sarcomatosis

One such example is abdominal soft tissue sarcoma, which tends to present with early peritoneal recurrence and no distant metastasis (57). These patients have a median survival of 13 months and both surgical resection and chemotherapy have failed to show durable responses (58). In a study by Hunt *et al.*, 28 patients underwent CRS and HIPEC over a 5-year period with either cisplatin or a cisplatin/mitoxantrone combination in two separate phase I trials (59). In patients that received HIPEC with cisplatin, the median survival was 16.9 months, while patients who received HIPEC with the combination treatment had a median survival of 5.5 months only. Complication rates were significant, 60% of the cisplatin group and 90% of the combination group developed grade 3/4 toxicities. Another study by Choudry *et al.* examined CRS and HIPEC in 15 patients with recurrent sarcomatosis of varying histologies (60). After CRS and chemoperfusion with mitomycin, cisplatin or doxorubicin, overall survival was 22.6 months. Grade 3/4 complications occurred in 24% of the patients. There has also been interest in exploring the role of CRS and HIPEC in a specific type of abdominal sarcoma, gastrointestinal stromal



tumors. Bryan *et al.* retrospectively reviewed 16 patients that received CRS/HIPEC for GIST-induced sarcomatosis and found a median overall survival of 3.33 years (61). The authors, and others, speculate that debulking followed by first- and second-line tyrosine kinase inhibitor therapy in the form of imatinib (Gleevec<sup>®</sup>) or sunitinib (Sutent<sup>®</sup>) reduces, or delays, the risk of relapse due to the delayed formation of resistant clones in the tumor.

Taken together, these results might support the use of the multimodality CRS and HIPEC approach in some patients afflicted by abdominal sarcomatosis, however, toxicity can be substantial and indicates a need for diligent patient selection in future clinical trials. Critically, a randomized study with a non-HIPEC control arm has not yet been performed and additional trials are warranted.

### ***CRS and HIPEC in adrenocortical cancer (ACC)***

ACC is a rare tumor with a poor prognosis. Mortality is in the 75-90% range over 5 years, and average survival from time of diagnosis is 14.5 months with 60% of patients eventually developing with unresectable intrabdominal disease (62,63). Systemic therapy for these patients is associated with a poor response and no effect on overall survival (64,65). Indeed, the largest randomized trial for metastatic ACC with etoposide, doxorubicin, and cisplatin showed a progression free survival of 5 months and a 23% response rate (66). Considering the lack of effective systemic treatments for patients with metastatic disease, more effective therapies are needed.

At the National Cancer Institute (NCI), a retrospective analysis was performed of 14 patients with peritoneal recurrence from ACC who were treated with post-operative EDP chemotherapy. Patients who did and did not respond to chemotherapy had an average survival of 30 and 14 months, respectively. This suggests that response to chemotherapy may correlate with an increase in survival. Furthermore, considering the advantages of the regional chemotherapy approach it gives reason to believe that there may be added benefit for these patients that respond, when HIPEC is applied directly to the tumor bed. Given these findings, a trial is currently being conducted at the NCI to establish the efficacy of CRS and HIPEC for peritoneal recurrence of ACC (67). Given the efficacy of systemic cisplatin in ACC, as well as the higher tolerated dosing when given as a heated perfusate, the investigators of the trial hypothesize that patients will achieve prolonged disease free and overall survival.

## **Conclusions**

Currently, there is still limited available data and literature defining a role for CRS and HIPEC in the management of patients with advanced gastric cancer, and further clinical research on this approach is still needed. Results thus far have suggested that CRS and HIPEC may have a role in select patients; those with a low peritoneal disease burden that can be completely reduced, or with disease that is positive by cytology only, are likely the best candidates for the approach. Clinical decisions should be made with the knowledge that toxicities can be substantial, and it is unlikely a curative option. Studies on CRS and HIPEC applied to less common diseases like soft tissue sarcomas or ACC metastatic to the peritoneal surface, while hampered by an inherent heterogeneity of included patients and histologies, mirror the trend observed in management of metastatic gastric cancer experiences but remain too scarce to give any general recommendations. Further development will require the establishment of a robust clinical trial framework at cooperating centers of excellence and more meaningful improvement in outcome will likely require the addition of novel drugs, or drug combinations, taking the unique site-specific genotype of metastases to different organs and compartments into account.

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## **Footnote**

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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# Excision repair cross-complementary group for chemotherapy efficacy in gastric cancer

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**Abstract:** Excision repair cross-complementary group 1 (ERCC1) is a significant protein in the nucleotide excision repair pathway. ERCC1 activity has been previously reported as a significant biomarker for the efficacy of platinum-based chemotherapy in some cancers such as lung, ovary, gastric and colorectal cancer. In gastric cancer, the results of previous studies on mRNA/immunohistochemical (IHC)/polymorphism of *ERCC1* in patients who received platinum-based chemotherapy varied among different studies. The large-scale translational analyses of JCOG 9912 trial revealed that a high level of ERCC1 is considered a poor prognostic factor in terms of overall survival (OS) in advanced gastric cancer patients who received systemic chemotherapy. The ERCC1 mRNA expression in the diffuse type adenocarcinoma was significantly higher than the expression in the intestinal type. For these patients with poor prognosis such as high ERCC1 value and diffuse type adenocarcinoma, a triplet regimen as first-line chemotherapy was considered to be more active than a doublet regimen. JCOG 1013 is a randomized phase III trial that investigates the superiority of a triplet regimen of docetaxel, S-1 and cisplatin in relation to S-1 and cisplatin in patients with unresectable or recurrent gastric cancer. This study also investigates differences in OS according to tumor tissue classification (intestinal type *vs.* diffuse type) as a key secondary endpoint. As a future approach, strict guidelines for standard protocols regarding sample collection and preservation of samples are required and we may need to develop the target-specific antibodies for functional ERCC1 isoforms. These improvements would solve the methodological heterogeneity of ERCC1 determinations and large-scale randomized trials to validate the roles of molecular markers, including ERCC1 expression, in advanced gastric cancer patients who receive platinum-based chemotherapy are required in the future.

**Keywords:** Excision repair cross-complementary group 1 (ERCC1); cisplatin; oxaliplatin; gastric cancer

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## Introduction

Gastric cancer is the most common carcinoma in Asia and the third leading cause of death in men and the fourth leading cause of death in women around the world (1). Detection of gastric cancer at an early stage increases the chances of accomplishing a complete surgical resection and contributes to a long survival. About 35 percent of advanced gastric cancer patients show local or distal recurrence after surgery (2). A standard treatment for patients with unresectable or recurrent gastric cancer is systemic chemotherapy, and the recent development of

new anti-cancer drugs has improved survival time in these population (3-5). On the other hand, the frequency of somatic gene mutations in advanced gastric cancer was low (6), thus indicating that further reverse translational research is required in order to identify predictive and prognostic factors that might help to individualize anti-cancer treatment.

A combination of fluoropyrimidine and platinum is the most commonly accepted first-line chemotherapy in patients with unresectable or recurrent gastric cancer (7-10). The objective response rate (ORR) of the combined chemotherapy

is almost 50-60% according to previous clinical trials. About 50% of patients cannot obtain a response to first-line chemotherapy, so new biological markers to select responders efficiently before treatment are required in order for individual treatment in advanced gastric cancer patients to succeed.

Excision repair cross-complementary group 1 (ERCC1) is a significant protein in the nucleotide excision repair (NER) pathway (11,12). ERCC1 and ERCC2 proteins are major components in the NER complex and act as rate-limiting enzymes in the NER pathway. The *ERCC1* gene is located on chromosome 19q13.2-q13.3 and encodes different isoforms by alternative splicing. The ERCC1/xeroderma pigmentosum complementation group F (XPF) plays significant roles in several DNA repair pathways. ERCC1/XPF is a heterodimeric DNA structure-specific endonuclease that is able to cleave the sugar-phosphate backbone at the double-strand—single-strand junction of any branched DNA and at 3'-protruding single-strand ends. This makes ERCC1/XPF essential in several different pathways associated with DNA repair, such as NER, interstrand cross-link repair (ICL-R), ROS-induced single-strand break repair (SSB-R), and two sub-pathways associated with double-strand break repair (DSB-R), which are called single-strand annealing (SSA) and microhomology-mediated end joining (MMEJ), respectively.

ERCC1 activity has been previously reported as a significant biomarker for the efficacy of platinum-based chemotherapy in solid tumors, such as ovarian (13,14), lung (15,16), gastric (17) and colorectal tumors (18). These studies indicated that a low expression of ERCC1 was associated with higher chemotherapeutic sensitivity.

The roles of ERCC1 in platinum-based chemotherapy in non-small cell lung cancer (NSCLC) were evaluated in two prospective multicenter randomized trials: GECF/98-02 trial and the International Adjuvant Lung Cancer Trial (IALT). Rosell *et al.* (GECF/98-02) evaluated the association between the outcome of gemcitabine plus cisplatin treatment and the mRNA level of ERCC1 in 56 patients with advanced (stage IIIb or IV) NSCLC (15). In this study, there were no significant associations between ERCC1 expression and the response to chemotherapy. The median overall survival (OS) was significantly longer in patients with low ERCC1 expression tumors compared to that of patients with high expression tumors. Multivariate analyses indicated that ERCC1 expression was an independent prognostic factor in advanced NSCLC.

The biology part of the IALT was an immunohistochemical

(IHC) biomarker analysis of the ERCC1 expression in 761 paraffin-embedded tumor samples. IALT was a randomized phase III trial to evaluate the ability of adjuvant chemotherapy to improve survival after complete resection in 1,867 patients in stage I-III of NSCLC (16). Adjuvant chemotherapy, as compared with observation, significantly improved OS in patients with ERCC1-negative tumors [adjusted hazard ratio (HR) 0.65; 95% confidence interval (CI) 0.50-0.86;  $P=0.002$ ] but not in patients with ERCC1-positive tumors (adjusted HR 1.14; 95% CI 0.84-1.55;  $P=0.40$ ). Among patients who did not receive adjuvant chemotherapy, OS in those with ERCC1-positive tumors was significantly longer than that in those with ERCC1-negative tumors (adjusted HR 0.66; 95% CI 0.49-0.90;  $P=0.009$ ). Accordingly, the clinical benefit from cisplatin-based adjuvant chemotherapy in NSCLC patients was associated with ERCC1 negativity (test for interaction,  $P=0.009$ ) in this trial.

The Gynecologic Oncology Group (GOG)-0158 and GOG-172 trials evaluated the roles of ERCC1 expression in patients who received platinum-based chemotherapy. The GOG-0158 trial was a randomized phase III trial that compared the efficacy and safety of paclitaxel plus carboplatin with paclitaxel plus cisplatin in stage III of epithelial ovarian cancer (EOC). Translational analyses of this phase III trial investigated platinum-DNA adducts and expression of mRNA for ERCC1 as biomarkers for taxane plus platinum (carboplatin and cisplatin) efficacy in 170 EOC patients (13). This study indicated that there was no difference in PFS and OS related to ERCC1 expression in patients who were treated with taxane-platinum chemotherapy (PFS: HR 0.978, 95% CI 0.655-1.461,  $P=0.915$ ; OS: HR 1.026, 95% CI 0.648-1.626,  $P=0.912$ ).

The GOG-172 trial was a randomized phase III trial of intravenous versus intraperitoneal cisplatin and paclitaxel administration in patients with optimally resected, stage III EOC or primary peritoneal carcinoma. A translational analysis of the GOG-172 trial investigated the association between the polymorphism of the *ERCC1* gene and outcomes of platinum-based chemotherapy. This study revealed that *ERCC1* codon 118 polymorphism was not associated with clinical outcome, but that the C8092A polymorphism, in contrast, was an independent predictor of PFS and OS in women with optimally resected EOC (14).

According to these translational analyses of ERCC1 expression in large-scale prospective clinical trials of NSCLC and EOC, the role of ERCC1 as a biomarker in platinum-based chemotherapy varies by type of carcinoma and the diagnostic methods used for detection of ERCC1

**Table 1** Previous small-size reports evaluated the role of ERCC1 expression and polymorphism in gastric cancer patients treated by platinum-based chemotherapy (except for translational studies of phase III trial)

mRNA	Number	Stage	Area	Regimens	Response rate (%)			Overall survival (MST: months)				
					Low	High	P value	Low	High	P value	Adjusted HR	P value
Metzger <i>et al.</i> [1998] (31)	38	Neoadjuvant	USA	5-FU/CDDP	–	–	–	Not reached	5.6	0.03	–	
Napieralski <i>et al.</i> [2005] (32)	63	Neoadjuvant	Asia	5-FU/CDDP	–	–	NS			NS	–	
Matsubara <i>et al.</i> [2008] (33)	140	Advanced	Asia	CDDP-based	55.8	18.8	0.008	14.3	9.6	0.002	2.38	<0.001
Huang <i>et al.</i> [2008] (34)	62	Adjuvant	Asia	FOLFOX	–	–	–	23.8	13.2	0.019	2.449	0.008
Wei <i>et al.</i> [2008] (35)	76	Advanced	Asia	FOLFOX	–	–	–	15.8	6.2	<0.0001	9.4	<0.0001
Lu <i>et al.</i> [2011] (36)	21	Advanced	Asia	XP	45.5	20.0	NS	–	–		–	
Chen <i>et al.</i> [2013] (37)	40	Neoadjuvant	Asia	FLEEOX	ND	ND	0.033			NS	–	
Liu <i>et al.</i> [2013] (38)	75	Adjuvant	Asia	L-OHP based	–	–	–	27	11	0.001	2.21	0.031

ERCC1, excision repair cross-complementary group 1; MST, median survival time; HR, hazard ratio; CDDP, cisplatin; FOLFOX, fluorouracil/leucovorin/oxaliplatin; XP, capecitabine plus cisplatin; NS, not significant; FLEEOX, fluorouracil/leucovorin/oxaliplatin/epirubicin/etoposide; ND, not described; L-OHP, oxaliplatin.

in tumor tissues. In this review, we mainly describe the prognostic role of ERCC1 in chemotherapy of advanced gastric cancer patients. First, we show the results of small-scale previous studies on the role of ERCC1 as a biomarker in platinum-based chemotherapy and the problems of evaluation of ERCC1 expression in advanced gastric cancer patients. Then, we describe the results of the JCOG 9912 trial, which is a randomized phase III trial that investigated the superiority of irinotecan plus cisplatin (IP) and the non-inferiority of S-1 compared with 5-FU continuous venous-infusion and the concept of JCOG 1103 trial in unresectable or recurrent gastric cancer patients in Japan (17,19).

### Previous small studies on the clinical roles of ERCC1 in platinum-based chemotherapy in patients with advanced gastric cancer

There are many previous reports published on studies that were mainly retrospective in individual institutions

and only included small populations. No translational research has been published on ERCC1 in large-scale prospective clinical trials on advanced gastric cancer patients who received systemic chemotherapy, except for those on mRNA levels of ERCC1 in the JCOG 9912 trial (17) and polymorphism of ERCC1 in a phase III of the Arbeitsgemeinschaft Internistische Onkologie (AIO) group (20). Except for these two large-scale prospective trials, ERCC1 expression or polymorphism as a biomarker of platinum-based chemotherapy in solid tumors were evaluated in blood samples by intensity of IHC (21-30), mRNA levels in tumor tissues and polymorphism of ERCC1 (39-47). Previous reports on the clinical role of ERCC1 in small studies on patients with gastric cancer are summarized in *Tables 1-3*. Biomarker analyses of ERCC1 were mainly carried out in Asian countries such as China, Korea and Japan (21-23,26-28,32-38,41,42,44-47), but several studies were performed in American and European populations (24,25,29-31,39,40,43). Cisplatin or oxaliplatin



**Table 2** Previous small-size reports evaluated the role of ERCC1 expression and polymorphism in gastric cancer patients treated by platinum-based chemotherapy (except for translational studies of phase III trial)

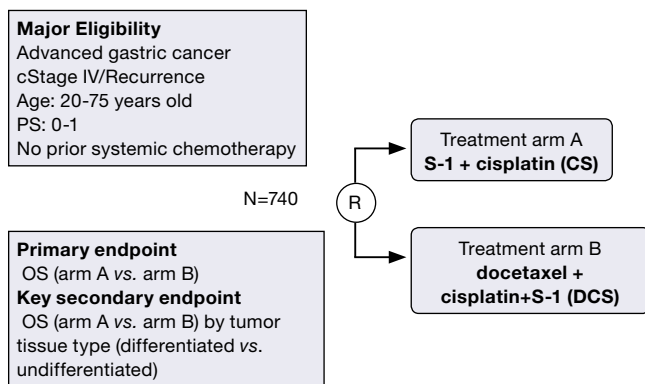
IHC	Number	Stage	Area	Regimens	Response rate (%)		Overall survival (MST: months)				
					Positive	Negative	P value	Positive	Negative	P value	Adjusted HR
Baek <i>et al.</i> [2006] (21)	32	Adjuvant	Asia	5-FU/CDDP	-	-	-	20.4	Not reached	0.008	-
Kwon <i>et al.</i> [2007] (22)	64	Advanced	Asia	FOLFOX	31.1	57.9	0.045	8.4	12.8	0.0396	1.91
Kim <i>et al.</i> [2009] (23)	151	Adjuvant (stage III-IV)	Asia	5-FU/CDDP	-	-	-	-	-	NS	-
Ozkan <i>et al.</i> [2010] (24)	41	Advanced	Turkey	CDDP-based	30.8	28.6	NS	-	-	NS	-
Fareed <i>et al.</i> [2010] (25)	57	Neoadjuvant	UK	ECF/ECX, CF	-	-	-	20.9	36.1	0.04	-
Yun <i>et al.</i> [2010] (26)	32	Advanced	Asia	ECX/CX	28	44	NS	-	-	NS	-
Choi <i>et al.</i> [2011] (27)	40	Advanced	Asia	S-1/CDDP	55.6	38.5	NS	70.3	55.4	NS	-
Hirakawa <i>et al.</i> [2013] (28)	43	Neoadjuvant	Asia	DCS	38.5	81.5	0.029	-	-	-	-
De Dosso <i>et al.</i> [2013] (29)	68	Adjuvant	Switzerland	CDDP-based	-	-	-	59.5	33	0.041	-
Squires <i>et al.</i> [2013] (30)	73	Peri-operative	USA	Any regimen ± RT	-	-	-	53.8	16.7	0.03	2.22

ERCC1, excision repair cross-complementary group 1; IHC, immunohistochemistry; MST, median survival time; HR, hazard ratio; CDDP, cisplatin; NS, not significant; FOLFOX, fluorouracil/leucovorin/oxaliplatin; ECF, epirubicin/cisplatin/ fluorouracil; CF, fluorouracil plus cisplatin; ECX, epirubicin/cisplatin/capecitabine; CX, cisplatin plus capecitabine; DCS, docetaxel/cisplatin/S-1; RT, radiation.

**Table 3** Previous small-size reports evaluated the role of ERCC1 expression and polymorphism in gastric cancer patients treated by platinum-based chemotherapy (except for translational studies of phase III trial)

Polymorphism codon 118 C/T	Number	Stage	Area	Regimens	Response rate (%)			Overall survival (MST: months)			Toxicity
					C/C	C/T + T/T	P value	HR (C/T vs. C/C)	HR (T/T vs. C/C)	HR (C/T + T/T vs. C/C)	
Goekkurt <i>et al.</i> [2006] (39)	52	Advanced	Germany	5-FU/LV/CDDP	40	25	NS	-	-	-	-
Ruzzo <i>et al.</i> [2006] (40)	175	Advanced	Italy	FU/CDDP	55.3	35.8	0.09	-	-	-	-
Keam <i>et al.</i> [2008] (41)	73	Advanced	Asia	FOLFOX	42.5	45.5	NS	-	-	1.251	NS
Huang <i>et al.</i> [2009] (42)	102	Adjuvant	Asia	FOLFOX	-	-	-	-	-	1.072	NS
Stocker <i>et al.</i> [2009] (43)	178	Neoadjuvant	Germany	5-FU/LV/CDDP	-	-	-	0.72	1.07	-	NS
Seo <i>et al.</i> [2009] (44)	94	Advanced	Asia	5-FU/CPT-11/L-OHP	26.2	21.2	NS	-	-	-	NS
Han <i>et al.</i> [2010] (45)	38	Advanced	Asia	FOLFOX	52.2	60	NS	-	-	-	-
Park <i>et al.</i> [2011] (46)	108	Advanced	Asia	S-1/CDDP	54.7	52.3	NS	0.94	1.918	-	NS
Qi <i>et al.</i> [2013] (47)	206	Adjuvant	Asia	FOLFOX4	47.2	32.6	0.033	-	ND	-	NS

ERCC1, excision repair cross-complementary group 1; MST, median survival time; HR, hazard ratio; LV, leucovorin; CDDP, cisplatin; NS, not significant; FOLFOX, fluorouracil/leucovorin/oxaliplatin; L-OHP, oxaliplatin; CPT-11, irinotecan; ND, not described.



**Figure 1** Schema of JCOG 1013 trial which is now ongoing in Japan. OS, overall survival; PS, performance status.

was administered as platinum-based chemotherapy in advanced gastric cancer patients in all studies.

We identified eight previous reports that evaluated the ERCC1 mRNA levels in gastric cancer patients who received the platinum-based chemotherapy. Most of these biomarker analyses were carried out in Asian countries. In all of these studies, the mRNA levels of ERCC1 in tumor tissues were measured by the quantitative real-time reverse transcriptase polymerase chain reaction (qRT-PCR), and the patients in these studies received systemic chemotherapy for advanced gastric cancer (33,37,38) or adjuvant chemotherapy before or after surgery (31,32,34,37,38). Some of the studies found that low levels of ERCC1 mRNA were significantly associated with better RR (33,37) and OS (33-35,38) compared with high levels of ERCC1 mRNA. On the other hand, three studies found no significant difference in terms of RR and OS irrespective of ERCC1 mRNA levels (32,36).

Ten studies evaluated the expression of ERCC1 by IHC in gastric cancer patients who received the platinum-based chemotherapy (21-30). Kwon *et al.* and Hirakawa *et al.* described that IHC negativity of ERCC1 was significantly associated with a better response to platinum-based chemotherapy compared with IHC positivity of ERCC1 (22,28). Four studies described no significant difference in terms of RR in spite of ERCC1 staining by IHC (24-27). In terms of OS, three studies described that patients with negative IHC status had longer OS compared with those with positive IHC status (21,22,25). On the other hand, De Dosso *et al.* and Squires *et al.* reported that patients with negative IHC status of ERCC1 had shorter OS compared with those with positive IHC status (29,30). Four studies indicated no association between IHC status of ERCC1 and OS (23,24,26,27).

We identified nine small retrospective analyses that evaluated the ERCC1 codon 118 C/T polymorphism in gastric cancer patients who received the platinum-based chemotherapy in advanced disease or adjuvant setting (39-48). In one report, the genotype of C/C was significantly associated with a better response to platinum-based chemotherapy compared with the genotypes of C/T or T/T in patients who received fluorouracil, leucovorin and oxaliplatin (FOLFOX4) regimen as adjuvant chemotherapy (47). On the other hand, seven studies found no significant difference in ORR between the genotypes of C/T or T/T and that of C/C (39-41,43-47). Five studies evaluated the value of ERCC1 codon 118 polymorphism in terms of OS in patients who received platinum-based chemotherapy (41-43,46,47), but there were no significant difference in OS associated with any of the genotypes of the ERCC1 codon 118 C/T polymorphism. A translational analysis of polymorphisms within the genes of *TS*, *MTHFR*, *MTR*, *OPRT*, *XPD*, *ERCC1*, *XRCC1*, *XPA*, *GSTP1*, *GSTT1*, and *GSTM1* in 134 gastro-esophageal cancer patients who were enrolled in a randomized phase III trial of the AIO group indicated that there were significant differences in ORR related to the presence of the ERCC1-118C/8092C haplotype (odds rate: 2.55, P=0.013). On the other hand, there was no association between survival benefit of platinum-based chemotherapy and polymorphism of ERCC1 (20).

According to these data, polymorphism 118C/T of ERCC1 may not be a predictive or prognostic factor in patients who received platinum-based chemotherapy in advanced gastric cancer patients.

### Problems associated with evaluation of ERCC1 as a biomarker

The results of above studies on mRNA/IHC/polymorphism of ERCC1 in patients who received platinum-based chemotherapy varied among different studies. A major reason for the variations was that the definition of cut-off values of ERCC1 levels varied among the studies. The unique cut-off values of mRNA levels included the median values (31,36,38), which are considered the best way to separate patients into low and high ERCC1 expression subgroups (33-35,37). Definition of positivity by IHC of ERCC1 varied according to intensity of IHC or percentage of stained tumor cells among previous studies. Baek *et al.* and Ozkan *et al.* defined positivity of IHC as staining of 10% or more of the tumor cells (21,24). Kwon *et al.* and Hirakawa *et al.* decided each score according to intensity

of IHC staining and percentage of stained tumor cells; positivity of ERCC1 was defined both by the grades of intensity and percentage of stained cells or as the grades of staining intensity plus staining of 2% or more of the tumor cells (22,28). Fareed *et al.* and Yun *et al.* defined tumor cells showing nuclear staining of ERCC1 as positive (25,26). In four studies, positivity of ERCC1 was defined by composite scores of both intensity of staining and percentage of stained tumor cells (23,27,29,30).

Soria *et al.* performed a validation study by IHC of the results of the IALT Biology study to confirm the predictive role of ERCC1 expression in 494 patients in the independent prospective trial of NSCLC (48). This IHC study was unable to validate the predictive effect of ERCC1 and showed that the available antibodies did not provide adequate discrimination for making therapeutic decisions regarding cisplatin. On the other hand, ERCC1-202 was detected as a unique functional isoform of ERCC1 that could predict the clinical benefit of cisplatin in this study. Development of a specific antibody and of specific primers and probes for qRT-PCR, such as the ERCC1-202 isoform, may solve the discordance of the results of translational analyses of ERCC1 expression in solid tumors.

Among other reasons for the varying results, previous reports had methodical heterogeneity in terms of (I) collecting samples such as endoscopic biopsy and surgical resection; (II) preservation of materials such as FFPE samples and frozen tissue samples; (III) patients' characteristics such as age, gender, performance status, clinical stage and chemotherapeutic regimens and timing by each study. Some meta-analyses have been published that evaluated the association between ERCC1 expression/polymorphism and efficacy of platinum-based chemotherapy in gastric cancer patients (49,50), but these data were not based on the individual data of previous studies. Finally, biomarker analyses of large-scale prospective studies are required to truly evaluate the clinical roles of ERCC1.

### **Biomarker analyses of ERCC1 mRNA levels in the JCOG 9912 trial**

The JCOG 9912 trial is a randomized phase III trial that investigated the superiority of IP and non-inferiority of S-1 compared with 5-FU with the primary endpoint of OS in unresectable or recurrent gastric cancer patients in Japan (19). This trial revealed non-inferiority of S-1 to 5-FU (HR 0.83; 95% CI 0.68-1.01;  $P < 0.001$ ) with regard to OS, but failed to show superiority of IP (HR 0.85; 95% CI 0.70-1.04;

$P = 0.055$ ) (19). Yamada *et al.* performed biomarker analyses, including ERCC1, on endoscopic biopsy specimens from primary lesions in 445 of 704 gastric cancer patients in the JCOG 9912 trial (17). In all of the patients, the ERCC1 and DPD mRNA expression in the diffuse type adenocarcinoma was significantly higher than the expression in the intestinal type. Multivariate analyses showed that high ERCC1 expression was associated with a shorter OS (HR 1.37; 95% CI 1.08-1.75;  $P = 0.010$ ). In a subgroup receiving IP ( $n = 84$ ), there was a significant difference in RR between patients with low levels and those with high levels of ERCC1 mRNA (52.5% *vs.* 29.6%,  $P = 0.045$ ). On the other hand, there were no PFS or OS differences between IP and S-1 among patients with low ERCC1.

Finally, no predictive marker for selecting 5-FU or IP rather than S-1 could be found in this study. High ERCC1 values were observed frequently in patients with diffuse-type adenocarcinoma and was an independent prognostic factors in all patients in JCOG 9912.

### **Next step in systemic chemotherapy in patients with metastatic gastric cancer in Japan—JCOG 1013 trial (ADOPT study)**

JCOG 1013 is a randomized phase III trial that investigates the superiority of a triplet regimen of docetaxel, S-1 and cisplatin (DCS) in relation to S-1 and cisplatin (CS) in patients with unresectable or recurrent gastric cancer. The schedule of the DCS regimen is as follows: Cisplatin (60 mg/m<sup>2</sup>) plus docetaxel (40 mg/m<sup>2</sup>) intravenously on day 1 and S-1 (80 mg/m<sup>2</sup>) on days 1-14, of a 4-week cycle. In addition to the primary endpoint of OS in all patients who are enrolled in this trial, the JCOG 1013 trial also investigates differences in OS according to tumor tissue classification [differentiated carcinoma (intestinal type) *vs.* undifferentiated carcinoma (diffuse type)] as a key secondary endpoint. A schema of the JCOG 1013 trial is shown in *Figure 1*. A biomarker study of JCOG 9912 revealed that *ERCC1* mRNA expression was significantly higher in the diffuse type adenocarcinoma compared with the intestinal type and that high ERCC1 was associated with a poor prognosis in unresectable or recurrent gastric cancer patients. This finding indicated that a therapeutic strategy of more active treatment of gastric cancer patients with advanced-stage diffuse-type adenocarcinoma and higher ERCC1 expression in the tumor is required. DCS regimens are expected to be effective in advanced gastric cancer patients with these poor prognostic factors. JCOG 1013

will clarify the difference in treatment selection of first-line chemotherapy between triplet and doublet regimens according to tumor tissue type (diffuse type/intestinal type) or ERCC1 levels (high/low) in unresectable and recurrent gastric cancer patients.

A triplet regimen as first-line chemotherapy was considered to be more active than a doublet regimen in a previous randomized phase III trial (V325) (51). In this study, the efficacy of docetaxel and cisplatin plus fluorouracil (DCF) was compared with cisplatin and fluorouracil (CF) as first-line chemotherapy in advanced gastric cancer; it revealed that the DCF regimen significantly improved ORR, time to progression and OS compared with the CF regimen. A high rate of febrile neutropenia was noted as a problem that might prevent continuation of the treatment in patients who received DCF in the V325 trial. In JCOG 1013, dose modification of S-1 and cisplatin was determined beforehand according to renal function in order to avoid a massive toxicity of the triplet regimen because renal dysfunction delays the excretion of 5-chloro-2,4-dihydropyridine (CDHP), which is a component of S-1, and elevates the serum level of 5-FU (52).

Adding docetaxel to the CS regimen as first-line chemotherapy may be a better strategy to improve the OS in advanced gastric cancer patients. The frequency of patients who could receive taxanes after first-line chemotherapy is lower in patients with poor prognosis compared with those with better prognosis. In Japan, a combined analysis of JCOG 9205 and JCOG 9912 indicated that the second-line chemotherapy is a significant factor to prolong the OS in advanced gastric cancer patients who received systemic chemotherapy (53).

## Conclusions

According to large-scale translational analyses of JCOG 9912 a high level of ERCC1 is considered a poor prognostic factor in terms of OS in advanced gastric cancer patients who received systemic chemotherapy. As a future approach, it would be advantageous to establish strict guidelines for standard protocols regarding sample collection and preservation of samples and to develop target-specific antibodies for IHC and primers and probes for qRT-PCR of functional ERCC1 isoforms. These improvements would solve the methodological heterogeneity of ERCC1 determinations. In addition, other molecular biomarkers associated with chemo-sensitivity should be investigated in future studies in order to identify predictive markers

of cytotoxic agents in advanced gastric cancer patients. Also, large-scale randomized trials to validate the roles of molecular markers, including ERCC1 expression, in advanced gastric cancer patients who receive chemotherapy are required in the future.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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# Cytokeratin 18 for chemotherapy efficacy in gastric cancer

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**Abstract:** Cytokeratin 18 (CK18) is the major component of intermediate filaments in epithelial cells and released into the blood in either intact (M65) or caspase-cleaved forms (M30) during apoptotic and necrotic cell death. M30 and M65 are relatively described as novel sandwich ELISA assays that determine different circulating forms of the protein CK18 in either plasma or serum and are proposed to be surrogate endpoints of different forms of cell death. Serum M65 and M30 levels have shown to be elevated in patients with different types of carcinoma. The measurement of M30 or M65 values from epithelial-derived tumors could be a simple, noninvasive way to monitor or predict tumor progression and prognosis. Recently, predictive significance of the increase in the serum M30 and M65 values after chemotherapy in patients advanced non-small cell lung cancer (NSCLC) and gastric cancer have been evaluated. It shown that increased serum M65 levels, 48 hours after chemotherapy, could be predicted tumor response in advanced-gastric cancer patients. Although these assays may be useful for evaluating treatment effects and survival in patients with gastric cancer, their importance should be tested after multiple chemotherapy sessions in larger prospective studies with long follow-up time. In this review, prognostic and predictive significance of CK18 for advanced-gastric cancer are summarized in the light of recent advances.

**Keywords:** Cytokeratin 18 (CK18); serum M30; serum M65; apoptosis; treatment response; gastric cancer; prognosis

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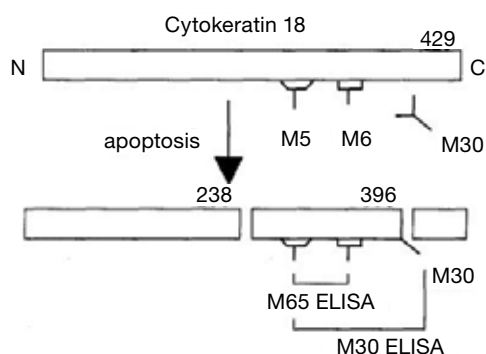
## Introduction

Although the overall incidence and mortality of gastric cancer have dramatically declined over the last few decades, it remains a major health problem and the second leading cause of cancer deaths worldwide (1,2). Radical surgery is the most efficient treatment for operable cancer, but recurrences are common, being detected in approximately 60% of patients (3). Therefore, identifying of poor prognostic factors that may predict the tumor recurrence and prognosis of patients is an important for selection appropriate treatment protocols. Several clinicopathological parameters such as tumor size, histological type, tumor differentiation, depth of tumor invasion, regional lymph node involvement, distant metastasis and tumor stage, have been reported as important prognostic factors (4). Recently, new prognostic biological and molecular indicators have been documented including oncogenes, cell-cycle

regulators, DNA repair genes, c-erbB-2 (5,6). Thus, understanding of the importance of these markers remains an important challenge in translational research.

Cytokeratin 18 (CK18) is an intermediate filament that released from cells into the circulation during both necrotic and apoptotic cell death. Caspase-cleaved CK18 (M30) and total CK18 (M65) are measured in the circulation by enzyme-linked immunoabsorbent assays (ELISA) (Figure 1). It is believed that to act as a quantitative biomarker of total cell death (8,9). Prognostic importance of both M30 and M65 assays have previously been evaluated and it has been shown that they may have an important prognostic and predictive biomarkers in several malignancies (10-15). Scott *et al.* indicated that these assays may be potential markers of tumor response to chemotherapy and were associated with increased risk of recurrence in gastrointestinal malignancy (16).

The anticancer activity of chemotherapeutic agents is directly associated with the induction of apoptosis in



**Figure 1** Cytokeratin 18 (CK18) in apoptotic cell death (7).

tumors. Whilst the apoptotic pathway is complex, the intrinsic mitochondrial pathway is the predominant apoptotic pathway in cancer cells. Among the several cellular substrates of the capsases, members of the cytokeratin family, including CK18, contribute to cellular collapse and apoptosis. Most cytotoxic drugs induce apoptosis, which increase significantly 24 hours after chemotherapy (17). Therefore, apoptosis can be measured in serum by several biomarkers by which the efficacy of cytotoxic chemotherapy can be detected (11,18). de Haas *et al.* showed that both serum M30 and M65 levels were increased after chemotherapy. These assays could also reflect chemotherapy induced cell-death in patients with testicular cancer (19). Recently, we analyzed prognostic significance of the increase in the serum M30 and M65 values after chemotherapy in two studies for patients advanced-non-small cell lung cancer (NSCLC) and gastric cancer (20,21). In addition, we showed that increased serum M65 levels after chemotherapy could be predicted tumor response in advanced-gastric cancer patients (21). This article reviews the importance of CK18 for the efficacy of chemotherapy in patients with gastric cancer in the light of recent advances.

### Prognostic significance of CK18 in cancer

The majority of chemotherapeutic agents kill tumor cells by some mechanisms including apoptosis and necrosis. Apoptosis may be an important mechanism for the evaluation of the efficacy of the anti-cancer therapy (7,22,23). Some biomarkers such as CK18 have been used for the detection of apoptosis of epithelial cells. M30 is a caspase-cleaved form of CK18 that it is released into circulation during apoptosis, whereas necrosis is supposed to

release M65 that is an intact or total form of CK18 (8,9,24). Two sandwiched ELISA assays, M30 and M65, can be used to determine different circulating forms of CK18 in either plasma or serum, and have been proposed to be surrogate biomarkers of different mechanisms of cell death (8,25). The M30 ELISA assay uses the M5 antibody as a catcher and the M30 antibody to detect caspase-cleaved CK18 produced during the early stages of apoptosis (25). The M65 assay also detects cleaved fragments but uses a different detection antibody from M30, which does not distinguish between the full-length protein and its fragments. The M65 assay theoretically measures both caspase cleavage and cellular release of intact CK18 (8). Serum M65 and M30 levels were shown to be elevated in patients with different types of carcinoma (10,12,14,16). The measurement of caspase-cleaved or total CK18 from epithelial-derived tumors could be a simple, noninvasive way to monitor or predict tumor progression (26) and prognosis (10,12,26).

de Haas *et al.* showed that serum M30 level was an important prognostic factor in testicular cancer (19). In a study performed by Dive *et al.*, they reported that the median M65 levels in patients with metastatic pancreas cancer were higher compared to patients with locally advanced or resectable pancreas cancer. Moreover, they found that M65 levels were associated with poor overall survival (OS) in the univariate analysis (27). Koelink *et al.* indicated that M65 levels were related to disease stage and tumor diameter in colorectal cancer patients (26). The caspase-cleaved/CK18 ratio, which decreased with tumor progression, was also predictive of disease-free survival (DFS), with a low ratio associated with worse DFS. In a study of patients with advanced gastric carcinoma, Yaman *et al.* found that both serum M30 and M65 levels were significantly increased in patients with advanced gastric cancer compared to control group (10). In addition, the patient population with higher M30 levels had significantly shorter median survival rates than the population with lower serum M30 levels, whereas there was no impact of serum M65 levels on survival. In contrast to their study, we showed that increased plasma levels of both M30 and M65 could predict progression-free survival (PFS) in patients with advanced-gastric cancer in our study (28).

Recently, Yildiz *et al.* analyzed the serum M30 and M65 levels in patients with epithelial ovarian cancer (EOC) (29). They found that the median M30 and M65 serum levels were significantly elevated in the EOC patients compared with the healthy controls. Furthermore, patients with higher M65 levels had shorter PFS, both M30 and M65

**Table 1** Selected trials evaluating prognostic significance of CK18 in solid tumors

References	Type of cancer	No. of patients	Results
de Haas <i>et al.</i> (19)	Testicular cancer	34	M30 level was an important prognostic factor
Dive <i>et al.</i> (27)	Pancreatic cancer	103	M65 levels in metastatic patients were higher than locally advanced or resectable patients Moreover M65 levels were associated with poor OS
Yaman <i>et al.</i> (10)	Gastric cancer	38	Higher M30 levels was significantly related with shorter OS
Bilici <i>et al.</i> (28)	Gastric cancer	34	Increased plasma M30 and M65 levels were associated with poor PFS in advanced-gastric cancer patients
Yildiz <i>et al.</i> (29)	Ovarian cancer	56	Higher M65 levels was associated with poor PFS. Both M30 and M65 levels were significantly higher for serous-type histology. Moreover, M65 levels were higher for chemotherapy-resistant patients and an elevated M65 level was the only significant independent prognostic factor
Oven Ustaalioglu <i>et al.</i> (30)	Non-small cell lung cancer	32	Increased M65 level was related with poor PFS and could predict PFS
Tas <i>et al.</i> (31)	Breast cancer	80	Neither serum M30 nor serum M65 were significantly associated with survival
Tas <i>et al.</i> (32)	Pancreatic cancer	26	Neither serum M30 nor serum M65 had significant effect on survival

CK18, cytokeratin 18; OS, overall survival; PFS, progression-free survival.

serum levels were significantly higher for serous-type histology and increased M65 serum levels were associated with advanced disease and higher grade. M65 levels were higher for chemotherapy-resistant patients and in the multivariate analysis an elevated serum M65 level was found to be only significant independent prognostic factor (29). Similarly, in our study including advanced-staged NSCLC, our findings demonstrated that serum 65 levels elevated in patients population compared to a healthy control group and increased M65 level could predict PFS (30). On the other hand, it found that there were discrepancies in other studies. Although M30 and M65 levels were detected to be increased in patients with breast cancer, pancreatic cancer and nasopharyngeal carcinoma compared to healthy control, their predictive and prognostic roles on survival were not proved (14,31,32). Selected trials evaluating prognostic significance of CK18 in solid tumors are summarized in *Table 1*.

### Changing of CK18 after chemotherapy in solid tumors

M30 and M65 levels have been previously found to be increased within 1 to 3 days after the chemotherapy in patients with breast and prostate cancer (13,33). However, de Haas *et al.* observed that most significant changes occurred

7 days after the chemotherapy in patients with testicular cancer, which may reflect the cumulative effect of the 5-day dosing regimen used in testicular cancer (19). Demiray *et al.* evaluated the serum M30 levels before and 24 and 48 hours after neoadjuvant chemotherapy in 42 patients with breast cancer (11). The authors found that the serum M30 levels increased significantly at 24 and 48 hours after chemotherapy and that this change was a predictor of the tumor response. Similar findings for M30 levels were reported for patients with breast cancer in Ulukaya *et al.*'s study (18).

We previously reported that the serum M30 and M65 levels were increased significantly after chemotherapy in patients with NSCLC (20). In addition, the elevated M30 values were an independent prognostic factor for both PFS and OS after chemotherapy. de Haas *et al.* showed that both serum M30 and M65 levels were significantly increased up to 7 days after chemotherapy in patients with testicular cancer (19). Furthermore, they found a significant decrease in the serum M30 and M65 levels during the first two weeks of chemotherapy compared to baseline values. Thus, the authors indicated that the overall decrease in M30 and M65 values may be indicative for response to treatment and reflect a decrease in tumor load because of chemotherapy-induced cell death.

Greystoke *et al.* explored the utility of serum total

CK18 (M65) and caspase cleaved CK18 (M30) as a pharmacodynamic biomarker in patients treated with chemotherapy for metastatic colorectal cancer (34). They showed that in patients with progressive disease on therapy repeated sampling revealed profiles with high pre-treatment and progressive upwardly after one cycle of chemotherapy.

### Prognostic and predictive significance of CK18 after chemotherapy for patients with gastric cancer

Firstly, the serum M30 and M65 levels were analyzed in a study carried out by Yaman *et al.* in patients with advanced-gastric cancer (10). They showed that the serum M30 and M65 values were significantly higher in patient population compared with healthy control group. In addition, only M30 levels were associated with worse survival. Thereafter, we also evaluated plasma M30 and M65 levels for advanced-gastric cancer patients (28). We found that plasma 65 levels for patients with gastric cancer were significantly higher those of healthy controls. Furthermore, both elevated plasma M30 and M65 levels were related with worse PFS and OS, but this relationship could not be proved in the multivariate analysis.

In our recent study, the significance of changes in the serum M30 and M65 levels after chemotherapy in patients with advanced-gastric cancer (21). We showed that both serum M30 and M65 serum levels were significantly increased 48 hours after start of chemotherapy. A multivariate analysis showed that only the increase of M30 values was an independent prognostic indicator for PFS, but not for OS. Although the increased M65 value was an important prognostic marker for both PFS and OS in the univariate analysis, its prognostic significance could not be confirmed by multivariate analysis. Moreover, patients with increased both serum M30 and M65 values after chemotherapy had better objective response rate compared to patients with low M30 and M65 levels. However, only the changing of M65 after chemotherapy was significantly found to be an independent factor in predicting response to chemotherapy. In other words, patients who responded to chemotherapy had 1.4-fold higher increase in serum M65 values compared with the non-responder.

Previous studies showed that CK18 assays may be beneficial in early assessment of treatment-related tumor death and subsequent prediction of response to therapy (35,36). On the other hand, early both M30 and M65 changes during chemotherapy may not be helpful, because

of overlap with host toxicity (37). We found significant changes of both serum M30 and M65 levels within 48 hours after the first chemotherapy cycle in patients with advanced-gastric cancer (21). This was in contrast to the results of Greystoke *et al.* (34), who did not show that any significant changes in the serum levels of both M30 and M65 within the first 48 hours, but they have indicated that for many patients there was a decrease in serum M65 levels, and to a lesser extent M30, from 1 week after chemotherapy. These findings were compatible with de Haas *et al.*'s study (19).

The effect of taxanes on mitotic catastrophe, characterized by the occurrence of aberrant mitosis has been demonstrated. Although mitotic catastrophe is not a type of cell death, it will result in cell death either by apoptosis or necrosis (38,39). Kramer *et al.* also reported that serum caspase-cleaved CK18 (M30) levels were increased during docetaxel treatment in patients with hormone refractory prostate cancer (33). Hence, the authors concluded that docetaxel induced apoptosis *in vivo*. The majority of patients with metastatic gastric cancer are treated with a combination chemotherapy including docetaxel. Therefore, significant changes in serum M30 and M65 levels for patients with advanced-gastric cancer receiving docetaxel are reasonable. There is an initial effect of chemotherapy on the population of cells that are chemo-sensitive leading to an initial reduction in overall tumour burden, with the later increases in circulating CK18 reflecting subsequent growth in the population of chemo-resistant cells. Therefore, both serum M30 and M65 levels could be used as surrogates of treatment response to monitor the development of chemo-resistance and lead to early changes in therapy. *Table 2* shows selected trials that analyzed prognostic and predictive significance of CK18 after chemotherapy for patients with gastric cancer and other cancer.

### Conclusions and future direction

CK18 may modulate intracellular signaling and apoptosis via interactions with various related proteins. There is evidence to show that CK18 is involved in the invasive or growth properties of tumors. Caspase-cleaved CK18 (M30) and total CK18 (M65) are measured in the circulation by enzyme-linked immunoabsorbent assays (ELISA). The measurement of M30 or M65 from epithelial-derived tumors could be a simple, noninvasive way to monitor or predict tumor progression and prognosis. However, there are conflicting results *in vitro* and *in vivo*. These discrepancies may be due to differences among the



**Table 2** Selected trials that analyzed prognostic and predictive significance of CK18 after chemotherapy for patients with gastric cancer and other cancer types

References	Type of cancer	No. of patients	Results
de Haas <i>et al.</i> (19)	Testicular cancer	34	Both serum M30 and M65 levels were significantly increased up to 7 days after chemotherapy. The overall decrease in M30 and M65 values may be indicative for response to treatment
Demiray <i>et al.</i> (11)	Breast cancer	42	M30 levels increased significantly at 24 and 48 hours after chemotherapy and that this change was a predictor of the tumor response
Ulukaya <i>et al.</i> (18)	Breast cancer	37	M30 levels significantly increased after chemotherapy. The baseline M30 levels increased about 3-times in patients showing tumor regression and its measurement may help clinicians to predict the effectiveness of chemotherapy
Ustaalioglu <i>et al.</i> (20)	Non-small cell lung cancer	32	M30 value after chemotherapy was an important prognostic factor for both OS and PFS
Bilici <i>et al.</i> (21)	Gastric cancer	31	Both serum M30 and M65 serum levels were significantly increased 48 hours after start of chemotherapy. The changing of M65 after chemotherapy was significantly found to be an independent factor in predicting response to chemotherapy
Greystoke <i>et al.</i> (34)	Colorectal cancer	74	The significant changes in both M30 and M65 levels within the first 48 hours after therapy could not be showed, but there was a decrease in serum M65 levels, and to a lesser extent M30, from 1 week after chemotherapy

CK18, cytokeratin 18; OS, overall survival; PFS, progression-free survival.

carcinoma types, therefore the precise roles of CK18 are currently unknown. But, particularly, in patients with gastric cancer, testicular cancer and colorectal cancer, serum M30 and/or M65 levels could be used as biomarkers to evaluate treatment response and they might guide in determining of the most appropriate combination chemotherapy regimen.

These assays may be useful for evaluating treatment effects and survival in patients with gastric cancer, but in combination with other cell death markers, their importance should be tested after multiple chemotherapy sessions in larger prospective studies with long follow-up time in future.

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### Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

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# Treatment improvement by addition of leucovorin to S-1 plus oxaliplatin in patients with advanced gastric cancer

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*Comment on:* Hironaka S, Sugimoto N, Yamaguchi K, *et al.* S-1 plus leucovorin versus S-1 plus leucovorin and oxaliplatin versus S-1 plus cisplatin in patients with advanced gastric cancer: a randomised, multicentre, open-label, phase 2 trial. *Lancet Oncol* 2016;17:99-108.

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Regional differences in gastric cancer are observed between Asian and Western countries concerning prevalence, clinicopathologic features, as well as treatment strategies. Cisplatin and fluoropyrimidine based therapies are used as backbone of first-line chemotherapy for advanced gastric cancer treatment, although there is preference for 5-fluorouracil (5FU) or capecitabine in the West while S-1 is mostly used in Asia. REAL-2 and Al-Batran *et al.* studies have shown that oxaliplatin was as effective as cisplatin in combination with capecitabine or 5FU in Western countries (1,2). In the same way, in Asian countries, Yamada *et al.* have demonstrated recently that oxaliplatin could replace cisplatin in combination with S-1 for gastric cancer in first-line treatment with favorable safety profile (3). A third agent (docetaxel or epirubicin) may be added (more commonly in Western countries) for patients with good performance status (1,4).

Several data demonstrated that leucovorin was able to improve the efficacy of fluorouracil by stabilising the ternary complex formed between fluorodeoxyuridine monophosphate (FdUMP) and thymidylate synthase (5), whereas adding leucovorin to capecitabine provided little additional benefit and more adverse events (6). S-1 is an oral fluorouracil antitumor drug that combines tegafur (prodrug of 5FU), 5-chloro-2,4-dihydropyridine (which inhibits dihydropyrimidine dehydrogenase activity) and potassium oxonate (which reduces gastrointestinal toxicity) (7). In advanced colorectal cancer, increasing evidence indicates

that addition of leucovorin to S-1 might improve its efficacy (8,9). Likewise, the addition of leucovorin to S-1 in gastric cancer treatment is equally expected to enhance the antitumor activity. However, no data have been reported yet in gastric cancer patients.

Recently, Hironaka and colleagues have evaluated in a randomized phase II study the activity and safety of S-1 plus leucovorin (n=49), versus S-1 plus leucovorin and oxaliplatin (n=47), versus S-1 plus cisplatin (n=49), as first-line chemotherapy in Japanese patients with advanced gastric cancer (7). In this study, the objective response rate (ORR), which was the primary endpoint, was higher in the S-1 plus leucovorin and oxaliplatin group (66%) compared to S-1 plus leucovorin (43%) (Fisher's exact test: P=0.038) or S-1 plus cisplatin groups (46%) (Fisher's exact test: P=0.063). The median progression-free survival was longer in the S-1 plus leucovorin and oxaliplatin group (8.3 months) compared to S-1 plus leucovorin (4.2 months; HR: 0.52, P=0.013) or S-1 plus cisplatin groups (5.6 months; HR: 0.60, P=0.054). The median overall survival was also longer in the S-1 plus leucovorin and oxaliplatin group (18.4 months) compared to S-1 plus leucovorin (15.6 months; HR: 0.76, P=0.27) or S-1 plus cisplatin groups (12.6 months; HR: 0.59, P=0.023) (7). This study suggests firstly that (I) addition of oxaliplatin to S-1 plus leucovorin improves efficacy of chemotherapy; and secondly that (II) S-1 plus leucovorin and oxaliplatin is more effective than S-1 plus cisplatin treatment. Haematological grade 3–4 toxicities were more

frequent in the S-1 plus cisplatin group (neutropenia, anaemia, and leucopenia), while non-haematological toxic effects, such as decreased appetite and diarrhea, were more common in the S-1 plus leucovorin and oxaliplatin group (7).

Based on these results and data from previous phase III study showing that S-1 plus oxaliplatin was non inferior than S-1 plus cisplatin in terms of survival (3), it can be extrapolated that leucovorin might provide an additional benefit when combined with S-1 plus oxaliplatin. However, in our opinion, it is difficult to definitely conclude on leucovorin's benefit as the S-1 plus oxaliplatin without leucovorin arm is missing in the present study. In fact, the only way to answer this question would have been to randomize patients to receive S-1 (alone or combined with oxaliplatin) with or without leucovorin.

In view of these findings, a phase III trial comparing S-1 plus leucovorin and oxaliplatin versus S-1 plus cisplatin in patients with HER2-negative gastric cancer is planned in Japan and Korea (NCT02322593). The supposed standard arm in this ongoing study is S-1 plus cisplatin. In our opinion, the real question is whether leucovorin could improve efficacy of S-1 plus oxaliplatin, since oxaliplatin is already a validated option in combination with 5FU or S-1 for advanced gastric cancer patients (2,3). If we consider that S-1 plus oxaliplatin is as effective as S-1 plus cisplatin, one could have considered S-1 plus oxaliplatin as the standard arm instead of S-1 plus cisplatin which was associated with more grade 3–4 toxicities in a previous randomized phase III study (neutropenia, anemia, hyponatremia and febrile neutropenia) (3). Furthermore, to our knowledge, there is no data concerning the potentiation of antitumor activity with the addition of leucovorin to S-1 plus cisplatin. Thus, we can suppose that the better clinical outcomes observed in S-1 plus leucovorin and oxaliplatin compared to S-1 plus cisplatin is mainly due to the addition of leucovorin to S-1 in oxaliplatin-based treatment arm, but not a superiority of oxaliplatin versus cisplatin. Another option would have been thus to ask both questions in a factorial design randomizing oxaliplatin versus cisplatin and leucovorin versus without leucovorin.

In conclusion, treatment and types of chemotherapy used in advanced gastric cancer vary according to geographic regions. Combination of fluoropyrimidine (including oral capecitabine or S-1) with a platinum salts (cisplatin or oxaliplatin) remains the most widely accepted reference regimen. In Asian countries, S-1 has been widely developed and is currently used as a standard first-line chemotherapy in combination with platinum. Preliminary studies have

shown that addition of leucovorin to S-1 demonstrated promising synergic effect with acceptable toxicity that needs to be confirmed in phase III randomized study. Likewise, there is a variation in clinical outcomes for gastric cancer patients across worldwide. This could be explained by difference in treatment strategies, tumor biology, and also in mutations or polymorphism in genes regulating oncogenic signaling pathways or involved in anti-tumor drug metabolism and pharmacokinetics, such as dihydropyrimidine dehydrogenase or thymidylate synthase for fluoropyrimidine. The ultimate goal in the future will be to personalize treatment according to the patient's genetic profile and tumor biology in order to select the most effective and safe treatment for each patient.

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### Footnote

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# Postoperative chemoradiotherapy vs. preoperative chemoradiotherapy for locally advanced (operable) gastric cancer: clarifying the role and technique of radiotherapy

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**Background:** Worldwide, almost one million new cases of stomach cancer were diagnosed in 2012, making it the fifth most common cancer, and the third leading cause of cancer deaths. The current tumor node metastasis (TNM) staging system represents a consensus between the East and the West, and will serve as a strong foundation upon which to build future evidence. In this review article, we first discuss the definition and optimal surgery for locally advanced gastric cancer, followed by the general principles when considering a pre *vs.* postoperative radiotherapy (RT) strategy. We then provide a synthesis of the existing randomized trial evidence in an attempt clarify the role of pre and postoperative RT in the management of locally advanced gastric cancer.

**Methods:** A Medline search 1966-Jun 2014 was undertaken. Randomized trials including patients with locally advanced gastric cancer (using established definitions), comparing RT [with or without chemotherapy (CT)], with surgery alone or other treatment modalities were included. Systematic reviews and evidence based practice guidelines that include this body of primary studies were preferentially discussed. Medline, Cochrane Library, Clinicaltrial.gov, Guidelines Clearinghouse were searched.

**Results:** Sixteen randomized trials, three systematic reviews and one practice guideline were included as the evidence base. In this group of studies, two reports compared postoperative chemoradiotherapy (CRT) with surgery alone. Driven predominantly by INT0116, they established the role of postoperative CRT to provide a survival benefit in a patient group that underwent surgery with predominantly D0-1 dissections. Preoperative RT (four studies) showed promise for survival benefit but the risks of bias in these trials were high. Postoperative CRT compared with CT alone (eight trials) showed no survival benefit with the addition of radiation although some evidence of activity can be observed with improved local regional control.

**Conclusions and future directions:** Technical expertise to enable the delivery of high quality RT to complex target volumes as is required in gastric cancer, and surgical standards to ensure the delivery of high quality surgery, have matured in recent years. Six trials with large sample sizes are currently ongoing to better define the role of preoperative CRT (two studies) and postoperative CRT (four studies), when used in conjunction with high quality surgery and RT, and contemporary CT regimens. The moderate likelihood of locoregional recurrences and the favorable therapeutic ratio with using RT preoperatively in other settings, provide optimism that preoperative CRT would have a pivotal role to play in locally advanced gastric cancer. Active accrual into ongoing trials is strongly encouraged.

**Keywords:** Gastric cancer; radiotherapy (RT); multimodality; locally advanced cancer

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## Introduction

Worldwide, almost one million new cases of stomach cancer were estimated to have occurred in 2012, making it the fifth most common cancer, and the third leading causing of cancer deaths (1). The 7<sup>th</sup> edition of the tumor node metastasis (TNM) staging system, revised based on the evidence that exists around prognostic factors and current treatment strategies, emphasizes the importance of depth of invasion and the number of locoregional nodes involved as major prognostic factors. For the first time, this represents a consensus approach of Eastern and Western countries (2,3). To facilitate reporting and provide guidance for patients with gastroesophageal (GE) junction cancers, they are now classified under esophageal cancer, although it is important to remind ourselves that many clinical trials designed for gastric cancers include a significant proportion of GE junction tumors and many esophageal cancer trials also included some proximal gastric cancers, complicating the interpretation of the literature and its application in clinical practice.

There are many heterogeneous subgroups under the broad heading of gastric cancers. Tumors arising from different anatomical locations have access to different routes of spread. Tumors with different histological (e.g., diffuse *vs.* others) and molecular [e.g., human epidermal growth factor receptor-2 (HER2)] (4) characteristics have different etiology (5), prognosis (4,6), and response to therapy (7). Patients from Asia, North America and Europe differ in terms of their toxicity profiles and response to treatments (8).

The objective of this review is to provide the rationale, evidence and technical considerations comparing the use of pre and postoperative radiotherapy (RT) in gastric cancer.

## What is locally advanced gastric cancer?

While what constitutes early gastric cancer is relatively well defined (9), there is considerable variability in what is considered locally advanced disease. DE Sol *et al.* (10) provided a summary of definitions extracted from recent trials highlighting this variation. A minority of authors use the term to describe the locoregional extent of disease irrespective of whether distant disease is present, while the more common approach refers to patients with no evidence of metastatic disease (M0), where invasion of muscularis and beyond is present, with or without nodal involvement. For example, the pivotal randomized trial reported by

Macdonald *et al.* (11) in the management of gastric cancer that resulted in the generalized adoption of postoperative chemoradiotherapy (CRT) employs the definition of stage Ib-IV (M0) as advanced cancers.

For the majority of investigators, the term locally advanced gastric cancer is a general term that is used to describe patients with a modest survival with surgery alone. For the purpose of this review, we will focus our deliberations with this definition in mind, where the risk of recurrence would justify the use of adjuvant or neoadjuvant therapies. In TNM terms, patients with locoregional disease, with T stage of submucosal involvement or higher or node positive disease (T2-4, N1-3, M0; TNM v7) are being staged as locally advanced gastric cancer, with a five-year overall survival (OS) rate following complete resection in the range of 57% (3).

Anatomical definition of lymph node stations for gastric cancer was described by the Japanese Gastric Cancer Association and has been widely adopted. Nodal stations 1-12 (1: paracardial nodes to 12: hepatoduodenal ligament nodes) and 14v (lymph nodes along inferior mesenteric vein) are defined as regional gastric lymph nodes, while metastasis to any other nodes are classified as M1 (12). While the prognostic value of the number of involved nodes is of critical importance, the anatomic extent of metastatic nodes also conveys prognostic significance, with extra-perigastric nodal stations conveying a worse prognosis than the perigastric nodes (13,14).

## What is optimal surgery?

A discussion on the role of neoadjuvant or adjuvant therapy is incomplete without a brief consideration of the clinical impact of the type and extent of surgery, the central curative modality for patients with gastric cancer. While the fundamental surgical principles of achieving a complete resection with negative margins, and the more recently adopted quality indicator of a minimum of nodes resected (e.g., 16) (15) are uniformly accepted, significant variations in approach exist in other areas of surgical decision-making.

The extent of gastric resection is based on oncologic principles. The location, extent and type of gastric cancer will dictate the extent of resection. Diffuse type cancers require a total gastrectomy, regardless of the location of the gross tumor. Total gastrectomy is required for large tumors or tumors of the lesser curve or body of the stomach. Antral cancers may be adequately resected with a distal gastrectomy if a 5 cm margin can be achieved. Proximal

gastric cancers are generally resected by a total gastrectomy because of the poor functional result due to intractable reflux esophagitis when the distal stomach is anastomosed to the esophagus. Locally advanced proximal cancers often require resection of the spleen and tail of pancreas because of direct extension of the primary tumor. If the tumor involves the distal esophagus, a 5 cm margin or more on the esophagus is required to reduce anastomotic recurrences. Rarely, a proximal gastrectomy with reconstruction using a short segment of pedicle jejunum is used for small tumors of the proximal stomach, allowing preservation of the antrum.

The major factor of ongoing debate is the extent of lymph node dissection. D1 dissection generally describes the removal of nodal stations 1-7 (perigastric nodes including pericardial, lesser curvature, greater curvature, supra and infrapyloric, along the trunk of L gastric artery) while D2 dissection refers to the removal of lymph node stations up to 12 (D1 and splenic hilar, hepatoduodenal ligament) (12). The effect of an extended lymphadenectomy provides greater clearance of locoregional nodes and potentially better sampling of the nodes. Extended *vs.* limited (D2 *vs.* D1) dissections were compared in several randomized trials and summarized most recently using a systematic review by Jiang *et al.* (16). Data from eight randomized trials conducted in Asia, Europe and Africa involving over 2,000 patients were included. Five-year OS was similar between the two approaches. However, postoperative mortality rates were significantly higher for patients treated with D2 dissection [D2 *vs.* D1, 18% *vs.* 11%; relative risk (RR) 0.58, 95% confidence interval (CI): 0.47-0.71]. Other morbidities (e.g., anastomotic leak, pancreatic leak, reoperation rates, wound infection, pulmonary complications and postoperative mortality) all favored D1 dissection, (D2 *vs.* D1, 37% *vs.* 21%; RR 0.62, 95% CI: 0.5-0.76), while perioperative hemorrhage risks were equivalent. Subgroup analysis would suggest that D2 dissection, without spleen and pancreas resection, is better tolerated with a trend towards lower gastric cancer mortality (D2 *vs.* D1, 41% *vs.* 48%; RR 1.19, 95% CI: 0.98-1.44).

Notwithstanding these conclusions, the modest cure rate achievable for most locally advanced cancers despite complete surgical resections (R0), the desire to optimize surgery by adhering to sound oncological principles, the subgroup data that suggest superior survival when D2 dissection is used (without routine splenectomies and pancreatectomies) provide the justification to advocate for gastrectomy with D2 dissections, in expert hands, as the optimal surgical standard. Indeed, using a RAND/UCLA

appropriateness study design, an expert panel considered D2 lymphadenectomy in all patients with tumors >T1N0. The panel also found the use of total gastrectomy for all patients and distal gastrectomies for patients with distal gastric cancers as appropriate (17).

Whether the factors leading to variations in surgical decisions were related to patient comorbidities, tumor extent or surgical expertise, different quality and extent of surgery is expected to have an impact on survival, treatment related morbidity and mortality and postoperative functional status. For patients with significant morbidities in the postoperative setting, many would not be suitable for additional adjunctive therapies even if there were indications to consider them. Judicial use of prognostic factors and clinical experience is the cornerstone for choosing the best approaches for individual patients.

### What is the role of RT?

RT, a locoregional treatment, is likely to be most impactful if there is a significant risk of local regional recurrence despite optimal surgery. This may occur as a result of seeding of the tumor bed, challenges in achieving good resection margin clearance, or microscopic residual lymphatic involvement. The rationale for the optimal timing of RT, pre *vs.* postoperative, and the optimal way of combining systemic therapies with RT hinges on a complex relationship between the modalities, additive or synergistic, and the effect on anticipated toxicities and relative therapeutic ratio. These factors will be discussed in the following section, followed by a discussion of the existing evidence, and ongoing trials.

### How effective is the state of the art surgery in securing local control?

Locoregional recurrence rates are often subject to detection and reporting biases. They are most likely to exist when locoregional recurrence pattern is not planned as an important outcome and where follow-up practices are not standardized. Consequently, some studies report on the site of first recurrence only, while others on recurrences at any time if they were followed. Geographic misses in relation to the extent of surgery, and the extent of RT, is labor intensive and generally not available to guide modifications on treatment delivery. Notwithstanding these biases, locoregional recurrence rates in the surgery alone arm are on the order of 20% (18) to 70% (19) depending on the

**Table 1** Pattern of recurrence following surgery alone (selected randomized trials)

RCTs	N	Local regional recurrence	
Hartgrink <i>et al.</i> (Dutch) (20)	D2 vs. D1 dissection 331 vs. 380 <sup>†</sup>	D2 31.8% (95/299)	D1 42.2% (154/365)*
Zhang <i>et al.</i> (21)	Preoperative RT vs. surgery alone 171 vs. 199	Preoperative RT 38.6%	Surgery 51.7% (P<0.025)
Cunningham <i>et al.</i> (18)	Preoperative CT vs. surgery alone 250 vs. 253	Perioperative CT 14.4% (36/250)	Surgery 20.6% (52/253) <sup>§</sup>
Macdonald <i>et al.</i> (19,22)	Postoperative CRT vs. surgery alone 120 vs. 177	Postoperative CRT 65.0% (78/120) <sup>‡</sup>	Surgery 71.8% (127/177)

<sup>†</sup>, Number achieving curative resection; \*, denominator equals total treated curatively minus postoperative deaths; <sup>§</sup>, denominator equals patients assigned to the group; <sup>‡</sup>, patients could have relapses at multiple sites, total number of relapses greater than number of patients. RCT, randomised controlled trial; RT, radiotherapy; CT, chemotherapy; CRT, chemoradiotherapy.

**Table 2** Pros and cons of pre vs. postoperative radiotherapy

Factor	Preoperative	Postoperative
Patient population	Decision based on clinical staging	Decision based on pathological staging
Toxicity burden	Toxicity of preoperative therapy may preclude surgery	Toxicity of surgery may preclude the use of postoperative therapy
Timing of surgery	Need to be delayed until completion of surgery	For all patients as first modality
Treatment volume	Generally smaller	Generally larger
Dose effect	Require less dose for the same local control benefit	Require more dose for the same local control benefit

quality and extent of the surgery. Even if we restrict our focus to trials with a high compliance for D2 dissections, locoregional recurrence remains a significant problem with a range of 32-42% (20). This pattern of locoregional recurrence would suggest a high potential that RT can have a major role in optimizing the management of patients with locally advanced gastric cancer (*Table 1*).

### Pros and cons of pre vs. postoperative RT—general principles

The issue of whether RT is best employed in the preoperative or postoperative setting [with or without chemotherapy (CT)] has been the subject of debate in the management of many cancers such as rectum (23), sarcoma (24), and esophageal cancer (25) to name a few. Some general principles apply (*Table 2*).

The accuracy of clinical staging, typically based on diagnostic tests, plays an important role in identifying the appropriate patients for preoperative therapy, avoiding

over treatment of early stage patients and the futile use of curative strategies in those who are harboring more advanced metastatic disease. For gastric cancer patients, the use of gastric protocols in the CT acquisition, incorporation of endoscopic ultrasound, laparoscopy and peritoneal washings are practices that are increasingly sophisticated to allow accurate preoperative staging.

The toxicity burden of multimodal therapies may differ based on the symptom profile and premorbid condition of the patient. Careful consideration of patients' baseline condition and suitability for combined modality is necessary to avoid unacceptable treatment related morbidity and mortality. Borderline patients taken through preoperative therapy may delay or preclude the definitive surgery. Some patients with acute complications from the primary (e.g., uncontrolled bleeding, obstruction) demand immediate surgery even if preoperative therapy may have a role to play. Postoperative therapy typically needs to be given within a finite period following surgery (e.g., 10 weeks) beyond which the anticipated benefits are expected to diminish.

**Table 3** Summary of randomized trials, systematic reviews and meta-analysis comparing pre or postoperative (CT) RT with other strategies

RCT	Number of studies	References
Postoperative CRT vs. surgery alone	2	(22,26)
Preoperative RT vs. surgery alone	4	(27-29,46)
Postoperative RT vs. postoperative CT	1	(30)
IORT vs. surgery	1	(31)
Postoperative CRT vs. postoperative CT	8	(32-39)
Systematic reviews and meta-analyses	4	(40-43)
Guidelines	1	(44)

RCT, randomised controlled trial; CRT, chemoradiotherapy; RT, radiotherapy; CT, chemotherapy; IORT, intraoperative radiotherapy.

In the original Macdonald trial 17% of patients stopped treatment because of toxicity, while major ( $\geq$  grade 3) toxicity occurred in 33% of patients.

The design of the RT target volume requiring treatment is generally smaller in the preoperative setting. The presence of the tumor typically displaces and minimizes the need to encompass normal structures (e.g., small bowel). In contrast, postoperative treatment typically requires inclusion of normal structures that would fill to original tumor site, and difficult to avoid when the tumor bed needs to be included. Surgery can open previously uninvolved planes that become potential routes of spread. Anastomosis and reconstructions may result in regions of interest located adjacent to sensitive structures (e.g., duodenal blind loop and its relationship to the L kidney, esophagogastric anastomosis), requiring expansion of treatment fields or suboptimal coverage of critical structures.

Finally, preoperative strategies generally require lower doses to achieve the same local control effect, with obvious benefits on the long term anticipated effect following treatment. This phenomenon is likely attributable to the increase in hypoxic tissues in the postoperative state.

### What is the evidence?

In an attempt to clarify the role of RT for gastric cancer, for the purpose of this review, emphasis is placed on

randomized trials that target the current definition (TNM 7<sup>th</sup> edition) of gastric cancer. Where GE or esophageal cancers represent >30% of the participants, the trials were excluded (unless subgroup data is available for gastric cancers). Similarly, systematic reviews, and meta-analyses that collate the evidence that emphasizes this body of primary studies are preferentially discussed. Clinicaltrial.gov was search for ongoing trials. Medline and Cochrane databases were searched. Guidelines Clearinghouse was searched for current evidence based guidelines (last searched Jun 2014).

A total of 16 randomized trials (11,21,26-39), four systematic reviews (40-43) addressing the role of RT in gastric cancer were identified with the most recent one published in 2014 (40). A single practice guideline (44) that is relevant to our question is listed under the National Guidelines Clearinghouse (45) and is included. A summary of the relevant references in the different study designs is included (*Table 3*).

### Preoperative RT vs. surgery alone (*Tables 4,5*)

Preoperative RT is the subject of investigation in four randomized trials. The studies were performed in Russia, Ukraine and China and published between 1994 and 2002. The quality of reporting is generally poor with limited information on the quality of the surgery, adequacy of nodal dissection and extent of tumor involvement especially when contrasted against contemporary standards. With the exception of the study from China with a sample size of 370 patients, the studies were small (and likely underpowered). None of the studies provided a justification for the sample size design. The dose fractionation used was hypofractionated (2 Gy in 5 fractions) with the addition of intraoperative RT. In one (28), and the addition of hyperthermia in another study (29). The study from China employed a dose fractionation of 40 Gy in 20 fractions. The techniques used were all simple with anterior posterior *vs.* posterior anterior beam arrangement (APPA) techniques to upper abdominal fields that have generally been replaced by more sophisticated planning techniques.

Notwithstanding the significant risk of bias inherent within these trials, the study by Zhang *et al.* (21), the largest within this group, observed a survival benefit of approximately 7% (10 years OS: 20% preoperative RT *vs.* 13% surgery alone;  $P < 0.05$ ), using a modest dose of 40 Gy in 20 fractions.

A meta-analysis performed by Fiorica *et al.* (41) in



**Table 4** Randomized trials comparing preoperative RT vs. surgery alone—study characteristics

Author	Year	Site	Eligibility	Characteristics	N		Study arm			
					Preoperative RT	Surgery alone	Surgery	RT dose	RT volume	Technique
Skoropad (27)	2002	Russia	Stomach Ca Adenocarcinoma	Esophagus involvement 22 preoperative RT, 16 surgery Diffuse NA SII/IV: 31 preoperative RT, 33 surgery R0 not stated, R1 preoperative RT 3, surgery 4 D1 100% Total gastrectomy 27 preoperative RT, 20 surgery No. nodes removed: NA No. nodes involved: NA	77 [51] <sup>§</sup>	75 [51] <sup>§</sup>	D1 dissection*	20 Gy in 5 fractions	Whole stomach, regional nodes along curvatures, celiac axis and branches 20x20 cm <sup>2</sup> field size with no shielding	APPA
Skoropad (28)	2000	Russia	Stomach Ca (esophageal involvement <3 cm included) Adenocarcinoma	Esophagus involvement not stated Diffuse NA T3-4 20 preoperative RT, 21 surgery N+ 17 preoperative RT, 13 surgery R0 not stated R1 3 preoperative RT, 3 surgery D1 100% Total gastrectomy 19 preoperative RT, 16 surgery No. nodes removed: NA No. nodes involved: NA	59 [40] <sup>§</sup>	53 [38] <sup>§</sup>	D1*	Preoperative RT 20 Gy in 5 fractions and IORT 20 Gy in 1 fraction	Preoperative RT: primary tumor and regional nodes (10x12 to 14-16 cm fields) IORT: tumor bed and celiac axis approximate 6-10 cm field	APPA (Co60) IORT: direction electron beam (8-22 MeV)
Zhang (21)	1998	China	Stomach Ca (cardia)	Esophagus involvement not stated Diffuse NA (one case SCC) SIII/IV preoperative RT 71.2% surgery 89.4% R0 not stated D2 not stated Total gastrectomy: NA No. nodes removed: NA No. nodes involved: NA	171	199	NA	40 Gy in 20 fractions	Cardia, lower segment of esophagus, fundus, lesser curve, hepatogastric ligament, superior border at 4-5 cm from cranial extent of tumor	APPA
Shchepotin (29)	1994	Ukraine	Stomach Ca	Esophagus involvement not stated Diffuse NA T2,3,4: 3%, 65%, 32% N+: 65% R0 not stated D1 not stated Total gastrectomy: 51% No. nodes removed: NA No. nodes involved: NA	98 preoperative RT	100	NA	20 Gy in 5 fractions HT: tumor temperature to 42 °C daily x4 days, 2 hours postoperative RT	Not specified	APPA

<sup>§</sup>, patients were randomized to be explored, and if curative resection possible, to receive protocol treatment. Numbers in square brackets are patients eligible after exploration; \*D1, complete dissection of perigastric nodes in all patients; RT, radiotherapy; Ca, cancer; NA, not available; R1, positive resection margins; APPA, anterior posterior vs. posterior anterior beam arrangement; IORT, intraoperative radiotherapy; SCC, squamous cell carcinoma; RTHT, radiotherapy and hyperthermia.



Table 5 Randomized trials comparing preoperative RT vs. surgery alone—outcomes

Author	Year	N <sup>†</sup>		FU		OS <sup>‡</sup>		Regional RFS			Toxicity <sup>‡</sup>		
		RT + surgery	Surgery	Median	RT + surgery	Surgery	P	RT + surgery	Surgery	P	RT + surgery	Surgery	P
Skoropad (27)	2002	77 [51] <sup>§</sup>	75 [51] <sup>§</sup>	NA	5-year: 59%, 10-year: 32%	5-year: 30%, 10-year: 18%	NS	NA	NA	-	Percentage with complications: 57%	Percentage with complications: 49%	NS
Skoropad (28)	2000	59 [40] <sup>§</sup>	53 [38] <sup>§</sup>	NA	5-year: 50%	5-year: 50%	NS	NA	NA	-	Percentage with complications: 35%	Percentage with complications: 50%	-
Zhang (21)	1998	171	199	10.6 years	5-year: 30%, 10-year: 20%	5-year: 20%, 10-year: 13%	<0.01	5-year: 38.6%	5-year: 51.7%	<0.025	Operative death: 1%, anastomotic leak: 1.8%	Operative death: 2.5%, anastomotic leak: 4%	NS
Shchepotin (29)	1994	98 preoperative RT, 96 preoperative RTHT	100 preoperative RT, 51% preoperative RTHT	NA	5-year: 45% (preoperative RT), 51% (preoperative RTHT)	5-year: 30%	<0.05	NA	NA	-	NA	NA	-

<sup>†</sup>, none of the studies provided a sample size justification; <sup>‡</sup>, none of the studies provided RFS as an outcome of interest; <sup>§</sup>, not all toxicity data presented are represented, only key representative parameters presented; <sup>§</sup>, patients were randomized to be explored, and if curative resection possible, to receive protocol treatment. Numbers in square brackets are patients eligible after exploration. RT, radiotherapy; FU, 5-fluorouracil; OS, overall survival; CI, confidence interval; RFS, relapse free survival; NA, not available; NS, not specified; RTHT, radiotherapy and hyperthermia.

2007 provided summary statistics across the relevant trials showing a survival benefit with RT alone with a odds ratio (OR) 0.54, 95% CI: 0.43-0.68 (41). A more recent update by Pang *et al.* in 2014 using a different set of selection criteria arrived at a similar observation and conclusions (40).

While the primary preoperative RT studies were conducted with less sophisticated RT techniques and quality of surgery, the observation remains potentially compelling that modest doses of local regional RT delivered prospectively can complement surgery to provide a survival advantage. It is tantalizing to hypothesize that with optimal combination quality surgery and CT; more significant gains can be accomplished.

### ***Postoperative CRT vs. surgery***

The pivotal postoperative CRT *vs.* surgery trial (INT0116) was first reported by Macdonald *et al.* (11) resulting in the general adoption of postoperative CRT in addition to surgery as the standard treatment for gastric cancer in North American and Europe. Updated results were subsequently published (22) with a median follow up of more than 10 years, confirming the original observation of OS benefit of 9% with a hazard ratio (HR) 1.32 (95% CI: 1.1-1.6; P=0.0046). Relapse free survival (RFS) was 11% with a HR of 1.51 (95% CI: 1.25-1.83; P<0.001). The pattern of recurrence, with 24% fewer relapses occurring in patients in the CRT arm, confirmed the degree of benefit predicted through the original pattern of failure analysis by Gunderson *et al.* in 1982 (47). Subgroup analysis showed patients with diffuse histology (typically associated with poorer prognosis occurring in younger, female patients) appear to benefit less, while patients with more nodes (N4+ *vs.* others) derived greater benefit. The authors suggested extreme caution in their interpretation given the small numbers within some of the subgroups (22). Moertel *et al.* (48) also in this category is of historic interest only and is not discussed further.

### ***Postoperative RT vs. postoperative CT***

Hallisey *et al.* (30) reported on the second British stomach cancer trial comparing postoperative RT alone with postoperative CT. Patients were randomized to one of three arms, surgery alone, postoperative RT (45 Gy in 25 fractions, boost 5 Gy) *vs.* postoperative CT [mitomycin, doxorubicin and 5-fluorouracil (5FU)]. Proportion of

patients with GE junction tumor was not stated. No survival advantage can be seen for 5 years OS (surgery *vs.* pRT *vs.* pCT: 20% *vs.* 12% *vs.* 19%).

### ***Postoperative CRT vs. postoperative CT (Tables 6,7)***

Six studies were designed to examine the incremental role of RT when added to postoperative CT and is the most frequently studied strategy in recent years, with four published in 2012 and two in 2010. In four of the studies, only patients who had a D2 dissection were included (32,33,35,37). Similarly, the RT used was most consistent with contemporary practice. All studies used a dose fractionation of 45 Gy in 25 fractions. All studies employed treatment targets consistent with standard practice (anastomosis, duodenal stump, local regional nodes, residual stomach, and tumor bed) with some modifications. Kim (32) and Lee (33) and Kwon (32,33,37) all excluded tumor bed treatments with the exception of T4 lesions. Coverage of the stomach remnant is more flexible permitting variations in favor of reducing dose to normal structures (e.g., kidneys). Two studies used intensity-modulated radiation therapy (IMRT) (34,35), one conformal RT (37) while three used older techniques (APPA) (32,33,36).

The different CT regimens used and the discussion around the optimal one is presented in the next section.

All but one study was underpowered. Three studies closed prematurely and lack the power to detect the difference they were looking for (32,36,37) and two (34,35) were small and almost certainly also underpowered. The ARTIST trial reported by Lee *et al.* (33) was the only study that successfully completed accrual and dominated this group of studies with 458 participants. It also suffered from sample size issues, with an unexpectedly high proportion of earlier stage tumors resulting in a lower event (recurrence) rate than anticipated.

There is some evidence to support improvements in local regional control (32,35) although the largest study (ARTIST) (33) did not find this benefit. While local regional control was extremely high (92% CT, 95% CRT) in the ARTIST trial, local RFS ranged from 63% CT to 84% CRT supporting the potential in improving outcomes by RT. No difference in survival, RFS and local regional relapse free was observed.

### **Choice of systemic regimen**

5FU has been the mainstay chemotherapeutic agent when

**Table 6** Randomized trials comparing postoperative CRT vs. postoperative CT—study characteristics

Author	Year	Site	Eligibility	Characteristics*	N		Surgery		Control arm		Study arm		Technique
					CRT	CT	CRT	CT	FL	FL	RT dose	RT volume	
Kim (32)	2012	Korea	Stomach Ca (no GE jc)	No GE jc	46	44	R0	FL	FL	45 Gy in 25 fractions	Standard RT except —tumor bed for T4 only	Standard RT except —tumor bed for T4 only	APPA
			Adenocarcinoma SII-IV (M0) AJCC 2002	Diffuse: 56% T2,3,4: 59%, 57%, 7% R0: 100% D2: 100%			D2					— modify stomach remnant coverage to maintain renal tolerance	
Lee (33) (ARTIST)	2012	Korea	Stomach Ca	No GE jc documented	230	228	R0	XP	XP	45 Gy in 25 fractions	Standard RT except —tumor bed for T4 only	Standard RT except —tumor bed for T4 only	APPA
			Adenocarcinoma SII-IV (M0) AJCC 2002	Diffuse: 60% SIV (M0): 12% R0: 100% D2: 100%			D2					— stomach remnant not routinely included	
Yu (34)	2012	China	Stomach Ca	No GE jc documented	34	34	R Ns	FL	FL	45 Gy in 28 fractions	Standard RT	Standard RT	IMRT
			Adenocarcinoma T3-4 and/or N+ R status Ns D1 or 2	Histology type: NS T2,3,4: 11%, 62%, 28% R0: NA D2: 69%			D1-2					No other modifications described	
Zhu (35)	2012	China	Stomach Ca (GE jc included)	GE jc: 9% CT, 16% CRT	56	59	R0	FL	FL	45 Gy in 25 fractions	Standard RT	Standard RT	IMRT
			Adenocarcinoma T3-4 ± N+ UICC 7 <sup>th</sup> edition R0 D2	Histology type: NA SIV (M0): 15% R0: 100% D2: 100%			D2						
				Total gastrectomy: 51% Nodes removed (mean): 41 CT, 46.5 CRT Nodes involved (mean): 9 CT, 8 CRT									
				Total gastrectomy: NA Nodes removed (median): 40 Nodes involved (median): 3									
				Total gastrectomy: NA Nodes removed: NA									
				Total gastrectomy: NS Nodes removed: NS Nodes involved ≥7: 21%									

**Table 6** (continued)

Table 6 (continued)

Author	Year	Site	Eligibility	Characteristics*	N		Control arm			Study arm		Technique
					CRT	CT	Surgery	CRT	CT	DP	RT dose	
Bamias (36)	2010	Greece	Stomach Ca (GEjc included) Adenocarcinoma T3 ± N+ (AJCC 2002) R0 D status Ns	GE jc: Ns (esophagogastrectomy 7%) Diffuse: 32% CRT, 59% CT T2,3,4: 3%, 18%, 75% R0: 100% D0: 56% D1+2: 44% Total gastrectomy: 40% Nodes removed (median): 14 Nodes involved (median): 4	72	71	R0 D0-2	XP	DP	45 Gy in 25 fractions	Standard RT —proximal T3 include medial L hemidiaphragm —proximal lesions may exclude pancreaticoduodenal nodes —antral lesions exclude splenic hilar	APPA
Kwon (37)	2010	Korea	Stomach Ca Adenocarcinoma SIIa-IV (M0) (AJCC 2002) R0 D2	No GE jc documented Diffuse: 65% CRT, 43% CT SIV (M0): 23% CRT, 10% CT R0: 100% D2: 100% Total gastrectomy: Ns Nodes removed (median): Na Nodes involved (median): Na	31	30	R0 D2	FP	FP	45 Gy in 25 fractions	Standard RT —preoperative tumor bed included	Conformal RT
Dent (38)	1979	S. Africa	Stomach Ca Adenocarcinoma All stages Resection not stated									

\*, when key characteristics are equally distributed between the arms, total for the whole study is presented. Where imbalance is noted, data by treatment arm is presented. CRT, chemoradiotherapy; CT, chemotherapy; RT, radiotherapy; Ca, cancer; GE jc, gastroesophageal junction cancers; AJCC, American Joint Committee on Cancer; R0, complete resection of disease *en bloc*, negative resection margins; D status (D0/1/2), describes extent of nodal dissection; FL, 5 cycles: (fluorouracil 425 mg/m<sup>2</sup>, leucovorin 20 mg/m<sup>2</sup>) x4 days, 4 weeks interval (as used in INT 0116); FL with RT, (fluorouracil 425 mg/m<sup>2</sup>, leucovorin 20mg/m<sup>2</sup>) x5 days x1 cycle, RT (45 Gy in 25 days, 5 days/week) with 2 cycles of FL (fluorouracil 400 mg/m<sup>2</sup>, leucovorin 20 mg/m<sup>2</sup> days 1-4, days 29-31), FL (fluorouracil 425 mg/m<sup>2</sup>, leucovorin 20 mg/m<sup>2</sup>, 4 weeks interval) x2 cycles; standard RT volumes, anastomosis, duodenal stump, regional nodes, residual stomach, tumor bed; APPA, anterior posterior versus posterior anterior beam arrangement; NA, not available; XP, 6 cycles: capecitabine 1 g/m<sup>2</sup> bid days 1-14, cisplatin 60 mg/m<sup>2</sup> day 1 every 3 weeks; XP with RT arms, XP (2 cycles), capecitabine 825 mg/m<sup>2</sup> bid daily during RT, XP (2 cycles); NS, not specified; IMRT, intensity-modulated radiation therapy; UICC, Union for International Cancer Control; DP, docetaxel 75 mg/m<sup>2</sup> day 1, cisplatin 75 mg/m<sup>2</sup> (or carboplatin AUC 5) days 1, 3, weekly, x6 cycles; DP during RT, same as CT alone, RT 3-4 weeks after cycle 3; FP, 5-fluorouracil 1 g/m<sup>2</sup> continuous infusion days 1-5, cisplatin 60 mg/m<sup>2</sup> day 1 x6 cycles; FP with XRT, 5-fluorouracil 1 g/m<sup>2</sup> continuous infusion days 1-5, cisplatin 60 mg/m<sup>2</sup> day 1, 3 weeks gap, 1 cycle, day 28 XRT x5 weeks with capecitabine 1,650 mg/m<sup>2</sup> daily in 2 doses, 4 weeks post RT, FP x3.

**Table 7** Randomized trials comparing postoperative CRT vs. postoperative CT—outcomes

Author	Year	N	Planned sample size	FU		OS		DFS		Local regional RFS				Toxicity <sup>†</sup>			Notes
				CRT	CT	CRT	CT	CRT	CT	P	CRT	CT	P	CRT	CT	P	
Kim (32)	2012	46	44	140	86.7 months [60-117]	5-year: 65.2% (51.4-79) 5-year: 54.6% (39.8-69.3)	5-year: 0.67 (0.25-1.75) 5-year: 0.67 (0.25-1.75)	5-year: 60.9% (36.8-75) 5-year: 50% (35.2-64.8)	5-year: 84.4% (72.7-96.1) 5-year: 62.7% (47.6-77.7)	0.04	≥ Grade 3 GI: 17.4% ≥ Grade 3 hemorrhage: 19.6%	≥ Grade 3 GI: 11% ≥ Grade 3 hemorrhage: 25%	NS	NS	NS	Study closed after accrual of 90 patients over 4 years due to slow accrual Subgroup analysis suggests stage III patients benefited more	
Lee (33) (ARTIST)	2012	230	228	448	53.2 months [37-77]	NA	NA	3-year: 78% 3-year: 74%	3-year: 95% 3-year: 92%	0.09	0.35	Treatment modifications: 35%, death*: 1	Treatment modifications: 52%, death*: 1	-	-	Final analysis was scheduled for when 227 events has occurred. The actual analysis was done when 127 events has occurred due to the lower event rate (due to the lower event rate as a result of large % of stage Ib/II patients) Subgroup analysis suggest N+ patients benefited more	
Yu (34)	2012	34	34	NA	NA	3-year: 67.7% 3-year: 44.1%	0.04	3-year: 55.8% 3-year: 29.4%	NA	NA	NA	Grade 1-2 anorexia: 74% Grade 1-2 N+V: 82% Grade 1-2 neutropenia: 71%	Grade 1-2 anorexia: 44% Grade 1-2 N+V: 74% Grade 1-2 neutropenia: 44%	<0.05	>0.05		

**Table 7** (continued)

Table 7 (continued)

Author	Year	N	Planned sample size	FU		OS		DFS		Local regional RFS			Toxicity <sup>†</sup>			Notes
				CRT	CT	CRT (95% CI)	CT (95% CI)	P	CRT (95% CI)	CT (95% CI)	P	CRT	CT	P		
Zhu (35)	2012	56	NS (OS was primary endpoint)	42.5 months (all patients alive completed 5 years FU)	5-year: 48.4%, 41.8% HR 1.35 (1-1.78)	0.1	5-year: 45.2%, 35.8%	5-year: 0.03	5-year: 0.04	≥ Grade 3 vomit: 0 ≥ Grade 3 diarrhea: 1.6% ≥ Grade 3 leucopenia: 7.5%	≥ Grade 3 vomit: 0 ≥ Grade 3 diarrhea: 0 ≥ Grade 3 leucopenia: 7.3%	-	-	-	-	
Bamias (36)	2010	71	200 To detect an increase in survival of 20% (35% CT, 55% CRT), power of 80% and alpha 0.05	53.7 months (0.1-77.8)	3-year: 57%, 61%	NS	3-year: 48%, 51%	NS	-	≥ Grade 3 febrile neutropenia: 7% ≥ Grade 3 diarrhea: 4%	≥ Grade 3 febrile neutropenia: 9% ≥ Grade 3 diarrhea: 7%	NA	Study close after accrual of 147 over 3 years due to decreasing accrual	-	-	
Kwon (37)	2010	30	170 To detect a 20% increase in DFS (30% CT, 50% CRT, HR 1.7) with a power of 80% and two-sided alpha of 0.05	77.2 months (2.4-92.8)	5-year: 70.1%, 70%	NS	5-year: 76.7%, 59.1%	0.2	5-year: 0.4	≥ Grade 3 neutropenia: 48% ≥ Grade 3 diarrhea: 3.2%	≥ Grade 3 neutropenia: 17% ≥ Grade 3 diarrhea: 0%	-	Study close after accrual of 61 over 2.5 years due to slow accrual	-	-	

<sup>†</sup>, not all side effects reported are included. Diarrhea, neutropenia and nausea and vomiting are preferentially presented, as they are typically the most common; \*, one patient (CRT) died of neutropenic sepsis, one patient (CT) died of pneumonia. CRT, chemoradiotherapy; CT, chemotherapy; FU, 5-fluorouracil; OS, overall survival; CI, confidence interval; DFS, disease free survival; RFS, relapse free survival; GI, gastrointestinal; NS, not specified; HR, hazard ratio; NA, not available.



used concurrently with radiation, either in bolus form at the beginning and end of radiation (11,32,34,35), continuous infusional form (49), or in oral form as capecitabine (33,37). However, the CT before and after the radiation has been more varied. Other than 5FU (11,32,34,35), the following other CT regimens have been used: epirubicin, cisplatin and 5FU (ECF) (49), capecitabine and cisplatin (33), 5FU and cisplatin (37), as well as cisplatin and docetaxel (36).

Two additional important trials need to be considered when addressing the choice of systemic backbone when combined with RT. The MAGIC trial (18) established the survival benefit provided by ECF perioperative CT compared with surgery alone. A survival benefit was clearly established (5 years OS, 36% CT *vs.* 23% surgery alone; HR 0.75, 95% CI: 0.6-0.83; P=0.009), as well as an advantage in progression free survival (HR 0.66; 95% CI: 0.53-0.71; P<0.001). The CALBG trial (49) was the only phase III trial that compared the optimal CT when used in conjunction with postoperative radiation. The control arm used 5FU as in the Macdonald protocol, while the experimental arm used ECF CT before and after RT. Both arms used infusional 5FU during radiation (as opposed to bolus 5FU at the beginning and end of RT). Both groups had similar OS, and therefore the trial did not meet its primary endpoint. However, toxicity was reported to be less in the ECF arm, and the final publication is awaited.

At Princess Margaret, we still use 5FU as per the Macdonald protocol, as this has the best and longest standing evidence. However, others have switched to infusional 5FU during RT, as is often done in other gastrointestinal cancers such as rectal cancer, and some other centers have used ECF before and after radiation.

In the ongoing trials, TOPGEAR (50) is designed with perioperative ECF (6 cycles) *vs.* the same regimen replacing the 3<sup>rd</sup> cycle of ECF with RT with 5FU or capecitabine. CRITICS (51) employs a similar strategy using epirubicin, cisplatin and capecitabine (ECC) ×3 cycles, *vs.* the same regimen with RT and concomitant cisplatin and capecitabine. Zhou (52) and Xie (53) *et al.* use 2 cycles of capecitabine and oxaliplatin (CapOx), Kang *et al.* use cisplatin and capecitabine in one study (54), and S1 and oxaliplatin in ARTIST II (55). Biological agents are actively being investigated especially in North America (Table 8).

### Summary

Taken together, these trials showed an interest in the use

of preoperative RT (reported between 1994 and 2002), although perhaps given the quality of the evidence and the variable results, the findings were not translated into adoption of this strategy into clinical practice. The Macdonald study [2002] single handedly changed clinical practice to the adoption of postoperative CRT with a 9% survival benefit. Recent efforts (reported between 2010 and 2012), employing contemporary surgery, RT and “standard” CT, were focused on establishing the incremental benefit of adding RT to CT in the postoperative setting, found improved local control, but no survival benefit. A single small dated study [1994] would suggest postoperative RT alone to be ineffective.

Preoperative RT alone offered some tantalizing evidence that it can also improve survival but the power of inference is lower. The significant local regional rates that are expected from locally advanced disease despite improved surgical quality (including safe delivery of D2 dissections) are powerful reasons to motivate a strong support for current studies that are designed to establish the effectiveness of preoperative CRT when used together with optimized CT and surgery.

## Technical considerations of RT

### Choice of dose fractionation

The typical dose fractionation of 45 Gy in 25 fractions is employed quite uniformly across current practice and in ongoing clinical trials, given the relatively large target volume (driven by the distribution of local regional nodes predominantly), and the intimate relationship with critical normal structures and their normal tissue tolerances.

### Choice of target volume

The choice of target volume is based on the principle to include all the local regional nodes at risk and the threat posed by direct microscopic extension.

Nodal regions encompassed would parallel what would be captured in an extended D2 dissection, where perigastric, celiac axis, pancreaticoduodenal, porta hepatis, are targeted. Para-aortic nodes are included where this corresponds to the cranial-caudal extent of the overall target volume. Splenic hilar nodes are included in proximal tumors.

To account for the risk of recurrence arising through direct extension of the primary, a margin surrounding the primary (in the preoperative setting), or a margin around

**Table 8** Ongoing clinical trials

PI/Study name	Study location(s)	Clinicaltrial.gov	Patient population	Sample size	Control arm	Study arm	Study start date	Projected completion date
<b>Preoperative</b>								
Leong TOPGEAR (50)	Australia, Europe, Canada	01924819	Stomach Ca GE jc if <2 cm of esophagus involvement T1-2N1 (T2N0 excluded), T3-4N + M0 D2 dissection recommended	750	ECF <sup>§</sup>	ECF RT: 45 Gy in 25 fractions	2009	2020
Zhou (52)	China	01815853	Stomach Ca T4anyNMO Dissection requirement: NA	620	Cap/Ox <sup>†</sup>	CapOx RT: 45 Gy in 25 fractions	2012	2022
<b>Postoperative</b>								
CRITICS (51)	Netherlands	00407186	Stomach Ca Slb-IVaM0 ≥ D1 dissection	788	ECC <sup>‡</sup>	ECC RT: 45 Gy in 25 fractions	2006	2014
Kang (54)	Korea	00323830	Slb, II, III, IV (T4N3M1nodes) D2 dissection	458	XP <sup>¶</sup>	XP RT: NA	2004	2011
Kang (55) ARTIST II	Korea	01761461	Gastric or gastroesophageal Ca SII/III, N + M0 ≥ D2 dissection	1,000	S1/Ox	S1/Ox RT	2013	2016
Xie (53)	China	01711242	Stomach Ca T3-4, N + M0 D2 dissection	300	Cap/Ox	CapOx RT: 45 Gy in 25 fractions	2012	2017

<sup>§</sup>, ECF: epirubicin 50 mg/m<sup>2</sup> day 1, cisplatin 60 mg/m<sup>2</sup> day 1, 5FU 200 mg/m<sup>2</sup>/day continuous intravenous infusion days 1-21, x3 cycles preoperative, 3 cycles postoperative. (5FU can be replaced by capecitabine 625 mg/m<sup>2</sup> twice daily); ECF/RT, cycle 3 ECF replaced by RT 45 Gy in 25 fractions, 5FU 200 mg/m<sup>2</sup>/d days 1-35 (5FU can be replaced by capecitabine 625 mg/m<sup>2</sup> twice daily); <sup>†</sup>, CapOx: capecitabine 1 g/m<sup>2</sup> days 1-14, oxaliplatin 130 mg/m<sup>2</sup> day 1, x2 cycles every 21 days; CapOx/RT, same chemo + RT 45 Gy in 25 fractions; <sup>‡</sup>, ECC: epirubicin 50 mg/m<sup>2</sup> day 1, cisplatin 60 mg/m<sup>2</sup> day 1, capecitabine 1 g/m<sup>2</sup> bid days 1-14, every 3 weeks, c3 cycles; ECC/RT, after ECC x3 cycles, 45 Gy in 25 fractions with cisplatin 20 mg/m<sup>2</sup> weekly, capecitabine 575 mg/m<sup>2</sup> bid daily during RT; <sup>¶</sup>, XP: capecitabine, cisplatin; S1/Ox, S and oxaliplatin; Ca, cancer; GE jc, gastroesophageal junction cancers; 5FU, 5-fluorouracil; RT, radiotherapy; NA, not available.

the perioperative tumor bed, residual stomach and excision margins on the tumor side, i.e., the anastomosis, and blind loop of the duodenum are used in the postoperative setting. The proximal hemi diaphragm is targeted for the same reasons in proximal tumors. In general terms, a clinical target volume (CTV) margin of 0.5-1 cm around the vasculature is used to capture the nodal groups. A margin of 0-0.5 cm around the primary for T1-2 lesions, and a margin of 0.5-1 cm for T3-4 primaries are typically used.

Certain modifications of these principles are generally permitted to reduce dose to normal structures under specific circumstances. For patients who have undergone a D2 dissection with adequate nodal sampling, omitting the preoperative tumor bed when the tumor is T3 or less, and omission of the entire residual stomach, are acceptable variations introduced in recent trials (32,33) with no adverse consequences reported.

At the conclusion of TOPGEAR, this study would have accrued 750 patients whereby half of the patients would have received preoperative CRT according to the method of target definition, with a thoughtful quality assurance program and is anticipated to provide high quality evidence on the appropriateness and effectiveness of the contouring guidelines used in this study.

### **Choice of treatment technique**

When preoperative CRT was first introduced, the Macdonald trial described the use of APPA or three field techniques (19). This is quickly superseded by the adoption of conformal techniques, intensity modulated and volumetric arc techniques.

With more sophisticated treatment approaches, special considerations need to be made during planning and treatment delivery to ensure reproducible and accurate targeting. Dietary guidelines are an attempt to ensure minimal and consistent stomach volumes throughout the planning and treatment period. At our institution, a cup of coffee and a slice of toast (or its equivalent) only 2 hours prior to RT is routinely recommended. Daily image guidance incorporating cone beam computed tomography is necessary to provide verification of fields designed with more sophisticated planning techniques with sharper dose gradients (e.g., conformal, IMRT) to avoid normal structures. Renal perfusion scan can provide differential renal function and is useful for refining beam geometry and permissible dose to the kidneys. Four dimensional-computed tomography scans provide individualized

assessment of respiratory organ motion assessment and planning target volume (PTV) margins (56).

A recent systematic review on comparison between standard and conformal three dimensional (3D) techniques supported superior normal tissue sparing with 3D CRT (57). More sophisticated techniques such as IMRT and tomotherapy, provide refinement in dosimetric advantages which could benefit particularly challenging cases although clinically significant differences at a population level is more difficult to demonstrate (58,59).

### **Ongoing phase III studies**

Globally, five randomized trials (50-53,55) are currently actively accruing, and one has completed accrual (54) and awaiting follow-up. Two studies examining the role of neoadjuvant RT when added to CT, and four studies addressed the role of RT in the adjuvant setting when added to CT.

### **Postoperative CT ± RT**

Kang *et al.* (54) has completed accrual in 2011 on a study in Korea comparing capecitabine, cisplatin (XP), with or without RT having recruited 458 patients, results pending. A second study by the same group (55) aims to accrue 1,000 patients, comparing S1/oxaliplatin with or without RT, scheduled to complete accrual in 2016. Xie *et al.* (53) is conducting a study in China targeting 300 patients comparing capecitabine/oxaliplatin with or without RT, scheduled to completed in 2017.

CRITICS (Clinicaltrials.gov NCT00407186) (51) is designed to compare perioperative CT with postoperative CRT uses 45 Gy in 25 fractions (with cisplatin and capecitabine), together with high quality surgery, pathology and RT quality control. This study initiated accrual in 2006 and is scheduled to complete accrual of its sample size of 788 patients.

### **Preoperative CT ± RT**

Zhou *et al.* is conducting a study in China comparing capcitabine/oxaliplatin in the preoperative setting in 620 patients, targeting completion of accrual in 2022 (52).

TOPGEAR (Clinicaltrial.gov NCT01924819) (50) is designed to deliver 45 Gy in 25 fractions, with 5FU in the preoperative setting during what would be the 3<sup>rd</sup> cycle of MAGIC CT. D2 dissection is strongly recommended. This study initiated accrual in 2009, and is scheduled to complete accrual of its sample size of 752 patients in 2020.

The design of this study is built upon three phase II

studies providing promising safety data. Postoperative use of CRT using ECF was tested in a phase II study demonstrating tolerability (60) ECF ×1 cycle followed by CRT (45 Gy in 25 fractions with concurrent 5FU) was tested in the phase II setting through TROG 03.02. The definition of the RT target volumes and normal tissue dose limits and general planning approach provided evidence of initial safety and feasibility. In this study, compliance rate of 94% was achieved, and grade 3-4 gastrointestinal (GI) toxicity was 28% and neutropenia 65%, febrile neutropenia 5.6% (60). Ajani *et al.* (61) reported on the first of two multi-institutional phase II neoadjuvant study (n=34) using 5FU/folinic acid (FA)/cis-diamminedichloroplatinum (CDDP) followed by CRT (45 Gy in 24 fractions with concurrent continuous intravenous infusion 5FU). The R0 resection rate was 70% and the pathological complete response (pCR) rate was 30% while median survival was 34 months. The second phase II study (62) (RTOG 99-04) (n=49) used 5FU/FA/CDDP ×2 cycles preoperative, followed by CRT (45 Gy with concurrent continuous intravenous infusion 5FU/paclitaxel). The R0 resection rate was 77%, pCR 26%. Both studies reported an acceptable toxicity profile.

## Conclusions

Differences in patterns of practice have resulted in different strategies to enhance the outcome of surgery between the East and the West. TNM staging system version 7 published in 2010 represent a consensus between these two worlds and would likely lay the foundation for advances that would capitalize on these variations. The philosophy that quality is important, especially in technical based modalities such as RT and surgery is critical, if optimal effect of combined modality is to be defined.

The technical ability to deliver RT to large complex volumes while minimizing exposure to normal structures has matured. Postoperative CRT improves the cure rate by approximately 9%, attributable to the effect of RT on securing local control when the majority of patients are managed by D0-1 dissections. Ongoing trials are expected to provide the answer to the question, what is the role of incorporating RT and CT to optimal surgery in both the preoperative or postoperative setting over the next 5-10 years. Based on sound principles, there is particular optimism that preoperative CRT may have a critical role to play. Assuming safety and effectiveness is confirmed in the neoadjuvant setting, future trials would

need to be initiated to clarify the role between pre and postoperative RT.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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# Emerging issues in multimodality treatment of gastric cancer

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**Abstract:** In recent years, the treatment of locally advanced resectable gastric cancer has evolved from an exclusively surgical to a multidisciplinary approach including chemotherapy and radiotherapy (RT). Worldwide several evidence-based preoperative and postoperative adjuvant strategies have been implemented in daily clinical practice. The determination of gastric cancer patients that benefit most from certain treatment modalities is a matter of debate. This review covers a comprehensive analysis of outcome and toxicity of clinical trials investigating multimodality treatment for locally advanced resectable gastric cancer to provide insight in patient groups that may benefit from certain treatments. Postoperative chemotherapy as monotherapy and doublet therapy has mainly been evaluated in Asian countries, where its efficacy has been clearly demonstrated. Whereas the added value of postoperative chemotherapy remains to be established in Western patient populations, perioperative doublet and triplet chemotherapy has been shown to improve overall survival (OS) in this part of the world. In addition, postoperative chemoradiotherapy (CRT) as an intensive locoregional treatment has been shown to reduce local recurrence rates and to improve OS. It has been suggested that postoperative CRT may particularly be of additional value in case of a microscopically incomplete R1 resection, a limited lymph node dissection (LND), and/or in case of regional lymph node metastases. Another attractive treatment strategy is preoperative CRT. Phase II trials reported good feasibility and patients' compliance, low toxicity rates, high R0 resection rates, and promising response rates. No results from randomized controlled trials applying preoperative CRT are available yet, but phase III randomized controlled trials investigating this strategy are currently accruing patients. In gastric cancer treatment, hematological and gastrointestinal toxicity are most frequently encountered in both chemotherapy and CRT either given preoperatively or postoperatively. Toxicity rates are higher with doublet and triplet chemotherapy than with monotherapy. Toxicity rates of the newer CRT regimens are lower than those of the older regimens, and lower than those of combination chemotherapy. For both chemotherapy and CRT, toxicity rates seem lower when treatment is given preoperatively, which probably explains the higher compliance with preoperative treatment. Based on multiple adjuvant preoperative and postoperative treatment regimens that have shown efficacy in patients with locally advanced resectable gastric cancer, all patients should be considered for multimodality treatment. Today, for gastric cancer patients the choice for a specific additional modality can only be based on patient and tumor characteristics regarding preoperative treatment, and surgical and pathological results regarding postoperative treatment. Taken together, preoperative chemotherapy and/or CRT are preferable to postoperative regimens. However, this has to be further confirmed in randomized controlled phase III studies.

**Keywords:** Chemoradiotherapy (CRT), adjuvant; chemotherapy, adjuvant; combined modality therapy; neoadjuvant therapy; stomach neoplasm

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## Introduction

Gastric cancer is the fifth most common malignancy worldwide with large geographic differences in incidence (1-3). The highest incidences are encountered in Eastern Asia (3), 35.4 and 5.4 per 100,000 per year for males and females respectively (2). In descending order are the incidences per 100,000 persons per year for males and females respectively 20.3 and 0.8 in Central-Eastern Europe (2), 14.2 and 2.0 in South America (2), 5.5 and 1.1 in Northern America, and 3.3 and 0.4 in Western Africa (2,3). Overall, gastric cancer is twice as common in men compared to women (2,3). These differences in gastric cancer incidence reflect etiologic heterogeneity (3,4).

Gastric cancer is worldwide the third most common cause of cancer death and responsible for 9% of cancer-related death yearly (2). Despite large geographic differences in survival (1-3), overall, mortality rates almost resemble the incidence rates (3). Whereas, the 5-year overall survival (OS) is around 25% in Europe and the United States, this is up to 60% in Asia (2,3,5). The higher survival rates in Asia are ascribed to mass screening programs in Japan, high accuracy of staging that is accompanied by stage migration, and high quality of surgery (3,6-9).

For gastric cancer, surgery remains indispensable for curative treatment. Patients with non-metastasized gastric cancer at diagnosis are eligible for potentially curative surgery if the tumor can be resected with free margins, i.e., resectable gastric cancer. However, even after potentially curative surgery gastric cancer patients have a high risk of locoregional recurrence, peritoneal carcinomatosis and distant metastases, in both Asian and Western countries (10-14). This risk increases with advanced tumor stage and can be as high as 88% locoregional recurrence, 44% peritoneal carcinomatosis, and 49% distant metastases in autopsy series (10). Recurrence patterns are also histological type dependent (15). For example, patients with a diffuse type gastric cancer (16) have a higher risk of peritoneal carcinomatosis than patients with an intestinal type, especially when the tumor has infiltrated the serosa (15).

Different multimodality treatments added to surgery have been investigated for locally advanced resectable gastric cancer. Whereas multiple multimodality strategies have been proven beneficial, which gastric cancer patients benefit most from which treatment modality remains a matter of debate. This review covers a comprehensive analysis of outcome and toxicity of clinical trials investigating multimodality treatment for locally advanced

resectable gastric cancer to provide insight in patient groups that may benefit from certain treatments.

## Surgery

The obvious goal of surgery is to achieve a microscopically complete resection of the primary tumor, known as an R0 resection, and full clearance of possibly affected regional lymph nodes (17). A microscopically tumor positive luminal resection margin, known as an R1 resection, has been reported in 2-22% of patients (18-21). Irrespective of its association with advanced tumor stage and aggressive tumor biology, an R1 resection has frequently been identified as an independent poor prognostic factor (18,21-24), justifying the use of peroperative frozen sections (25). Clear guidelines regarding patient management in case of an R1 resection are lacking. When an R1 resection is assessed by frozen section examination during surgery and a tumor negative resection margin can still be obtained, extended surgery is a clear option (26). Extended surgery is, however, disputable if that entails a distal esophagectomy or pancreaticoduodenectomy both carrying substantially increased morbidity (27). When an R1 resection is assessed postoperatively, options vary from watchful waiting (28), to re-resection in patients with limited nodal disease (23) or re-resection whenever feasible (20,24). The possible benefit of performing a re-resection is mainly based on the rationale that obtaining tumor negative margins can negate the adverse prognostic impact of tumor positive margins (29).

The development of gastric cancer surgery entailed the selection of patients who could benefit from a partial, instead of a total gastrectomy. Currently it is standard of care to perform a partial gastrectomy when tumor free margins can be obtained in distally located tumors as this is proven safely with regard to tumor control, and is accompanied by beneficial effects on nutritional status, quality of life (30,31) and reduced surgical morbidity and mortality (32,33). However, the risk of an R1 resection in diffuse type gastric cancer according to the Lauren classification (16) is high and may be reason to extend the surgical resection or even to consider a total gastrectomy irrespective of the tumor location, especially in young patients (21).

The extent of the lymph node dissection (LND) has been subject of extensive research. Traditionally, in the East more extended LND, i.e., D2 (lymph node stations 1-11 according to the Japanese classification of gastric cancer) or D3 (lymph node stations 1-14) (34), are routinely

performed and their benefit regarding OS is confirmed by randomized controlled trials (13,14). An even more extended lymphadenectomy including para-aortic lymph nodes, i.e., D4 (lymph node stations 1-16), does not seem to add to the survival benefit (13). In Western countries, a D1 LND (lymph node stations 1-6) used to be common practice and a shift towards standard performance of a D2 LND has in recent years (12,35). The benefit of a D2 LND was not adopted until the 15-year follow-up results of the randomized Dutch Gastric Cancer Trial showed that a D2 LND was associated with significantly less gastric cancer-related death and less local recurrences compared to a D1 LND (12). Short term results had not shown an OS benefit for patients who had undergone a D2 LND compared to a D1 LND (36,37). A similar observation was made in the MRC randomized trial (33). In both trials the lack of benefit on OS was explained by the higher postoperative mortality in the D2-group that was caused by the higher percentages of pancreatico-splenectomies to enable dissection of lymph node stations 10 and 11 (33,37); i.e., the higher short-term mortality offset the long-term benefit on OS. This hypothesis was confirmed by a subgroup analysis of patients who had undergone a D1 or D2 LND without pancreatico-splenectomy that showed a significantly higher 15-year OS in those who had a D2 LND (22% *vs.* 35%; HR, 1.34; 95% CI: 1.09-1.65; P=0.006) (12). Patients with advanced disease and lymph node metastases may benefit more from a D2 LND than those with limited disease (37,38), except for patients with lymph node metastases in the splenic hilus (lymph node station 10). Nodal metastases at this site indicate a very poor prognosis which will not improve after removal of the affected lymph nodes that necessitates a splenectomy (25,37). At current times, surgeons are advised to perform a D2 LND involving lymph node stations 1-9 and 11 with the removal of at least 15 nodes without routine spleen and pancreatic tail resection, sometimes also nominated as a D1+ LND (12,17). With this approach, surgical mortality and morbidity rates can be reduced, as confirmed by an Italian randomized D1-D2 trial (38). Taken together, in recent years this has led to the adoption of the standard performance of a D2 LND in Western countries.

In general, a D2 LND reduces the risk of locoregional recurrence down to 7-28% (11,13,14), but does not influence the risk of peritoneal carcinomatosis or distant metastases (11-14). Also, although gastric cancer surgery has been optimized and the 5-year OS has been improved, the prognosis still remains dismal. Hence, disappointing long-term results after optimal surgery emphasize the need

to develop multimodality treatments that are more effective.

## Chemotherapy

### Postoperative chemotherapy

The rationale for adding postoperative chemotherapy to the treatment of locally advanced resectable gastric cancer is to improve OS by eradicating remaining micrometastases that upon outgrowth are responsible for relapse. Multiple, predominantly fluoropyrimidine-based, postoperative chemotherapy regimens have been investigated resulting in conflicting evidence of efficacy, with mainly positive results for trials conducted in Asia and negative results for trials conducted in Western countries (*Table 1*).

One of the first clinical trials that clearly showed survival benefit by adding postoperative chemotherapy was conducted in Japan (41). Patients (n=1,059) were randomized after potentially curative surgery including at least a D2 LND, for observation-only *vs.* postoperative treatment with S-1 monotherapy for 1 year. The results of the first interim analysis were disclosed because the 3-year OS in the S-1 group was significantly higher: 80.1% *vs.* 70.1% (HR, 0.68; 95% CI: 0.52-0.87; P=0.003) (41). This was later confirmed by a significantly higher 5-year OS: 71.7% *vs.* 61.1% (HR, 0.67; 95% CI: 0.54-0.83) (42). These results have led to standard postoperative treatment with S-1 after surgery for stage II and III gastric cancer patients in Japan and other East-Asian countries (45).

Another postoperative chemotherapy regimen for stage II and III gastric cancer consists of capecitabine in combination with oxaliplatin (CAPOX) that has been investigated in Korea (40,45). Data of this so-called CLASSIC trial (n=1,035) have not been finalized yet, but the results of the first interim analysis were also disclosed because the 3-year disease free survival (DFS) was significantly higher in patients randomized for 6 months capecitabine and oxaliplatin than those randomized for observation-only after surgery in combination with a D2 LND: 74% *vs.* 59% (HR, 0.56; 95% CI: 0.44-0.72; P<0.0001). A trend towards improved OS in the CAPOX-arm was also observed after 3 years (HR, 0.72; 95% CI: 0.52-1.00; P=0.0493). The data are however immature and patient follow-up is ongoing (40). The addition of postoperative CAPOX seemed to reduce locoregional recurrences and distant metastases, but not peritoneal carcinomatosis (40). The addition of postoperative S-1, on the other hand, significantly reduced locoregional

**Table 1** Selection of five most recent randomized clinical trials investigating postoperative chemotherapy for locally advanced resected gastric cancer

Trial	Inclusion	N	Radicality of resection (n, %)	Extent of LND (n, %)	5-year DFS (%)	5-year OS (%)	OS (median in months)
Tsuburaya <i>et al.</i> 2014 (39)	1: 12 cycles UFT 267 mg/m <sup>2</sup> /day p.o. on days 1-28, q 4 weeks (57% of patients completed 12 cycles); 2: 16 cycles S-1 80 mg/m <sup>2</sup> bid. p.o. on days 1-14, q 3 weeks (60% of patients completed 16 cycles); 3: 3 cycles Pac 80 mg/m <sup>2</sup> /day i.v. on days 1, 8 (and 15), q 3-4 weeks, followed by 9 cycles UFT 267 mg/m <sup>2</sup> /day p.o. on days 1-28, q 4 weeks (65% of patients completed 12 cycles); 4: 3 cycles Pac 80 mg/m <sup>2</sup> /day i.v. on days 1, 8 (and 15), q 3-4 weeks, followed by 12 cycles S-1 80 mg/m <sup>2</sup> bid. p.o. on days 1-14, q 3 weeks (67% of patients completed 15 cycles)						
	T4a-4b	1: 374; 2: 374; 3: 374; 4: 373	1+2+3+4, R0: NR; R1: NR	1+2+3+4, D1: 0; D2: 100	3-year 1+2: 54 vs. 3+4: 57; 1+3: 53 vs. 2+4: 58*	3-year 1+2: 56 vs. 3+4: 59; 1+3: 54 vs. 2+4: 61*	1: NR; 2: NR; 3: NR; 4: NR
Bang <i>et al.</i> 2012 (40)	A: observation, subjected to regular follow-up; B: 8 cycles Cap 1,000 mg/m <sup>2</sup> bid. p.o. on days 1-14, + Ox 130 mg/m <sup>2</sup> /day i.v. on day 1, q 3 weeks (67% of patients completed 8 cycles)						
	Stage II-IIIb	A: 515; B: 520	A+B R0: 100; R1: 0	A+B D1: 0; D2: 100; D3: NR	3-year, A: 59; B: 74*	3-year, A: 78; B: 83*	A: –; B: –
Sakuramoto <i>et al.</i> 2007 and Sasako <i>et al.</i> 2011 (41,42)	A: observation, subjected to regular follow-up; B: for 1 year S-1 40 mg/m <sup>2</sup> bid p.o. on days 1-28, q 6 weeks (64% of patients completed 1 year of treatment)						
	Stage II-III	A: 530; B: 529	A+B R0: 100; R1: 0	A+B D1: 1; D2: 998; D3: 60	A: 53; B: 65*	A: 62; B: 76*	A: –; B: –
Kulig <i>et al.</i> 2010 (43)	A: observation, subjected to regular follow-up; B: 3 cycles Etop 120 mg/m <sup>2</sup> /day i.v. on days 4, 5, 6, + Dox 20 mg/m <sup>2</sup> /day i.v. on days 1, 7, + Cis 40 mg/m <sup>2</sup> /day i.v. on days 2, 8, q 4 weeks (65% of patients completed 3 cycles)						
	T2-4/N– or T1-4/N+	A: 154; B: 155	A+B R0: 100; R1: 0	A: D1 31 [20], D2 51 [33], D3 72 [47]; B: D1 29 [21], D2 49 [35], D3 63 [44]	A: 45; B: 51	A: 40; B: 44	A: 36; B: 41
Di Costanzo <i>et al.</i> 2008 (44)	A: observation, subjected to regular follow-up; B: 4 cycles Cis 40 mg/m <sup>2</sup> /day i.v. on days 1, 5, + Epi 30 mg/m <sup>2</sup> /day i.v. on days 1, 5, + LV 100 mg/m <sup>2</sup> /day i.v. on days 1-4, + 5-FU 300 mg/m <sup>2</sup> /day i.v. on days 1-4, q 3 weeks (58% of patients completed 4 cycles)						
	Stage IB-IV (T4N2M0)	A: 128; B: 130	A+B R0: 256 [99]; R1: 2 [1]	A+B D1: 93 [36]; D2: 110 [43]; D3: 28 [11]; D4: 5 [2]	A: 42; B: 42	A: 49; B: 48	A: 58; B: 57

Treatment completion rates are calculated in reference to all the randomized patients per arm, and include chemotherapy given in a modified dose. Stage is according to the classification in use by the trial itself. \*, significantly different; –, outcome not yet available. LND, lymph node dissection; DFS, disease free survival; OS, overall survival; UFT, Tegafur-Uracil; S1, S1-fluoropyrimidine; Pac, paclitaxel; R0, microscopically complete resection; R1, microscopically incomplete resection; NR, not reported; D1, lymph node stations 1-6; D2, lymph node stations 1-11; D3, lymph node stations 1-14; Cap, capecitabine; Ox, oxaliplatin; Etop, etoposide; Dox, doxorubicin; Cis, cisplatin; Epi, epirubicin; LV, leucovorin; 5-FU, 5-fluorouracil.

recurrences and peritoneal carcinomatosis, but not distant metastases (41). Together, these large-scale Asian trials provide sufficient evidence for the efficacy of postoperative fluoropyrimidine-based chemotherapy after potentially curative surgery in combination with a D2 LND.

The most recently published Asian trial investigating postoperative chemotherapy for gastric cancer, Stomach cancer Adjuvant Multi-Institutional group Trial (SAMIT, n=1,495), compared four treatment groups in a two-by-two factorial design (39). The four treatments consisted of UFT-monotherapy, S-1 monotherapy, paclitaxel followed by UFT, and paclitaxel followed by S-1. Sequential chemotherapy treatment did not improve DFS nor OS compared to monotherapy. S-1 seemed superior to UFT (3-year DFS UFT: 53.0%; 95% CI: 49.2-56.6; S-1: 58.2%; 95% CI: 54.4-61.8; HR, 0.81; 95% CI: 0.70-0.93; P=0.0048; P non-inferiority =0.151).

Multiple randomized controlled trials investigating postoperative chemotherapy for resected gastric cancer have been conducted in the West (43,44,46-49). And yet, none of these has provided similar positive results as the Asian trials. The lack of effectiveness was initially ascribed to the use of old regimens (46,47) but newer regimens did not prove to be effective either (44,48,49). Multiple factors have been suggested to play a role in the different outcomes after chemotherapy for Asian and Western populations, among others patient- and tumor characteristics including ethnic variability in genes regarding the drug metabolizing enzymes (40,42,50,51), the poor compliance of patients to the full chemotherapy regimen (44), the use of different surgical techniques (45) or the small sample sizes. Several meta-analyses have been performed to investigate a possible positive effect of postoperative chemotherapy, but also showed conflicting results (52-56). The (subgroup) meta-analysis that included only Western trials showed a non-significant small benefit of postoperative chemotherapy for resectable gastric cancer (53,55,57). Hence, postoperative chemotherapy is not routinely advised for gastric cancer patients in the West (35).

### ***Preoperative and perioperative chemotherapy***

The main rationale for administration of preoperative chemotherapy is to improve OS by eradicating micrometastases as early as possible and to improve surgical results by downsizing and/or downstaging of the tumor (Table 2). The first randomized controlled trials that observed a beneficial effect of adding perioperative

chemotherapy for resectable gastric cancer was the British Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC, n=503) trial (60). Patients were randomly assigned to surgery-only or preoperative chemotherapy followed by surgery and postoperative chemotherapy, consisting of epirubicin, cisplatin and fluorouracil. The results showed significantly improved R0 resection rates, 5-year relapse-free survival (HR, 0.66; 95% CI: 0.53-0.81; P<0.001) and an absolute 5-year OS benefit of 13% for the perioperative chemotherapy-arm (36% *vs.* 23%; HR, 0.75; 95% CI: 0.60-0.93; P=0.009). The benefits of perioperative chemotherapy were not at the cost of higher surgical morbidity and mortality (60). The French FNCLCC-FFCD trial (n=224) was the second randomized controlled trial in which the role of perioperative chemotherapy in gastric cancer was investigated, although in the majority of patients the tumor was located in the lower esophagus or at the gastro-esophageal junction (58). In this trial chemotherapy consisted of 2-3 preoperative and 3-4 postoperative cycles of fluorouracil and cisplatin, to a total of 6 cycles. Again, perioperative chemotherapy significantly improved R0 resection rates (84% *vs.* 73%; P=0.04), 5-year DFS and 5-year OS, without increasing surgical morbidity and mortality (58). After perioperative chemotherapy both local (60) or locoregional recurrences (58) and distant metastases were decreased (58,60). Consequently, in Europe perioperative chemotherapy became the new standard of care in patients with resectable gastric cancer (35).

More recently, multiple phase II and III studies investigating preoperative chemotherapy have also been initiated in Asia (45,62-64). In Asia, this approach was firstly investigated in patients who are at high risk for peritoneal carcinomatosis and distant metastases, i.e., locally advanced marginally resectable Bormann type 3 and 4 (65), para-aortic/bulky nodal disease (66), and/or serosa positive/T4a (67) gastric cancer. Phase III trials are initiated following promising results of phase II trials. For example, the JCOG 0501 trial randomizes patients with resectable Bormann type 3 or 4 gastric cancer for surgery followed by postoperative S-1 for 1 year, *vs.* perioperative chemotherapy consisting of 2 preoperative cycles S-1 and cisplatin followed by surgery and postoperative S-1 for 1 year (ClinicalTrials.gov number NCT00252161). The results of these trials will contribute to define the role of preoperative chemotherapy in Asia.

In the MAGIC and FNCLCC-FFCD trials a significant proportion of the patients could not start and/or complete postoperative chemotherapy as planned (58,60).



**Table 2** Randomized clinical trials investigating preoperative or perioperative chemotherapy for locally advanced initially resectable gastric cancer

Trial	Inclusion	N	Radicality of resection (n, %)	Extent of LND (n, %)	5-year DFS (%)	5-year OS (%)	OS (median in months)
Ychou <i>et al.</i> 2011 <sup>†</sup> (58)	A: surgery only; B: preoperatively 2-3 cycles 5-FU 800 mg/m <sup>2</sup> /day i.v. on days 1-5, + Cis 100 mg/m <sup>2</sup> /day i.v. on day 1, q 4 weeks (87% of patients completed 2-3 cycles), and postoperatively 3-4 cycles 5-FU/Cis as described before (36% of patients completed 3-4 cycles) to a total of 6 cycles (NR what % completed 6 cycles)	A: 111; B: 113	A: R0 81 [73]; B: R0 95 [84]	A: D0-2 NR; B: D0-2 NR	A: 19; B: 34*	A: 24; B: 38*	A: NR; B: NR
Schuhmacher <i>et al.</i> 2010 <sup>†</sup> (59)	A: surgery only; B: preoperative 2 cycles Cis 50 mg/m <sup>2</sup> /day i.v. on days 1, 15, 29, + LV 500 mg/m <sup>2</sup> /day i.v. on days 1, 8, 15, 22, 29, 36, + 5-FU 2,000 mg/m <sup>2</sup> /day i.v. on days 1, 8, 15, 22, 29, 36 (63% of patients completed 2 cycles)	A: 72; B: 72	A: R0 48 [67]; B: R0 59 [82]	A: D1 5 [7], D2 63 [88]; B: D1 2 [3], D2 93 [93]	A: NR; B: NR	2-year, A: 70; B: 73	A: 53; B: 65
Cunningham <i>et al.</i> 2006 <sup>†</sup> (60)	A: surgery only; B: preoperatively 3 cycles Epi 50 mg/m <sup>2</sup> /day i.v. on day 1, + Cis 60 mg/m <sup>2</sup> /day i.v. on day 1, + 5-FU 200 mg/m <sup>2</sup> /day i.v. on days 1-21, q 3 weeks (86% of patients completed 3 cycles), and postoperatively 3 cycles Epi/Cis/5-FU as described before (42% of patients completed 3 cycles) to a total of 6 cycles (41% completed 6 cycles)	A: 253; B: 250	A: R0 166 [66]; B: R0 169 [68]	A: D1 50 [20], D2 96 [38]; B: D1 39 [16], D2 93 [37]	A: NR; B: NR	A: 23; B: 36*	A: NR; B: NR
Hartgrink <i>et al.</i> 2004 <sup>‡</sup> (61)	A: surgery only; B: preoperatively 4 cycles 5-FU 1,500 mg/m <sup>2</sup> /day i.v. on day 2, + LV 30-60 mg/m <sup>2</sup> /6h i.v. on days 3, 4, + Dox 30 mg/m <sup>2</sup> /day i.v. on day 15, + MTX 1,500 mg/m <sup>2</sup> /day i.v. on day 2, q 4 weeks (52% of patients completed 4 cycles)	A: 30; B: 29	A: R0 19 [63]; B: R0 18 [62]	A: D0-2 NR; B: D0-2 NR	A: NR; B: NR	A: 34; B: 21	A: 30; B: 18

All percentages are calculated in reference to all the included patients. Treatment completion rates include chemotherapy given in a modified dose. Stage is according to the classification in use by the trial itself. \*, significantly different; †, included also patients with adenocarcinoma of the lower third of the oesophagus or gastro-oesophageal junction; ‡, trial was prematurely closed. LND, lymph node dissection; DFS, disease free survival; OS, overall survival; 5-FU, 5-fluorouracil; Cis, cisplatin; NR, not reported; R0, microscopically complete resection; D0, no removal of lymph node stations; D1, lymph node stations 1-6; D2, lymph node stations 1-11; LV, leucovorin; Epi, epirubicin; Dox, doxorubicin; MTX, methotrexate.

Therefore, the beneficial effect observed in these trials is often attributed to the preoperative chemotherapy only. Subsequently, studies that investigate the benefit of purely preoperative chemotherapy were again initiated. An example is the EORTC 40954 trial (n=144), that randomized patients for surgery-only or preoperative chemotherapy followed by surgery. This trial was closed prematurely due to a low accrual rate, and failed to demonstrate an OS benefit despite the significant higher R0 resection rate in the preoperative chemotherapy group (59). Today, it remains difficult to acknowledge the beneficial effect of preoperative and postoperative chemotherapy separately.

### ***Toxicity of and treatment compliance with chemotherapy***

The most common adverse events of preoperative and/or postoperative chemotherapy in gastric cancer patients were hematological and gastrointestinal (40,41,58,60). Less severe toxicity, grade 1 and 2, was very common in this patient population (40,41,58,60). Especially with combination chemotherapy, grade 1 and 2 side effects can be present in up to 99% of patients (40,58,60). The common occurrence of adverse events is reflected in the high percentages of chemotherapy dose modifications up to 42-90% (40,41).

More severe toxicity, grade 3 and 4, was present in up to 27% of patients per scored item (Table 3). In comparison

**Table 3** Grade 3-4 hematological and gastrointestinal toxicity of preoperative and postoperative chemotherapy reported in selected clinical trials

Toxicity grade 3-4	Bang <i>et al.</i> <sup>1</sup> (40)	Sakuramoto <i>et al.</i> <sup>2</sup> (41)	Ychou <i>et al.</i> <sup>3</sup> (58)	Cunningham <i>et al.</i> <sup>4</sup> (60)
Granulocytopenia/ neutropenia (%)	22	NR	20; NR	22; 27
Leukopenia (%)	0	1	6; NR	11; 11
Thrombocytopenia (%)	8	0.2	6; NR	0.4; 3
Nausea (%)	8	4	9 <sup>§</sup> ; NR	6; 12
Vomiting (%)	7	1	9 <sup>§</sup> ; NR	5; 10
Anorexia/decreased appetite (%)	5	6	NR	NR
Diarrhea (%)	2	3	2; NR	3; 4

<sup>1</sup>, percentages relative to 496 patients who received at least 1 cycle of CAPOX; <sup>2</sup>, percentages relative to 517 patients who received S-1; <sup>3</sup>, percentages relative to 109 patients who started preoperative chemotherapy. Percentages of toxicity during postoperative chemotherapy not reported; <sup>4</sup>, percentages relative to 237 patients who started preoperative chemotherapy and 137 patients who started postoperative chemotherapy. <sup>§</sup>, percentage reported for nausea and vomiting combined. NR, not reported.

to the patients who were treated with surgery-only, several severe grade 3-4 adverse events were more common in the patients treated with chemotherapy (40,41). Unfortunately not all before mentioned trials reported adverse events for the surgery-only group, hampering comparison (58,60). Interestingly, no significant differences in preoperatively and postoperatively occurring adverse events was found in the MAGIC trial (60), which could be explained by the selection of patients that started postoperative chemotherapy. Severe side effects depend on the chemotherapy regimen and were reported more frequently for combination chemotherapy compared to for example S-1 monotherapy with the exception of anorexia (40,41,58,60). This finding was also observed in the SAMIT trial with the exception of anorexia, nausea and vomiting (39). The reported percentages of deceased patients related to the treatment with chemotherapy were between 0-3% (39-41,43,44,58,60).

In the MAGIC trial 5% of patients stopped preoperative chemotherapy due to toxicity. Reasons for discontinuation of postoperative chemotherapy were not reported (60). In the FNCLCC-FFCD trial toxicity was the main reason to discontinue preoperative chemotherapy in 8% of patients, reasons for discontinuation of postoperative chemotherapy were again not reported (58). Discontinuation of postoperative S-1 due to adverse events or complications occurred in 14% (41) and discontinuation of CAPOX because of adverse events occurred in 10% of patients (40).

However, this might be an underestimation due to the selection of patients for these trials who had to be well recovered after surgery.

In the five most recent randomized controlled trials that investigated postoperative chemotherapy (*Table 1*), compliance with the entire treatment regimen was 58-67% (39-41,43,44). In these trials, no information on the number of patients who were not eligible for postoperative treatment (and thus not for the trial), was provided. This limits the opportunity to discuss feasibility and treatment compliance with postoperative chemotherapy in a clinical setting. In the MAGIC and the FNCLCC-FFCD trial, compliance with chemotherapy was higher when administered before surgery than after surgery. While more than 95% and 85% (or 90% of those started) of patients could start and complete preoperative chemotherapy respectively, only around 50% and 40% (or 75% of those started) could start and complete postoperative chemotherapy respectively (58,60).

## Chemoradiotherapy (CRT)

### Postoperative CRT

The high rate of locoregional recurrences after potentially curative surgery for advanced gastric cancer makes CRT an attractive postoperative treatment modality (*Table 4*). The first randomized study that observed an OS benefit for gastric cancer patients by adding another treatment

**Table 4** All randomized clinical trials investigating postoperative chemoradiotherapy for locally advanced resectable gastric cancer

Trial	Inclusion	N	Radicality of resection (%)	Extent of LND (n, %)	5-year DFS (%)	5-year OS (%)	OS (median in months)
Lee et al. 2012 (68)	A: 6 cycles Cap 1,000 mg/m <sup>2</sup> bid. p.o. on days 1-14, + Cis 60 mg/m <sup>2</sup> /day i.v. on day 1, q 3 weeks (75% of patients completed 6 cycles); B: 2 cycles Cap/Cis as described above, followed by RT 45 Gy + Cap 825 mg/m <sup>2</sup> bid p.o. for 5 weeks, followed by 2 cycles Cap/Cis as described above (chemotherapy completion rate: 82%, RT completion rate: 87%, overall completion rate: 82%)						
	Stage II-IV (M0)	A: 228; B: 230	A + B R0: 100; R1: 0	A + B D1: 0 [0]; D2: 458 [100]	3-year A: 74.2; B: 78.2	3-year, A: -; B: -	A: -; B: -
Yu et al. 2012 <sup>†</sup> (69)	A: 5 cycles 5-FU 425 mg/m <sup>2</sup> /day i.v. on days 1-5 + LV 25 mg/m <sup>2</sup> /day i.v. on days 1-5, q 4 weeks (100% of patients completed 5 cycles) B: 1 cycle 5-FU/LV as described above, followed by RT 45 Gy + 5-FU 400 mg/m <sup>2</sup> /day i.v./LV 25 mg/m <sup>2</sup> /day i.v. on RT-days 1-4 and 31-33, followed by 2 cycles 5-FU/LV as described above (chemotherapy completion rate: 88%, RT completion rate: 88%, overall completion rate: 88%)						
	T3-4 and/or N+	A: 34; B: 34	A + B R0: 100; R1: 0	A + B D1: 21 [31]; D2: 47 [69]	3-year A: 29.4; B: 55.8*	3-year A: 44.1; B: 67.7*	A: -; B: -
Zhu et al. 2012 <sup>¶</sup> (70)	A: 5 cycles 5-FU 400 mg/m <sup>2</sup> /day i.v. on days 1-5 + LV 20 mg/m <sup>2</sup> /day i.v. on days 1-5, q 4 weeks (94% of patients completed 5 cycles); B: 1 cycle 5-FU/LV as described above, followed by RT 45 Gy + 5-FU/LV as described above on RT-days 1-4 and 31-33, followed by 2 cycles 5-FU/LV as described above (chemotherapy completion rate: 95%, RT completion rate: 96%, overall completion rate: 91%)						
	T3-4 and/or N+	A: 175; B: 205	A + B R0: 100; R1: 0	A + B D1: 0 [0]; D2: 380 [100]	A: 35.8; B: 45.2*	A: 41.8; B: 48.4	A: 38; B: 54
Kim et al. 2012 <sup>‡</sup> (71)	A: 5 cycles 5-FU 425 mg/m <sup>2</sup> /day i.v. on days 1-5 + LV 20 mg/m <sup>2</sup> /day i.v. on days 1-5, q 4 weeks (93% of patients completed 5 cycles); B: 1 cycle 5-FU/LV as described above, followed by RT 45 Gy + 5-FU 400 mg/m <sup>2</sup> /day i.v./LV 20 mg/m <sup>2</sup> /day i.v. on RT-days 1-4 and 29-31, followed by 2 cycles 5-FU/LV as described above (chemotherapy completion rate: 91%, RT completion rate: 89%, overall completion rate: 87%)						
	Stage III-IV (M0)	A: 44; B: 46	A + B R0: 100; R1: 0	A + B D1: 0 [0]; D2: 90 [100]	A: 50; B: 61	A: 55; B: 65	A: NR; B: NR
Kwon et al. 2010 <sup>‡</sup> (72)	A: 6 cycles 5-FU 1,000 mg/m <sup>2</sup> /day i.v. on days 1-5, + Cis 60 mg/m <sup>2</sup> /day i.v. on day 1, q 3 weeks (73% of patients completed 6 cycles, including patients with delays and dose reductions); B: 1 cycle 5-FU/Cis as described above, followed by RT 45 Gy + Cap 825 mg/m <sup>2</sup> bid. p.o. on RT-days, followed by 3 cycles 5-FU/Cis as described above (chemotherapy completion rate: NR, RT completion rate: NR, overall completion rate: 74%)						
	Stage IIIA-IV (M0)	A: 30; B: 31	A + B R0: 100; R1: 0	A + B D1: 0 [0]; D2: 61 [100]	A: 59.1; B: 76.7	A: 70.0; B: 70.1	A: -; B: -
Kim et al. 2005 <sup>§</sup> (73)	A: Observation, subjected to regular follow-up; B: 1 cycle 5-FU 400 mg/m <sup>2</sup> /day i.v. on days 1-5 + LV 20 mg/m <sup>2</sup> /day i.v. on days 1-5, followed by RT 45 Gy + 5-FU/LV as described before on RT-days 1-4 and 31-33, followed by 2 cycles 5-FU/LV as described before on days 1-5, q 4 weeks (chemotherapy completion rate: 78%, RT completion rate: 86%, overall completion rate: 75%)						
	Stage IB-IV (M0)	A: 446; B: 544	A + B R0: 100; R1: 0	A + B D1: 0 [0], D2: 990 [100]	A: 47.9; B: 54.5*	A: 51.0; B: 57.1*	A: 62.6; B: 95.3*
Macdonald et al. 2001 and Smalley et al. 2012 (74,75)	A: observation, subjected to regular follow-up; B: 1 cycle 5-FU 425 mg/m <sup>2</sup> /day i.v. on days 1-5 + LV 20 mg/m <sup>2</sup> /day i.v. on days 1-5, followed by RT 45 Gy + 5-FU 400 mg/m <sup>2</sup> /day i.v./LV 20 mg/m <sup>2</sup> /day i.v. on RT-days 1-4 and 31-33, followed by 2 cycles 5-FU 425 mg/m <sup>2</sup> /day i.v. on days 1-5 + LV 20 mg/m <sup>2</sup> /day i.v. on days 1-5, q 4 weeks (chemotherapy completion rate: NR, RT completion rate: NR, overall completion rate: 64%)						
	Stage IB-IV (M0)	A: 275; B: 281	A + B R0: 100; R1: 0	A + B D0: NR [54]; D1: 199 [36]; D2: 54 [10]	3-year A: 31; B: 48*	A: 25; B: 42*	A: 27; B: 36*

All percentages are calculated in reference to all the included patients. Treatment completion rates include chemotherapy given in a modified dose. Stage is according to the classification in use by the trial itself. -, outcome not yet available; \*, significantly different; †, trial was prematurely closed; ¶, per protocol analysis available only; §, not a randomized clinical trial. LND, lymph node dissection, DFS, disease free survival, OS, overall survival; Cap, capecitabine; Cis, cisplatin; RT, radiotherapy; R0, microscopically complete resection; R1, microscopically incomplete resection; D0, no removal of lymph node stations; D1, lymph node stations 1-6; D2, lymph node stations 1-11; 5-FU, 5-fluorouracil; LV, leucovorin; NR, not reported.

modality was the US intergroup-0116 trial (n=556) (74). This trial randomly assigned patients who had undergone an R0 resection to observation-only or postoperative CRT. Postoperative CRT, consisting of 45 Gy irradiation with concurrent fluorouracil/leucovorin on radiotherapy (RT) days 1-4 and 31-33, and preceded by 1 cycle and followed by 2 cycles of fluorouracil/leucovorin during 5 days, improved the median OS by 9 months (36 *vs.* 27 months; HR, 1.35; 95% CI: 1.09-1.66; P=0.005) and the median relapse-free survival by 11 months (30 *vs.* 19 months; HR, 1.52; 95% CI: 1.23-1.86; P<0.001) (74). In the updated analysis of this trial at a median follow-up time of 10 years for living patients, the benefit of postoperative CRT persisted equally strongly (HR for OS 1.32; 95% CI: 1.10-1.60; P=0.0046; HR for RFS 1.51; 95% CI: 1.25-1.83; P<0.001) (75). The lower rate of locoregional recurrence in the postoperative CRT group compared to the observation-only group (24% *vs.* 47%) confirms that the survival benefit of CRT is mainly caused by increased locoregional control. These results have led to the standard use of postoperative CRT in the United States (76,77). In Europe and Asia the administration of postoperative CRT is limited to specific indications (35,45).

Several data indicate that postoperative CRT is especially effective in gastric cancer patients with lymph node positive disease. The ARTIST trial (n=458), in which patients were randomized to postoperative CRT including 4 cycles chemotherapy *vs.* chemotherapy-only after an R0 resection with a D2 LND, showed no significant difference in DFS between study arms. However, for patients with pathological tumor positive lymph nodes, DFS at 3 years was significantly better in the CRT-arm (77.5%) than in the chemotherapy-arm (72.3%) (68). In addition, a survival benefit for node positive gastric cancer patients treated with RT was reported by a meta-analysis performed by Ohri *et al.* (HR, 0.73; 95% CI: 0.62-0.86; P<0.001) (78). Furthermore, in the prospective trials with beneficial outcomes, the majority of patients had node positive disease (69-71,73,74), and subgroup analysis suggests a stronger benefit when more lymph nodes are affected (75).

As the majority of patients in the INT-0116 trial had undergone a D0 LND (54%) (74), it has been argued that postoperative CRT compensated for suboptimal surgery although subset analysis did not show a lack of benefit for patients with a D2 LND (75). Thereafter, several studies have investigated the efficacy of postoperative CRT after a D2 LND but thus far no conclusive evidence has been provided (68-73,78,79). The largest of these

studies, an Korean observational study (n=990) with a similar CRT regimen as in the INT-0116 trial, showed a significant relapse free and OS benefit for patients treated with postoperative CRT after D2 gastric cancer surgery compared to patients who were treated with D2 surgery alone (73). In a Chinese trial (n=380) by Zhu *et al.* in which patients were randomized to postoperative CRT *vs.* chemotherapy after an R0 gastric cancer resection with a D2 LND, the 5-year local recurrence rate was significantly decreased in the CRT-arm (70), which was also observed in similarly designed other studies (69,71). In a second Chinese trial (n=68) that was prematurely closed, also a significantly increased OS for patients treated with postoperative CRT was observed (69). The abovementioned meta-analysis showed a significantly improved DFS after D2 surgery followed by CRT, but not an improved OS (78). The detection of an OS benefit was hampered by the small sample size. Also, all studies used for the analysis tested CRT against chemotherapy. Moreover, the heterogeneity of the included trials regarding RT treatment regimens was large (78). Taken together, postoperative CRT reduces locoregional recurrences (69,73,74,78,79) that results in a survival benefit (69,73,74,78), also after adequate D2 gastric cancer surgery (69,73).

As yet, postoperative CRT in gastric cancer treatment has been investigated almost invariably in patients who had undergone an R0 resection (68-74). However, as postoperative CRT increases locoregional control after surgery, patients with an R1 resection may benefit from such intensified local treatment as well. In a retrospective analysis (n=83) from Dikken *et al.* postoperative CRT after an R1 resection decreased the local recurrence rate (6% *vs.* 29% in the surgery-only R1 group, HR, 5.36; P=0.02) and improved the 2-year OS rate (66% *vs.* 29% in the surgery-only R1 group, HR, 2.91; P=0.002) (79). Another retrospective study (n=110) found that in patients treated with postoperative CRT after an R0 or R1 resection, an R1 resection was not associated with a higher tumor recurrence rate, nor did it lead to poorer OS (80). This finding suggests that the poor prognosis associated with an R1 resection may be offset by the use of postoperative CRT. This hypothesis was further investigated in a national Dutch cohort study (n=409). OS after an R1 resection was better in patients who were treated with postoperative CRT compared to patients who did not receive postoperative CRT (81). These results lend support to the use of postoperative CRT in patients who have undergone an R1 gastric cancer resection.

### **Preoperative CRT**

CRT can be administered preoperatively in patients with advanced disease in order to improve R0 resection rates by downstaging and to enhance locoregional tumor control (Table 5). Major concerns of applying this strategy for gastric cancer were delay of or withdrawal from surgery due to toxicity of the CRT, and an increase in surgical morbidity and mortality. To our knowledge no randomized controlled trial applying this strategy in gastric cancer has been completed nor published. In contrast, in patients with esophageal and gastro-esophageal junction cancer, there is convincing evidence from randomized controlled trials that preoperative CRT leads to improved OS (88,94). The phase III German trial (n=62) by Stahl *et al.* that was prematurely closed, randomized patients with an adenocarcinoma located at the gastro-esophageal junction for induction chemotherapy followed by preoperative CRT and surgery *vs.* preoperative chemotherapy followed by surgery (88). CRT consisted of 2 cycles' induction chemotherapy of fluorouracil, leucovorin and cisplatin, followed by 30 Gy irradiation in 3 weeks with concurrent cisplatin and etoposide. Chemotherapy consisted of 2.5 cycles of fluorouracil, leucovorin and cisplatin. Analysis showed a trend towards higher pathological complete response (pCR) and improved OS in the CRT-arm. The currently accruing TOP GEAR trial initiated by the Australasian Gastro-Intestinal Trials Group (ClinicalTrials.gov number NCT01924819) randomizes patients with resectable gastric or gastro-esophageal junction cancer for perioperative chemotherapy and surgery *vs.* induction chemotherapy, followed by preoperative CRT, surgery and postoperative chemotherapy. This trial has not completed accrual yet, and results have to be awaited.

For gastric cancer specifically, several phase I and II studies have investigated the feasibility and efficacy of preoperative CRT since 2002 (Table 5) (82-87,89-93). In all of these studies preoperative CRT has been documented as a feasible treatment strategy, because toxicity of CRT was not the predominant reason of withdrawal from surgery. Indeed, 73-100% of patients could complete the preoperative CRT as planned, and 76-100% could proceed to surgery. Furthermore, surgical mortality rates (0-8%) were well within the range of reported percentages in trials investigating surgery-only (37,95). Encouraging R0 resection rates of 67-92% and pCR rates of 5-29% have been reported (82-93). Locoregional control was reported in approximately 70-80% at 5-year (96,97). Distant metastases have been frequently

reported as most common site of relapse (85,87,89,97). This is also true for peritoneal carcinomatosis (82,91,96) while this was significantly decreased after preoperative CRT for esophageal cancer (98).

The high pCR rates raise the question whether preoperative CRT could also induce resectability in patients with locally advanced, but initially irresectable gastric cancer. In the phase I/II study by Trip *et al.*, a subset of patients initially had irresectable disease without signs of peritoneal carcinomatosis confirmed by laparoscopy and without signs of distant metastases on diagnostic imaging (82). Eight out of 12 patients (67%) with initially irresectable gastric cancer underwent R0 surgery after preoperative CRT. In this study, preoperative CRT consisted of RT to a total dose of 45 Gy with concurrent weekly paclitaxel and carboplatin.

### **Toxicity of and treatment compliance with CRT**

In general CRT for gastric cancer is an intense but feasible regimen. Several different CRT regimens were used in clinical trials, of which toxicity rates vary (Table 6). In several studies a treatment regimen according to the INT-0116 trial was administered postoperatively. Patients suffered most from hematological (7-54%) and gastrointestinal (1-33%) toxicity grade 3 or higher (69,70,73,74). Based on developments in chemotherapeutic agents, and concurrent CRT regimens in other types of cancer, Jansen *et al.* performed a series of phase I/II studies to optimize concurrent postoperative CRT for gastric cancer with the aim to define a less toxic regimen. The RT dose was set at 45 Gy, and the concurrent chemotherapy consisted of capecitabine with or without cisplatin (99-101). Acute toxicity was low with 7% grade 3-4 hematological, 5% grade 3-4 nausea, and 2% grade 3-4 vomiting. Similar toxicity rates were observed in other phase III trials that administered postoperative RT in combination with concurrent capecitabine only (68,72).

Although preoperative CRT is not yet investigated in randomized controlled phase III trials, the reported toxicity rates in phase II trials were in line with toxicity rates of postoperative CRT, and for specific regimens even lower. Nonetheless, it remains difficult to conclude that either preoperative or postoperative CRT is less toxic, because the toxicity profiles of preoperative and postoperative CRT have not yet been compared in a randomized controlled phase III trial and because of the use of different CRT regimens. Notable, however, are the low toxicity rates

**Table 5** All pilot and phases 1-3 clinical trials investigating preoperative chemoradiotherapy for locally advanced gastric cancer

Trial	Inclusion	N	Radicality of resection (n, %)	Extent of LND (n, %)	Surgical mortality (n, %)	pCR (n, %)
Trip <i>et al.</i> 2014 <sup>†</sup> (82)	RT 45 Gy + Pac 50 mg/m <sup>2</sup> /day i.v. on RT-days 1, 8, 15, 22, 29 + Car AUC 2 i.v. on RT-days 1, 8, 15, 22, 29 (chemotherapy completion rate: 92%, RT completion rate: 96%, overall completion rate: 92%), followed by surgery (88% of patients proceeded to surgery)					
	Resectable and irresectable T3-4/N0-2	25	R0: 18 [72]; R1: 3 [12]; R2: 1 [4]	D1: 13 [52]; D2: 9 [36]	1 [4]	4 [16]
Matsuda <i>et al.</i> 2014 (83)	RT 40 Gy + S-1 80-120 mg p.o. on RT-days 1-15 + Cis 15-25 mg/m <sup>2</sup> /day i.v. on RT-days 1, 15, followed by S-1 80-120 mg p.o. on days 1-28 + Cis 15-25 mg/m <sup>2</sup> /day i.v. on days 1, 15, 29 (chemotherapy completion rate: 89%, RT completion rate: 89%, overall completion rate: 89%), followed by surgery (89% of patients proceeded to surgery)					
	Resectable T3-4/N+	9	R0: 8 [89]; R1: 0 [0]	D1: 0 [0]; D2: 8 [89]	0 [0]	2 [22]
Michel <i>et al.</i> 2014 <sup>†#</sup> (84)	4 cycles of LV 400 mg/m <sup>2</sup> /day i.v. on day 1 + Iri 180 mg/m <sup>2</sup> /day i.v. on day 1 + 5-FU 400 mg/m <sup>2</sup> /day i.v. on day 1 + 5-FU 2,400 mg/m <sup>2</sup> /46h i.v. on days 1, 2, q 2 weeks, followed by RT 50 Gy + 5-FU 200 mg/m <sup>2</sup> /day i.v. on RT-days 1-33 (chemotherapy completion rate: 93%, RT completion rate: 86%, overall completion rate: 74%), followed by surgery (83% of patients proceeded to surgery)					
	Resectable	42	R0: 28 [67]; R1: 1 [2]; UK: 2 [5]	D1: NR; D2: NR	6 [14]	3 [7]
Pera <i>et al.</i> 2012 <sup>†</sup> (85)	RT 45 Gy + Ox 85 mg/m <sup>2</sup> /day i.v. on RT-days 1, 29 + Cis 55 mg/m <sup>2</sup> /day i.v. on RT-days 1, 29 + 5-FU 750 mg/m <sup>2</sup> /day i.v. on RT-days 1-4 and 29-32 (chemotherapy completion rate: NR, RT completion rate: NR, overall completion rate: 90%), followed by surgery (76% of patients proceeded to surgery)					
	Resectable T2-4/N0N+	41	R0: 29 [71]; R1: 1 [2]; R2: 1 [2]	D1: NR; D2: NR	3 [7]	G + GEJ: 3 [7]
Lee <i>et al.</i> 2012 <sup>†</sup> (86)	RT 41.4 Gy + S-1 60-80 mg/m <sup>2</sup> /day bid p.o. on RT-days 1-29 + Ox 40 mg/m <sup>2</sup> /day i.v. on RT-days 1, 8, 15, 22 (chemotherapy completion rate: NR, RT completion rate: NR, overall completion rate: 92%), followed by surgery (100% of patients proceeded to surgery)					
	Resectable T2/N+ or T3-4/any N	12	R0: 11 [92]; R1: 0; R2: 1 [8]	D1: NR; D2: NR	0 [0]	1 [8]
Inoue <i>et al.</i> 2012 (87)	RT 50 Gy + S-1 65 mg/m <sup>2</sup> /day p.o. on RT-days 1-14, 22-35 (chemotherapy completion rate: 83%, RT completion rate: 100%, overall completion rate: 83%), followed by surgery (100% of patients proceeded to surgery)					
	Resectable T3/N2 or T4/N1	12	R0: 11 [92]; R1: 0; R2: 1 [8]	D1: 2 [17]; D2: 10 [83]	0 [0]	1 [8]
Stahl <i>et al.</i> 2009 <sup>††</sup> (88)	2 cycles of 5-FU 2,000 mg/m <sup>2</sup> /day i.v. on days 1, 8, 15, 22, 29, 36 + LV 500 mg/m <sup>2</sup> /day i.v. on days 1, 8, 15, 22, 29, 36 + Cis 50 mg/m <sup>2</sup> /day i.v. on days 1, 15, 29, q 6 weeks, followed by RT 30 Gy + Cis 50 mg/m <sup>2</sup> /day i.v. on RT-days 1, 8, + Etop 80 mg/m <sup>2</sup> /day i.v. on RT-days 3-5, (chemotherapy completion rate: NR, RT completion rate: NR, overall completion rate: 73%), followed by surgery (79% of patients proceeded to surgery)					
	Resectable T3-4/Nx	62	R0: 43 [69]; R1+R2: 2 [3]	D1: NR; D2: NR	5 [8]	7 [11]

Table 5 (continued)



Table 5 (continued)

Trial	Inclusion	N	Radicality of resection (n, %)	Extent of LND (n, %)	Surgical mortality (n, %)	pCR (n, %)
Wydmański <i>et al.</i> 2007 (89)	RT 45 Gy + 5-FU 325 mg/m <sup>2</sup> /day i.v. on RT-days 1-3/5, 29-31/33 +/- LV 20 mg/m <sup>2</sup> /day i.v. on RT-days 1-3/5, 29-31/33 (chemotherapy completion rate: 95%, RT completion rate: 100%, overall completion rate: 95%), followed by surgery (93% of patients proceeded to surgery)					
	Resectable	40	R0: 30 [75]; R1: 2 [5]; R2: 0 [0]	D1: NR; D2: NR	0 [0]	7 [18]
Ajani <i>et al.</i> 2005 <sup>†</sup> (90)	2 cycles of 5-FU 750 mg/m <sup>2</sup> /day i.v. on days 1-5 + Cis 15 mg/m <sup>2</sup> /day i.v. on days 1-5 + Pac 200 mg/m <sup>2</sup> /day i.v. on day 1, q 4 weeks, followed by RT 45 Gy + 5-FU 300 mg/m <sup>2</sup> /day i.v. on RT-days 1-5, 8-12, 15-19, 22-26, 29-33 + Pac 45 mg/m <sup>2</sup> /day i.v. on RT-days 1, 8, 15, 22, 29 (chemotherapy completion rate: NR, RT completion rate: NR, overall completion rate: NR), followed by surgery (98% of patients proceeded to surgery)					
	Resectable T1/N1 or T2-3/any N	41	R0: 32 [78]; unknown: 1 [2]	D1: NR; D2: NR	0 [0]	8 [20]
Ajani <i>et al.</i> 2004 <sup>†</sup> (91)	2 cycles of 5-FU 200 mg/m <sup>2</sup> /day i.v. on days 1-21 + LV 20 mg/m <sup>2</sup> /day i.v. on days 1, 8, 15 + Cis 20 mg/m <sup>2</sup> /day i.v. on days 1-5, q 4 weeks, followed by RT 45 Gy + 5-FU 300 mg/m <sup>2</sup> /day i.v. on RT-days 1-5, 8-12, 15-19, 22-26, 29-33 (chemotherapy completion rate: NR, RT completion rate: NR, overall completion rate: NR), followed by surgery (82% of patients proceeded to surgery)					
	Resectable T1/N1 or T2-3/any N	34	R0: 23 [68]; R1: NR; R2: NR	D1: NR; D2: NR	1 [3]	10 [29]
Roth <i>et al.</i> 2003 (92)	1 cycle 5-FU 800 mg/m <sup>2</sup> /day i.v. on days 1-4 + LV 60 mg/m <sup>2</sup> bid. i.v. on days 1-4 and 60 mg/m <sup>2</sup> /day i.v. on days 22-25 + Cis 100 mg/m <sup>2</sup> /day i.v. on day 1, followed by RT 31.2-45.6 Gy + 5-FU/LV/Cis as described before on RT-days 1-4 (chemotherapy completion rate: 95%, RT completion rate: NR, overall completion rate: NR), followed by surgery (100% of patients proceeded to surgery)					
	Resectable T1-2/ N+ or T3-4/any N	19	R0: NR; R1: NR; R2: NR	D1: 0 [0]; D2: 19 [100]	0 [0]	1 [5]
Lowy <i>et al.</i> 2001 (93)	RT 45 Gy + 5-FU 300 mg/m <sup>2</sup> /day i.v. on RT-days 1-5, 8-12, 15-19, 22-26, 29-33 (chemotherapy completion rate: NR, RT completion rate: 92%, overall completion rate: 92%), followed by surgery (76% of patients proceeded to surgery), followed by intraoperative RT 10 Gy for all patients who underwent resection					
	Resectable T1/N+ or T2-4/any N	25	R0: 18 [72]; R1: 1 [4]; R2: 0 [0]	D1: NR; D2: NR	1 [4]	2 [8]

All percentages are calculated in reference to all the included patients. Treatment completion rates include chemotherapy given in a modified dose. Stage is according to the classification in use by the trial itself. <sup>†</sup>, included also patients with adenocarcinoma of the lower third of the esophagus or gastro-esophageal junction; <sup>‡</sup>, trial was prematurely closed; <sup>#</sup>, in this trial was postoperative CRT also investigated. LND, lymph node dissection; pCR, pathologic complete response; RT, radiotherapy; Pac, paclitaxel; Car, carboplatin; R0, microscopically complete resection; R1, microscopically incomplete resection; R2, macroscopically incomplete resection; D1, lymph node stations 1-6; D2, lymph node stations 1-11; S-1, S1-fluoropyrimidine; Cis, cisplatin; LV, leucovorin; Iri, irinotecan; 5-FU, 5-fluorouracil; NR, not reported; Ox, oxaliplatin; Etop, etoposide; G, gastric cancer; GEJ, gastro-esophageal junction cancer.

**Table 6** Grade 3-4 hematological and gastrointestinal toxicity of preoperative and postoperative chemoradiotherapy reported in selected clinical trials

Toxicity grade 3-4	Lee <i>et al.</i> <sup>1</sup> (68)	Macdonald <i>et al.</i> <sup>2</sup> (74)	Trip <i>et al.</i> <sup>3</sup> (82)	Matsuda <i>et al.</i> <sup>4</sup> (83)
Granulocytopenia/neutropenia (%)	48	54 <sup>+</sup>	4	11
Leukopenia (%)	0	54 <sup>+</sup>	12	11
Thrombocytopenia (%)	1	54 <sup>+</sup>	0	11
Nausea (%)	12	33 <sup>§</sup>	4	11
Vomiting (%)	3	33 <sup>§</sup>	0	0
Anorexia/decreased appetite (%)	0	33 <sup>§</sup>	4	0
Diarrhea (%)	1	33 <sup>§</sup>	0	11

<sup>1</sup>, percentages relative to 227 patients who started postoperative treatment; <sup>2</sup>, percentages relative to 273 patients who started postoperative CRT; <sup>3</sup>, percentages relative to 25 patients who started preoperative chemoradiotherapy; <sup>4</sup>, percentages relative to 9 patients who started preoperative chemoradiotherapy. <sup>+</sup>, percentage reported for hematologic side effects combined; <sup>§</sup>, percentage reported for gastrointestinal side effects combined.

reported for the CRT regimen with concurrent carboplatin and paclitaxel (*Tables 5,6*) (82), as was also observed in the CROSS trial that administered a similar regimen preoperatively for patients with resectable esophageal cancer (94). The reported percentages of deceased patients related to the treatment with postoperative or preoperative CRT including any additional chemotherapy were between 0-1% (68-74,82,83).

Compliance rates to postoperative CRT including any induction chemotherapy were reported between 64% and 91% (68-74). This seems higher with the newer optimized CRT regimens that use concurrent oral fluoropyrimidines. For example the RT completion rate in the ARTIST trial was 87%, even after 2 courses of induction chemotherapy (68), and up to 89-97% in the phase I/II studies of Jansen *et al.* (99-101). Compliance rates to preoperative CRT including any induction chemotherapy were reported from 74% up to 95% as investigated in phase I and II studies (82-87,89,93). With the older CRT regimens including any induction chemotherapy, toxicity was the reason to discontinue treatment in 10-19% of patients (69,72-74), while this was around 5% with the newer CRT regimens (68,82,83,100).

Besides acute toxicity of CRT for gastric cancer, late toxicity is important as well, however, few studies reported on this. With CRT for gastric cancer, a large area of the upper abdomen is irradiated, whether this is administered preoperatively or postoperatively (102). As a result, surrounding tissues of the liver, kidneys and spleen, are irradiated as well. The most important late toxicity is radiation-induced nephrotoxicity. This is radiation dose-

and volume-dependent, progressive in time, and associated with renovascular hypertension (103-105). The radiation dose to both kidneys (106) should be kept as low as possible to better preserve its function which can be accomplished by the use of highly conformal RT techniques such as Intensity Modulated Radiation Therapy (IMRT) (107) and Image Guided Radiation Therapy (IGRT). A relatively low-dose of concurrent cisplatin (20 mg/m<sup>2</sup> i.v. weekly), a well-known nephrotoxic drug, can be administered safely with regard to nephrotoxicity (104,107). However, the consequences of the combination of concurrent cisplatin in a CRT regimen with administering high-dose cisplatin for example as part of preoperative chemotherapy, are not yet established (107,108).

In contrast to the high amount of consideration that is placed on the kidneys, the spleen is not accounted for when administering CRT for gastric cancer, despite the fact that it is encompassed in the high dose region. However, nowadays the extremely important and unique immunological and hematological functions of the spleen are acknowledged (109-112). Following surgical splenectomy or in case of functional hyposplenism, patients are at an increased risk for fatal thromboembolic events and overwhelming postsplenectomy infections (OPSI) by encapsulated bacteria (109,110). For this matter, guidelines regarding preventive measures, including immunization against encapsulated bacteria such as *Streptococcus pneumoniae* and prophylactic and on-demand antibiotics have been implemented. Although radiation of the spleen has been associated with hyposplenism, it is largely unknown whether and to what extent the functions of the spleen are affected by radiation,

and to what extent we can draw a parallel from radiating the spleen to surgical splenectomy (109), or hyposplenism (111). Guidelines regarding the management of patients that have received irradiation to the spleen have not yet been established.

## Discussion

Based on the accumulating evidence of the past decade that multimodality treatment improves OS in locally advanced resectable gastric cancer, all patients should be discussed by multidisciplinary teams and considered for multimodality treatment. The variety on multimodality regimens creates opportunities to improve the treatment of gastric cancer patients by considering subgroups that benefit most from certain treatments.

Both chemotherapy and CRT added to the surgical resection of gastric cancer have shown to improve OS in randomized controlled trials (40,41,60,74). Only a few trials have compared chemotherapy and CRT directly, which were all conducted in Asia (68-72). The outcomes of the completed trials did not show an OS benefit for either one of the treatments, but a trend favoring CRT could often be observed. The meta-analysis by Ohri *et al.* including these trials, detected a significant beneficial effect of postoperative CRT over chemotherapy (78). Currently, two large-scale phase III randomized controlled trials investigate the possible superiority of CRT to chemotherapy, i.e., the Dutch CRITICS trial initiated by the Dutch Colorectal Cancer Group (ClinicalTrials.gov number NCT00407186) that randomizes patients for perioperative chemotherapy *vs.* preoperative chemotherapy followed by surgery and postoperative CRT, and the Australian TOP GEAR trial that randomizes patients for perioperative chemotherapy *vs.* preoperative CRT followed by surgery and postoperative chemotherapy.

One subgroup of gastric cancer patients is formed by patients who have undergone an R1 resection. As an R1 resection is associated with a dismal prognosis, many physicians question whether these patients should continue with a potentially curative treatment regimen. These patients were invariably excluded from randomized controlled trials, and to perform a trial exclusively with these patients is not feasible and may be unethical. Therefore, evidence for optimal treatment is and will be limited to retrospective analyses and/or subgroup analyses of large randomized trials in which no deviations from the randomized treatment arm are made after an R1

resection. Several retrospective analyses from our group have shown a clear benefit from postoperative CRT for gastric cancer patients who had undergone an R1 resection (79-81). In these articles, only a few patients received preoperative chemotherapy, and therefore questions remain on the efficacy of postoperative CRT after an R1 resection when preoperative chemotherapy has been administered. Subgroup analyses of the CRITICS trial might inform us on the efficacy of postoperative CRT under these circumstances (113).

Preferably, an R1 resection and its associated dismal prognosis should be prevented. Preoperative CRT is a promising approach to obtain an R0 resection (82,88,94). This treatment might also have the potential to induce resectability in initially irresectable gastric cancer (82). Pathologic complete response rates after preoperative CRT are independently prognostic for OS in several studies, as well as pCR rates after preoperative chemotherapy (90,114,115). Pathologic CR rates tend to be higher after preoperative CRT compared to chemotherapy alone though (60,88). Rightfully, preoperative CRT is nowadays not anymore confined to the higher located gastro-intestinal tumors such as esophageal and gastro-esophageal junction tumors, but also applied in more proximally located gastric tumors, for example within the TOP GEAR trial.

The majority of gastric cancer patients in the Western part of the world present themselves with lymph node metastases at diagnosis, forming a large subgroup of patients with node positive disease. Consequently, these patients also form the majority in clinical trials investigating the addition of chemotherapy (40,41,58,60) as well as CRT (68,74). In subgroup analyses, postoperative CRT is more beneficial when node positive disease is present than when no lymph node metastases are present (75,78). Moreover, in the subset of node positive patients in the ARTIST trial, postoperative CRT was more beneficial than chemotherapy-only (68). However, this does not mean that node negative patients do not benefit from CRT or from chemotherapy. Hopefully the ARTIST-II trial (ClinicalTrials.gov number NCT01761461) that includes only node positive patients, will further clarify the role of postoperative CRT and chemotherapy in this group of patients.

Other subgroups of patients can be based on the extent of the surgical LND. A lot of debate focusses on the efficacy of additional treatment modalities when optimal surgery, i.e., at least a D1+ LND, has been performed, because in the past the majority of patients in all large-scale clinical trials conducted in the West underwent suboptimal surgery, and outcomes between

clinical trials conducted in the West or East that differ in surgical quality, are conflicting. Conceptually, the combination of multimodality treatment and a D2 LND could be overtreatment if these two modalities would both prevent the same relapses, i.e., locoregional recurrences or secondary distant metastases resulting from residual affected lymph nodes. Based on positive outcomes of multimodality treatment, both chemotherapy and CRT, after a D2 LND from all (subsets of) Eastern and Western clinical trials (40,41,60,68,73,74), we can only assume that multimodality treatment is beneficial irrespective to the extent of the LND. Future trials will give further insight in this issue as recently a D2 LND has become the standard of care in Western countries and is applied in currently ongoing trials (113), and as Asian trials are initiated that routinely apply D2 LND.

A major problem concerning the addition of extra treatment modalities to surgery in the treatment of gastric cancer is the accompanied toxicity, when this leads to non-compliance with treatment and especially to the delay of or withdrawal from potentially curative surgery. The reported outcomes of clinical trials thus far refute these concerns. The reported toxicity rates of preoperative chemotherapy and CRT are in general lower than those of postoperative treatment. Furthermore, toxicity rates of the newer optimized CRT regimens are lower than of chemotherapy, either preoperatively or postoperatively. In addition, compliance with preoperative chemotherapy and CRT regimens is higher than with postoperative treatment. Importantly, this higher compliance offers the chance to administer more intensified, combination chemotherapy or CRT. Moreover, preoperative regimens improve pathology-related surgical results without increasing surgical morbidity and mortality. Taken together, preoperative chemotherapy and/or CRT are preferable to postoperative regimens. However this has to be further confirmed in phase III studies.

To conclude, future randomized controlled trials for locally advanced resectable gastric cancer should include preoperative multimodality treatment.

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### Footnote

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## Expanding treatment options for metastatic gastric cancer

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*Comment on:* Li J, Qin S, Xu J, *et al.* Randomized, Double-Blind, Placebo-Controlled Phase III Trial of Apatinib in Patients With Chemotherapy-Refractory Advanced or Metastatic Adenocarcinoma of the Stomach or Gastroesophageal Junction. *J Clin Oncol* 2016;34:1448-54.

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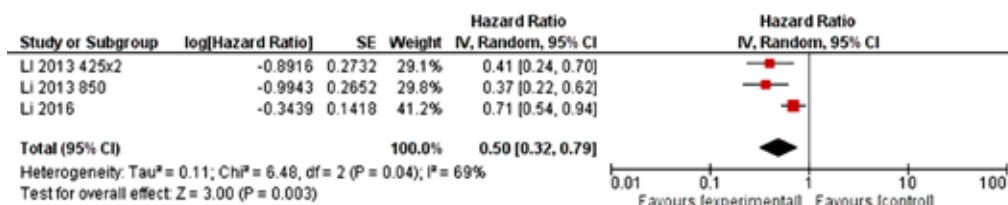
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Li *et al.* published a clinical study evaluating the efficacy and safety of Apatinib (a small-molecule tyrosine kinase inhibitor of vascular endothelial growth factor receptor 2 (VEGFR-2) versus placebo in the treatment of patients with gastric or gastroesophageal junction adenocarcinoma for whom at least two lines of prior chemotherapy had failed (1).

This is a randomised, double-blind study performed in 32 centers in China. A total of 273 patients were randomly assigned to apatinib or placebo. Apatinib showed to significantly improve the overall survival with an acceptable safety profile. In fact, the median survival was significantly improved in the Apatinib arm compared with the placebo (6.5 *vs.* 4.7 months; hazard ratio: 0.709). With regard to other efficacy end points, the median progression free survival was 2.6 months for the apatinib arm and 1.8 months for the placebo arm with a hazard ratio of 0.444. Finally, the proportion of patients who reported an objective response was 2.8% in patients treated with apatinib versus 0% in the placebo group and patients who reported a disease control rate was 42.1% in the apatinib group versus 8.8% in the placebo group. Quality of life determined using the European organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC; QLQ-C30) showed that was no significant differences between the two groups. In regard to adverse events, apatinib was generally well tolerated; the main reasons for dose reduction were hand-foot syndrome, proteinuria, and hypertension with about the 20% of patients who modified the dose of apatinib for side effects. Although, there is an

imbalance in the percentage of patients with an ECOG performance status of 0 in favor of the apatinib arm (27.3%) compared with placebo arm (16.5%), no statistically significant difference was observed between the patient's characteristics of the two arms.

Metastatic gastric or gastroesophageal junction cancer is a lethal disease characterized by a very short overall survival, underlining a critical need of new therapeutic options. Therefore, the prognosis of metastatic gastric cancer is still very poor with a median overall survival that not exceed the year (2). For metastatic gastric or gastroesophageal junction cancer patients, chemotherapy, with platinum-based and fluoropyrimidine combination regimens is considered the mainstay of first line of treatment (3). Unfortunately, although several molecular targets have been investigated, only trastuzumab in the HER2-positive setting and ramucirumab led to a clinical improvement in the survival of metastatic patients (4). Trastuzumab is a humanized recombinant monoclonal antibody that selectively binds to the extracellular domain of HER2 that account for only the 20% of patients (4). Ramucirumab, a monoclonal antibody vascular endothelial growth factor (VEGFR)-2 inhibitor, showed alone or in combination with paclitaxel, a benefit in efficacy and survival in patients with metastatic gastric cancer who progressed after a first-line chemotherapy (4). Several different targeted agents against different molecular pathway showed no advantage on survival (5). Therefore, there is an urgent need for further active treatments beyond second and further lines of chemotherapy in metastatic



**Figure 1** Forest plots of hazard ratios for overall survival comparing apatinib to the placebo in third line of treatment in metastatic gastric cancer. The Chi-squared test showed moderate heterogeneity between the trials. The random effects model was used.

setting mainly because the number of patients suitable for a third-line of chemotherapy is growing (4). In this scenario, Li *et al.* proposed apatinib in a group of patients heavily pretreated; in fact more than the 30% of patients are progressed after 3 or more lines of therapy with a very low percentage of patients intolerant of second-line treatment. In addition, the 20% of patients are with >2 metastatic sites and peritoneal metastases that are widely considered negative prognostic factors. For these reasons and considering the very worst prognosis of metastatic gastric cancer and of the limitation of therapeutical options, the improvement in efficacy of apatinib is clinically relevant and may impact on the future prognosis of patients.

This is not the first clinical evidence of the efficacy of apatinib in gastric cancer. In fact, in 2010, a phase I study investigated the pharmacological activity and the maximum dose tolerable of apatinib for 34 patients with gastrointestinal tract cancer (6). Interestingly, the 7 patients achieving partial response were mainly with gastric cancer. In addition in 2013, a phase II, randomized, double-blind, placebo-controlled trial involving metastatic gastric or gastroesophageal junction cancer patients who do not respond to or who experience progression with second-line chemotherapy (7), showed an improvement of survival with apatinib versus placebo. Two different regimes of apatinib were investigated (850 mg once daily and 425 mg twice daily). The median overall survival values were 2.50 months in the placebo group and 4.83 and 4.27 months respectively in the apatinib group. The toxicity was low and easily manageable. A pooled analysis of both trials (*Figure 1*) showing that apatinib in third line of treatment in metastatic gastric or gastroesophageal junction cancer was associated with a significant survival improvement with a cumulative hazard ratio of 0.50. A moderate heterogeneity between the two trials was observed in the interaction test.

Nonetheless, there are several open questions that should be assessed in the near future. (I) What is the

efficacy of apatinib in previous lines of treatment? It is well known that first reports of another anti-VEGFR-2 therapy such as ramucirumab plus chemotherapy failed to show a progression free survival or overall survival advantage versus chemotherapy alone in front line of treatment (8). However, this is a small study with several bias in the selection of patients (4), and it is not possible to translate these negative results also for apatinib and therefore future trials are awaited to clarify the role of apatinib in previous lines of therapy (9); (II) is possible a combination of apatinib with other anti-neoplastic agents? We know that ramucirumab plus paclitaxel as second line treatment demonstrated a considerable superior activity (4); therefore it may be the same for apatinib; (III) is there a place for apatinib in maintenance therapy? For this question, several trials are launched and first results are awaited (9). Finally, we deem that in the near future, it will be more important to focus on the possible predictive biomarkers of response (such as VEGF; VEGFR2 expression) to help in selection of the optimal candidates to this novel therapy (10). In conclusion, although the evidences are small, apatinib seems one of the most promising agent for gastric or gastroesophageal junction carcinoma.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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# Use of positron emission tomography scan response to guide treatment change for locally advanced gastric cancer: the Memorial Sloan Kettering Cancer Center experience

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**Background:** Early metabolic response on 18-fluorodeoxyglucose-positron emission tomography (FDG-PET) during neoadjuvant chemotherapy is PET non-responders have poor outcomes whether continuing chemotherapy or proceeding directly to surgery. Use of PET may identify early treatment failure, sparing patients from inactive therapy and allowing for crossover to alternative therapies. We examined the effectiveness of PET directed switching to salvage chemotherapy in the PET non-responders.

**Methods:** Patients with locally advanced resectable FDG-avid gastric or gastroesophageal junction (GEJ) adenocarcinoma received bevacizumab 15 mg/kg, epirubicin 50 mg/m<sup>2</sup>, cisplatin 60 mg/m<sup>2</sup> day 1, and capecitabine 625 mg/m<sup>2</sup> bid (ECX) every 21 days. PET scan was obtained at baseline and after cycle 1. PET responders, (i.e.,  $\geq 35\%$  reduction in FDG uptake at the primary tumor) continued ECX + bev. Non-responders switched to docetaxel 30 mg/m<sup>2</sup>, irinotecan 50 mg/mg<sup>2</sup> day 1 and 8 plus bevacizumab every 21 days for 2 cycles. Patients then underwent surgery. The primary objective was to improve the 2-year disease free survival (DFS) from 30% (historical control) to 53% in the non-responders.

**Results:** Twenty evaluable patients enrolled before the study closed for poor accrual. Eleven were PET responders and the 9 non-responders switched to the salvage regimen. With a median follow-up of 38.2 months, the 2-year DFS was 55% [95% confidence interval (CI), 30–85%] in responders compared with 56% in the non-responder group (95% CI, 20–80%, P=0.93).

**Conclusions:** The results suggest that changing chemotherapy regimens in PET non-responding patients may improve outcomes. Results from this pilot trial are hypothesis generating and suggest that PET directed neoadjuvant therapy merits evaluation in a larger trial.

**Keywords:** Gastroesophageal cancer; locally advanced; 18-fluorodeoxyglucose-positron emission tomography (FDG-PET); neoadjuvant chemotherapy

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## Introduction

Gastric cancer is an aggressive neoplasm and patients with locally advanced disease have a poor prognosis despite curative intent surgery. Adjuvant therapy has been shown to improve survival when added to surgery, with improvements seen for post-operative chemotherapy with radiotherapy (INT-0116) or without (S-1, CLASSIC trials) (1-3). Large randomized trials have also established the benefit of perioperative chemotherapy over surgery alone (4,5). Despite these positive results of additional therapy to curative intent resection, patient outcomes remain poor, despite the additional benefit of systemic therapy.

Response to preoperative chemotherapy of localized gastric and gastroesophageal junction (GEJ) adenocarcinoma, as measured by clinical parameters and pathological response, has been associated with improved patient outcomes and survival following surgery (6). Positron emission tomography (PET) scan has been studied as a tool to assess response to neoadjuvant chemotherapy (7). German investigators showed that an SUV reduction of 35% or greater after induction chemotherapy differentiated patients into two prognostic groups, with the PET responders having significantly better overall survival (OS) than non-responders. Metabolic response was associated with a high histopathologic response rate of 44% compared to 5% in non-responders ( $P=0.001$ ) (8). The subsequent MUNICON study focusing on GEJ cancers showed PET non-responders who stopped preoperative chemotherapy after two weeks and proceeded directly to surgery continue to have significantly poorer survival, compared to PET responders who completed 3 months of preoperative therapy. To validate the potential prognostic and predictive value of early PET scan imaging during preoperative therapy for esophagogastric cancer, we performed a phase II trial of irinotecan and cisplatin in locally advanced gastric cancer. Early PET response from baseline to day 35 was highly predictive for disease free survival (DFS) ( $P=0.01$ ) and histopathologic response ( $P=0.007$ ). Patients continuing the same chemotherapy in the setting of PET no response had significantly worse median DFS of 14.4 months (95% CI, 8.3 months–infinity) compared to >23.3 months (median not reached) for PET responders (9).

The use of novel therapeutics as well as innovative therapeutic strategies is needed to improve survival in patients with resectable gastric cancer. The use of early PET assessment after induction chemotherapy to modify treatment is one such promising strategy. There have been no studies testing whether PET can be used to improve outcomes by

changing the chemotherapy regimen in non-responders, allowing otherwise non-responding patients to achieve a significant response to a salvage therapy prior to surgery.

The use of anti-angiogenic therapy is another promising avenue of research in esophagogastric trials. There has been compelling evidence linking tumor growth and metastases with angiogenesis (10,11). In esophagogastric cancer, increased vascular endothelial growth factor (VEGF) levels have been shown to correlate with advanced tumor stage, the presence of nodal and distant metastasis, and poorer survival (12,13). Based on this pre-clinical rationale, bevacizumab, a chimeric murine monoclonal antibody against human VEGF, has been extensively studied in solid tumors. When the current trial was being developed, our group had performed two phase II trials combining bevacizumab with either irinotecan/cisplatin or modified docetaxel, cisplatin, 5-fluorouracil (5-FU) (mDCF) in patients with advanced gastric and GEJ adenocarcinoma with encouraging rates of response, progression free survival (PFS), and OS with acceptable toxicity (14,15). Bevacizumab was being evaluated in the MAGIC 2 trial of perioperative chemotherapy in locally advanced gastric/GEJ cancer, so the feasibility of adding bevacizumab to neoadjuvant therapy was an additional focus of the current trial.

The objective of this phase II study of patients receiving preoperative chemotherapy and bevacizumab for locally advanced, resectable gastric or GEJ cancer is to examine the effectiveness of PET directed early switching to salvage chemotherapy in the non-responding group, as measured by 2-year DFS.

## Methods

### *Eligibility criteria*

Eligible patients had histologically proven locally advanced but resectable gastric or GEJ adenocarcinoma (tumor stage T any N+ M0 or T2b–T4N any, M0) and 18-fluorodeoxyglucose-PET (FDG-PET) avid. Staging laparoscopy was recommended. If a laparoscopy was not performed, an endoscopic ultrasound (EUS) was required to confirm locally advanced, but resectable gastric cancer. An FDG avid tumor was defined as primary tumor with an SUV  $\geq 3.5$  or a tumor to liver SUV ratio  $\geq 1.5$ , and felt to be “probably” or “definitely malignant” [i.e., likelihood score of 3 or 4 on a scale from (0–4) by the reference nuclear medicine physician].

Tumors involving the GEJ had to have the bulk of their

disease in the stomach (Siewert II or III). All patients were at least 18 years old and candidates for surgical resection. Patients had a Karnofsky performance score (KPS)  $\geq 70\%$  and renal, liver, and bone marrow function that met the following parameters: serum creatinine  $\leq 2.5$  mg/dL, urinalysis demonstrating  $< 2+$  proteinuria and/or urine protein/creatinine ratio  $< 1.0$ ; total serum bilirubin  $\leq 2 \times$  upper limit of normal (ULN), serum AST, ALT, and alkaline phosphatase  $\leq 2.5 \times$  ULN, PT (INR)  $\leq 1.5$ ; absolute neutrophil count  $\geq 1,500/\text{mm}^3$ , and platelet count  $\geq 100,000/\text{mm}^3$ . Informed consent was obtained. The trial was approved by the institutional review board at Memorial Sloan Kettering Cancer Center. The trial was registered at clinicaltrials.gov (NCT00737438).

Patients were excluded if they had baseline blood pressure  $> 150/100$  mmHg despite adequate medical management, significant co-morbidities including cardiac disease, history of abdominal fistula or perforation, serious non-healing wound or ulcer, peripheral vascular disease or stroke, or significant hearing loss.

#### *Pretreatment evaluation and PET scan*

Patients underwent a FDG-PET/CT scan before the initiation of preoperative chemotherapy (baseline PET) and after cycle 1 of therapy (follow-up PET). Patients fasted for 4–6 hours before PET imaging to ensure euglycemic glucose metabolism. Blood glucose levels were measured before each PET scan and if glucose  $\leq 200$  mg/dL, FDG was injected. Approximately 60 minutes post-injection, PET/CT images were acquired. Low dose CT was used for attenuation correction and anatomic localization. First, PET images of the stomach region (1 or 2 bed positions) were acquired for 6–10 minutes (min) per bed position (body weight  $\leq 70$  kg: 6 min; 71–90 kg: 8 min;  $> 90$  kg: 10 min per bed position). The purpose of this longer acquisition was to maximize signal to noise ratio in the stomach region. Then a PET scan of the torso (mid skull to upper thigh) was obtained at 3 min per bed position. Images were reconstructed using standard clinical parameters. Baseline and follow-up scans were obtained on the same machines and same time ( $\pm 10$  min) after injection. Images were reviewed independently by a nuclear medicine physician and entered into separate data sheets.

#### *Treatment*

All patients received preoperative therapy with bevacizumab

15 mg/kg, epirubicin 50 mg/m<sup>2</sup>, cisplatin 60 mg/m<sup>2</sup> on day 1 and capecitabine 625 mg/m<sup>2</sup> bid orally on days 2–21 (ECX). Each cycle of therapy was 21 days. Near the completion of cycle 1 of therapy (during week 3, days 18–21), patients underwent the follow-up PET scan.

Patients with a metabolic response (i.e.,  $\geq 35\%$  reduction in FDG uptake at the primary tumor on the follow-up scan compared to the baseline FDG uptake) continued ECX for 2 additional cycles (cycle 2 and 3). Bevacizumab was administered with cycle 2 but not cycle 3. There was a planned 10-week time interval (70 days) between the last bevacizumab treatment and surgery.

Patients who had a poor PET response (i.e.,  $< 35\%$  FDG reduction on the follow-up PET scan compared with baseline) were switched to a salvage regimen of docetaxel 30 mg/m<sup>2</sup> and irinotecan 50 mg/m<sup>2</sup> administered on day 1 and day 8 of a 21 day cycle for 2 cycles (DI). Patients received bevacizumab 15 mg/kg for the first cycle of salvage docetaxel/irinotecan only. There was again a planned 10-week time interval between the last bevacizumab treatment and surgery. The treatment schema is shown in *Figure 1*.

Post-operatively, patients continued to receive the treatment they last received (ECX/bevacizumab or salvage DI/bevacizumab) for three additional cycles.

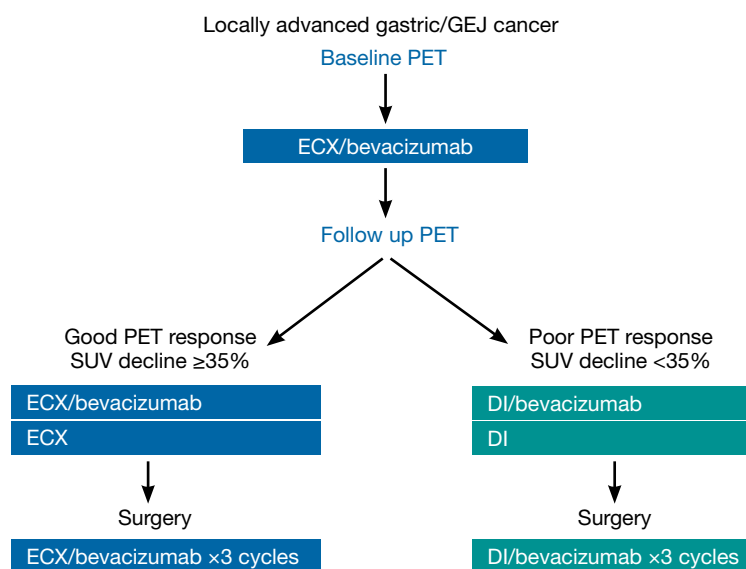
Patients who were not cisplatin candidates (i.e., creatinine clearance 40–60/cc, older age, marginal performance status, etc.) were allowed to receive oxaliplatin 130 mg/m<sup>2</sup> on day 1 every 21 days. Patients who were not able to receive capecitabine (i.e., insurance restriction, unable to swallow) were allowed to receive infusional 5-FU instead of capecitabine after discussion with the principal investigator. 5-FU was administered at 200 mg/m<sup>2</sup> day  $\times$  21 days (held for 48 hours prior to follow-up PET scan).

#### *Surgery*

Following completion of induction chemotherapy, patients underwent repeat staging evaluation. All patients without evidence of metastatic disease then proceeded to surgery. The surgical procedure performed included radical subtotal or total gastrectomy with at least a D1 lymph node dissection. A D2 dissection was recommended.

#### *Pathologic response*

Evaluation of pathologic response was performed by a pathologist. Response assessment was based on examination of multiple microscopic sections, and areas of tumor



**Figure 1** Study schema.

treatment effect scored on a percent histological response scale (0–100%), which is correlated to the Mandard regression score (16). Pathologic response was classified as follows: pathologic complete response (pCR) regression score 1 (100% treatment effect); pathologic partial response (pPR) regression score 2 (90% treatment effect); no response (pNR) regression scores 3 to 5 (0–80% treatment effect).

### Statistical consideration

The primary endpoint of the study was to examine the effectiveness of PET directed early switching to salvage chemotherapy as measured by 2-year DFS in the PET non-responder population. We estimated the 2-year DFS, from the time of resection, for the non-responding group to be 30%. We expected a ratio of PET responders versus non-responders of 1:1. Assumptions were based on the Lordick (6) and Ott (5) trials and our previous data (10). With a planned enrollment of 60, we expected 30 patients (50%) to proceed to salvage chemotherapy. Using an exact single stage design, with 30 patients in the non-responding group, we can differentiate 2-year DFS from 30% to 53% with type I error rates of 5% and 81% power. If 14 of the 30 patients in the salvage group are alive and disease free at 2-year, then this combination and treatment algorithm will be considered reasonable. DFS and OS curves were generated using the Kaplan–Meier method and compared by the log-rank test. Fisher’s exact test and Wilcoxon rank sum test were used to evaluate baseline and post-treatment

characteristics and toxicity.

## Results

### Patient characteristics

Between August 2008 and November 2011, 23 of the planned 60 patients were enrolled before the study closed for poor accrual. Twenty of the patients are evaluable (1 patient was excluded because the primary tumor was not FDG avid, 1 taken off study for toxicity after the first cycle of chemotherapy and 1 patient withdrew consent prior to initiating treatment). Of the 20 evaluable patients, there were 14 males (64%), 8 females (39%) with a median age 62 (range, 33–78) years old, and median KPS of 90. Ten (50%) had intestinal histology, 6 (30%) diffuse type, and 4 (20%) mixed type. Eight (40%) of primary tumors were located in the GEJ with 12 (60%) in the body or distal stomach. Patients in the study underwent extensive staging: 13/20 (65%) received endoscopic ultrasound and 19/20 (95%) underwent staging laparoscopy with baseline T and N stage shown in *Table 1*.

### Metabolic response

PET metabolic response was assessed after the first cycle of ECX/bevacizumab: 11 (55%) patients were PET responders and 9 (45%) were PET non-responders. No significant differences were noted in the baseline characteristics of

**Table 1** Baseline characteristics

Characteristics	PET responders N=11	Non-responders N=9	P value
Age years	61.5 (range, 52–78)	59 (range, 33–69)	1.0
Males	7	3	0.8
Females	4	6	
Race % white	82%	67%	1.0
KPS median [range]	80 [80–90]	90 [80–90]	1.0
Comorbidities	0 [0–3]	0 [0–3]	0.65
Medications	3 [1–12]	3 [1–12]	0.50
Histology, Lauren's			0.46
Diffuse type	2	4	
Intestinal type	8	2	
Mixed type	1	2	
Adenosquamous	0	1	
Histology, differentiation			0.09
Moderate	4	1	
Poor	7	8	
Location			0.28
GEJ/cardia	6	2	
Body	2	3	
Distal stomach	3	4	
Baseline staging			
T2N0	1	0	
T3N0	2	2	
T3N1	7	4	
T4N1	0	1	
T4N2	0	1	
TxN+	1	0	
TanyNx	0	1	
TanyN+	4	6	1.0
Laparoscopy	10	9	1.0
EUS	7	6	0.64

PET, positron emission tomography; KPS, Karnofsky performance score; GEJ, gastroesophageal junction; EUS, endoscopic ultrasound.

responders versus non-responders with regard to age, sex, race, performance status, staging evaluation, location of primary tumor (*Table 1*). The two groups were equivalent in regards to stage II disease (T2–3N0) and node positive patients ( $P=1.0$ ). There was no difference in the tumor location ( $P=0.28$ ) or histology ( $P=0.46$ ) between the

groups; however there was a trend towards more poorly differentiated tumors in the non-responders ( $P=0.09$ ).

The tumors of PET responder patients had a significantly higher median baseline SUV of 11.8 (interquartile range, 10.4) versus 5.5 (interquartile range, 6) for PET non-responders. All of the PET responder patients had a SUV decline  $\geq 35\%$  (range, 35–100% decline from baseline). In the non-responders, the SUV decline ranged from 8–30% and 3/9 (33%) patients had an increase in SUV compared to baseline.

### Surgery

Of the 20 patients, 19 (95%) underwent surgical resection: 14 had gastrectomies and 5 underwent Ivor-Lewis esophagectomies. One patient had progressive disease prior to surgery. Of the 19 resected patients, 17 (89%) had R0 resections, 2 (11%) patients had R1 resections (*Table 2*). R0 resections could be performed in 10 of 11 PET responders (91%) versus 7 of 9 non-responder patients (88%). D2 lymph node dissections were performed in 18/19 (95%) of resected patients with a median number of 23 lymph nodes sampled (range, 15–43), no difference seen in the two groups. One patient in the non-responder group died from post-operative complications.

### Pathologic response

In the PET responder group, 1 patient achieved a pCR and 3 patients had a partial pathologic response. The SUV decrease was not statistically different in patients achieving complete pathologic response compared to those with partial response ( $P=0.2$ ). No pathologic response was noted in the non-responder group. Clinical downstaging was seen in 5 (45%) patients in the PET responder group but in only 1 (11%) non-responder. Pathologic and clinical downstaging responses are shown in *Table 2*.

### Therapy completion/toxicity

In the PET responders, 8 (73%) patients received any post-operative chemotherapy and, of those, 6 (55%) completed all planned treatment. Of the non-responder patients, 5/9 (55%) completed all post-operative chemotherapy. Reasons for not completing post-operative treatment were: R1 resection, post-operative death, prolonged post-operative recovery, and chemotherapy toxicity.

Toxicity was assessed for the 20 evaluable patients (*Table 3*).

**Table 2** Post treatment characteristics of patients who underwent surgery

Patients who underwent surgery (N total =19/20)	PET responders (N=11/11)	Non-responders (N=8/9)	P value
<b>Surgical resection</b>			
R0 resection	10	7	1.0
R1 resection	1	1	
<b>Pathologic response</b>			
Complete PR	1	0	1.0
Partial PR	3	0	0.22
No response	7	8	
<b>Clinical downstaging</b>			
TNM downstaging	5	1	0.16
T and N downstaging	2	1	1.0
T downstaging	3	2	1.0
N downstaging	2	1	1.0
Received any post-operative treatment	8	5	0.64
Completed all chemotherapy	6	5	1.0

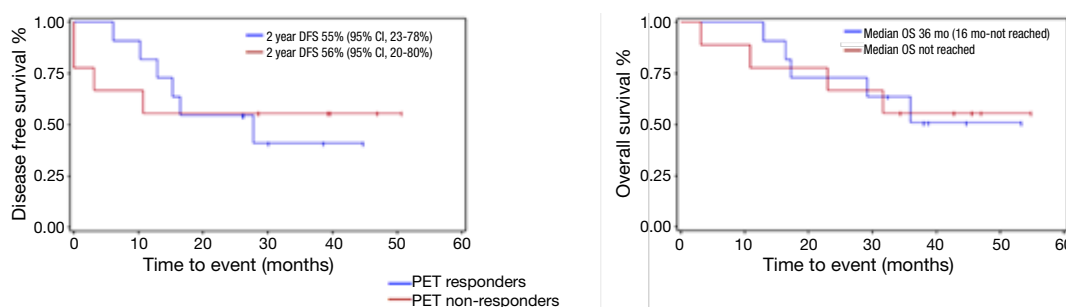
PET, positron emission tomography; PR, partial response.

**Table 3** Toxicity data

Toxicity	PET responders		Non-responders	
	Grade 3	Grade 4	Grade 3	Grade 4
<b>Non-hematological</b>				
Fatigue	2 (18%)	0	1 (11%)	0
Nausea/vomiting	2 (18%)	0	0	0
Diarrhea	2 (18%)	0	1 (11%)	0
Mucositis	1 (9%)	0	1 (11%)	0
Dehydration/anorexia	1 (9%)	0	2 (22%)	0
Electrolyte imbalance	5 (45)	1 (9%)	0	0
Glucose abnormalities	2 (18%)	0	1 (11%)	0
LFT elevation	0	0	1 (11%)	0
Hypertension	0	0	1 (11%)	0
Thrombosis/embolism	0	1 (9%)	0	0
Leak	1 (9%)	0	1 (11%)	0
Pain	2 (18%)	0	1 (11%)	0
<b>Hematological toxicity</b>				
Leukopenia	1 (9%)	1 (9%)	1 (11%)	0
Neutropenia	4 (36%)	1 (9%)	2 (22%)	0
Lymphopenia	3 (27%)	1 (9%)	2 (22%)	0
Anemia	2 (18%)	0	2 (22%)	0
Thrombocytopenia	1 (9%)	0	0	0
Neutropenic fever	1 (9%)	0	0	0

PET, positron emission tomography; LFT, liver function test.





**Figure 2** Disease free survival and overall survival curves by PET response status. PET, positron emission tomography.

Significant chemotherapy related toxicity included grade 3 fatigue (15%), diarrhea (15%), dehydration/anorexia (15%), electrolyte imbalance (25%), neutropenia (30%), lymphopenia (25%), and anemia (20%). One patient developed febrile neutropenia (5%). Grade 4 thromboembolism was seen in 1 patient (5%) and 2 patients developed a gastrointestinal leak (10%). Bevacizumab-related toxicity included grade 3 hypertension in 1 patient (5%). There was no significant difference in all grade 3 toxicity ( $P=0.07$ ) or grade 4 toxicity ( $P=0.09$ ) between the responder and non-responder groups.

The median follow up was 38.2 months (range, 26 to 50.7 months). Analysis of all 20 evaluable patients showed a median DFS of 27.9 months [95% confidence interval (CI), 10.3 months–not estimable]. The median OS was 36 months (95% CI, 17.2 months–not reached). In the PET responder group, the 2-year DFS was 55% (95% CI, 23–78%) compared with 56% in the non-responder group (95% CI, 20–80%) as shown in *Figure 2*. There was no significant difference in DFS between the two groups ( $P=0.93$ ).

## Discussion

Current adjuvant therapy strategies in gastric cancer, including perioperative chemotherapy and post-operative chemotherapy with or without radiotherapy, achieved only a modest improvement in survival in gastric cancer. The majority of patients with this disease treated in the West still die of recurrent disease, and the need to identify new agents and treatment strategies is a priority.

In our prospective pilot trial, neoadjuvant chemotherapy was switched to a non-cross resistant regimen in metabolic non-responding patients in an attempt to improve the 2-year DFS rate in patients with gastric and GEJ cancer. Response to preoperative chemotherapy for patients with localized gastric and GEJ cancer has been recognized as a strong prognostic

factor. Several studies have demonstrated the ability of FDG-PET to assess response to preoperative treatment in esophagogastric cancer and indicate that early PET scan metabolic response is associated with improved outcomes (8,17). Ott *et al.* found that metabolic responders had a pathologic response rate of 44% and 3-year survival of 70% compared a response rate of 5% and 3-year survival of 35% in non-responders who continued the same chemotherapy (4). In the MUNICON trial, patients who did not achieve an early PET response discontinued chemotherapy and underwent surgical resection. Despite this change, non-responders had worse median relapse free survival (14.1 *vs.* 29.7 months,  $P=0.002$ ) and OS (25.8 months versus median not reached,  $P=0.015$ ) compared to PET responders. We included bevacizumab based on our promising phase II data in advanced disease, and the use of this agent in an ongoing neoadjuvant randomized trial (18).

In comparison to prior studies showing a poor outcome in PET non-responders continuing neoadjuvant therapy, our current pilot study results suggest an improvement in the 2-year DFS in the PET non-responding group when these patients were changed to a potentially non cross-resistant chemotherapy. The 2-year DFS was 55% (95% CI, 30–85%) in the PET responders compared with 56% in the non-responders (95% CI, 20–80%). Median OS was 36 months in the PET responders and not yet reached in non-responders, with no significant difference in median OS (log rank test  $P=0.95$ ).

The contribution of bevacizumab in this trial is difficult to interpret. There was no excessive toxicity seen with the addition of bevacizumab to the neoadjuvant regimen. The phase III global study of bevacizumab on the AVAGAST trial failed to show a survival benefit when bevacizumab is added to first line chemotherapy, despite improvements in response rates and PFS (19). The MAGIC 2 trial combining bevacizumab with neoadjuvant chemotherapy

in esophagogastric cancer is ongoing, with preliminary data indicating no adverse toxicity impact on therapy or surgical outcomes (20).

We clearly acknowledge the limitations of a study with only 20 patients. However, we do feel that this study provides exploratory data on the use of PET scan to help identify potential early treatment failures and guide treatment in gastric cancer. The results suggest that PET non-responding patients, who have had historically worse outcomes, can change regimens and may be able to achieve survival comparable to those with an initial PET response. The PET non-responder group had a greater percentage of patients with diffuse type and poorly differentiated cases, and overall had lower baseline SUV levels. PET scan may be less sensitive in gastric adenocarcinoma with these features. Toxicity was similar between the two groups, suggesting change in chemotherapy is feasible.

## Conclusions

In our study, patients with suboptimal PET response to induction chemotherapy were changed to an alternative regimen prior to surgical resection. The results from this trial are hypothesis-generating and clearly need more evaluation to see if this strategy changes outcomes. These preliminary results have helped engender the basis for an alliance/CALGB multicenter randomized trial using PET scan response to direct therapy preoperative in locally advanced gastric cancer (NCT02485834) (21).

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* The study was approved by the institutional review board at Memorial Sloan Kettering Cancer Center and written informed consent was obtained from all patients.

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# Late recurrence of gastric cancer with isolated brain metastasis

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**Abstract:** A 70-year-old woman presented to our clinic in 2007 after an evaluation for dysphagia revealed a poorly differentiated adenocarcinoma of the gastroesophageal junction. Workup for metastatic disease was negative at presentation. She had a complete response to treatment, which was completed in November 2007. She continued to follow up regularly until 2011 when she presented again with neurologic symptoms and was found to have an isolated brain metastasis. She underwent resection of the lesion, and pathology was consistent with her originally diagnosed gastric cancer. The patient received adjuvant radiation therapy, however, unfortunately had rapid progression of disease 1 month later and was transitioned to hospice. Here, we report a rare case of late recurrence of gastric cancer with isolated brain metastasis with a review of literature.

**Keywords:** Gastric cancer; recurrence; brain metastasis

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## Introduction

Brain metastasis from gastric cancer is rare and almost always accompanied by disseminated disease. We report an unusual case of a patient diagnosed with a sole metastatic lesion to the brain more than 4 years after presentation with locally advanced gastric adenocarcinoma, without extra-cranial disease.

## Case presentation

JH presented in January of 2007 at the age of 70 with dysphagia and was found to have an ulcerating circumferential tumor of the gastroesophageal junction that was confirmed a poorly differentiated adenocarcinoma. Imaging studies revealed non-metastatic disease. She received neoadjuvant chemotherapy with FOLFIRI (5FU/leucovorin/irinotecan) and underwent total gastrectomy in July 2007. Pathology showed an ypT2bN2M0 poorly differentiated adenocarcinoma extending into the subserosa and involving the proximal cardia and distal esophagus. Gallbladder, small bowel and the rest of the gastric pathology were negative for malignancy. The residual

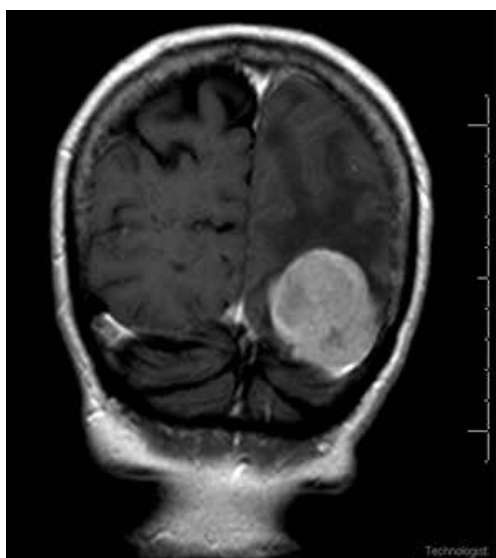
tumor was 3 cm × 3 cm × 1 cm in size with an R0 resection, the closest margin being 1.5 cm. Perineural and vascular invasion were present. Lymph node examination showed 4 of 27 nodes positive. Six cycles of adjuvant FOLFIRI chemotherapy were given and completed in November 2007. The patient was followed with regular surveillance first at her treating facility, Roswell Park Cancer Institute and subsequently at UCONN Health.

In early 2011 she began experiencing headaches, memory problems and word-finding difficulty. A neurological exam demonstrated right hemianopsia, nominal aphasia, recent and immediate memory problems, and an abnormal clock-drawing test. MRI of her brain in March 2011 showed a single 4.4 cm × 3.8 cm × 4.5 cm well-circumscribed lesion in the paramedian aspect of the left occipital lobe with surrounding vasogenic edema (*Figure 1*). Scans for other sites of metastatic disease were negative. The patient underwent stereotactic left parieto-occipital craniotomy with resection of the lesion. Pathology revealed a poorly differentiated adenocarcinoma comparable with her previous gastric cancer (*Figure 2A,B*). HER2 was not over-expressed (immunohistochemical 0/3) (*Figure 2C*).

Post-operative radiation was administered using partial

brain technique. A total of 50 Gy was delivered over 20 fractions using intensity modulated radiotherapy (IMRT) and image guided radiotherapy (IGRT) techniques with daily megavoltage CT on a Hi-Art Tomotherapy System<sup>®</sup> (Figure 3). The patient improved post-operatively, but developed several large nodular lesions on her scalp 1 month later. Biopsy of the scalp lesion and CSF analysis confirmed progressive metastatic involvement. She deteriorated rapidly and was transitioned to hospice.

Autopsy revealed metastatic poorly differentiated gastric carcinoma at the previous craniotomy site within the



**Figure 1** MRI post contrast T1 gadolinium image. Coronal view: 4.4 cm × 3.6 cm × 4.5 cm well-circumscribed heterogeneously enhancing soft tissue mass in the paramedian aspect of the left occipital lobe with surrounding vasogenic edema.

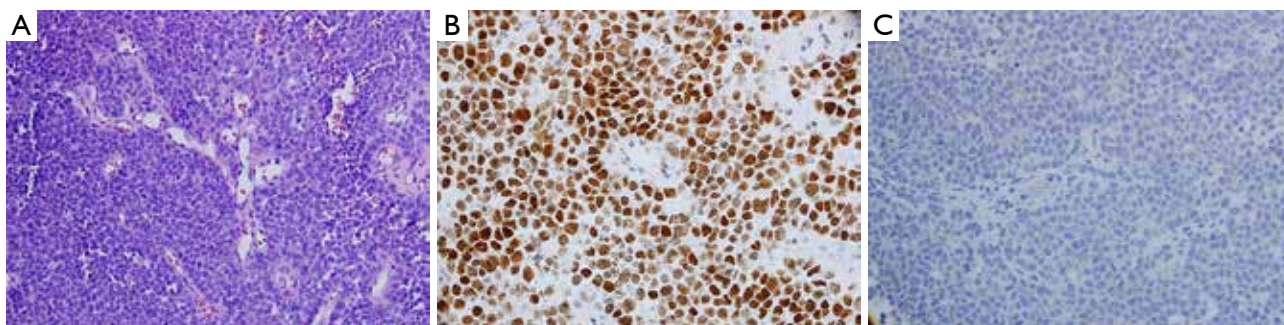
radiated field, also diffusely involving the leptomeninges, cerebellum and spinal cord, and focally involving the underlying brain parenchyma in the right parieto-occipital lobe, hippocampus, midbrain, cerebellum and pituitary gland. There was no evidence of malignancy in the bone, bone marrow, thorax, abdomen or pelvis or any site outside the brain.

## Discussion

Gastric cancer remains a lethal malignancy both in the United States and globally. It is the 14th most common cancer in the United States with 24,590 new cases documented each year, resulting in more than 10,000 deaths annually (1). With 723,000 deaths worldwide, it is the third leading cause of cancer death for both sexes second only to lung cancer (2).

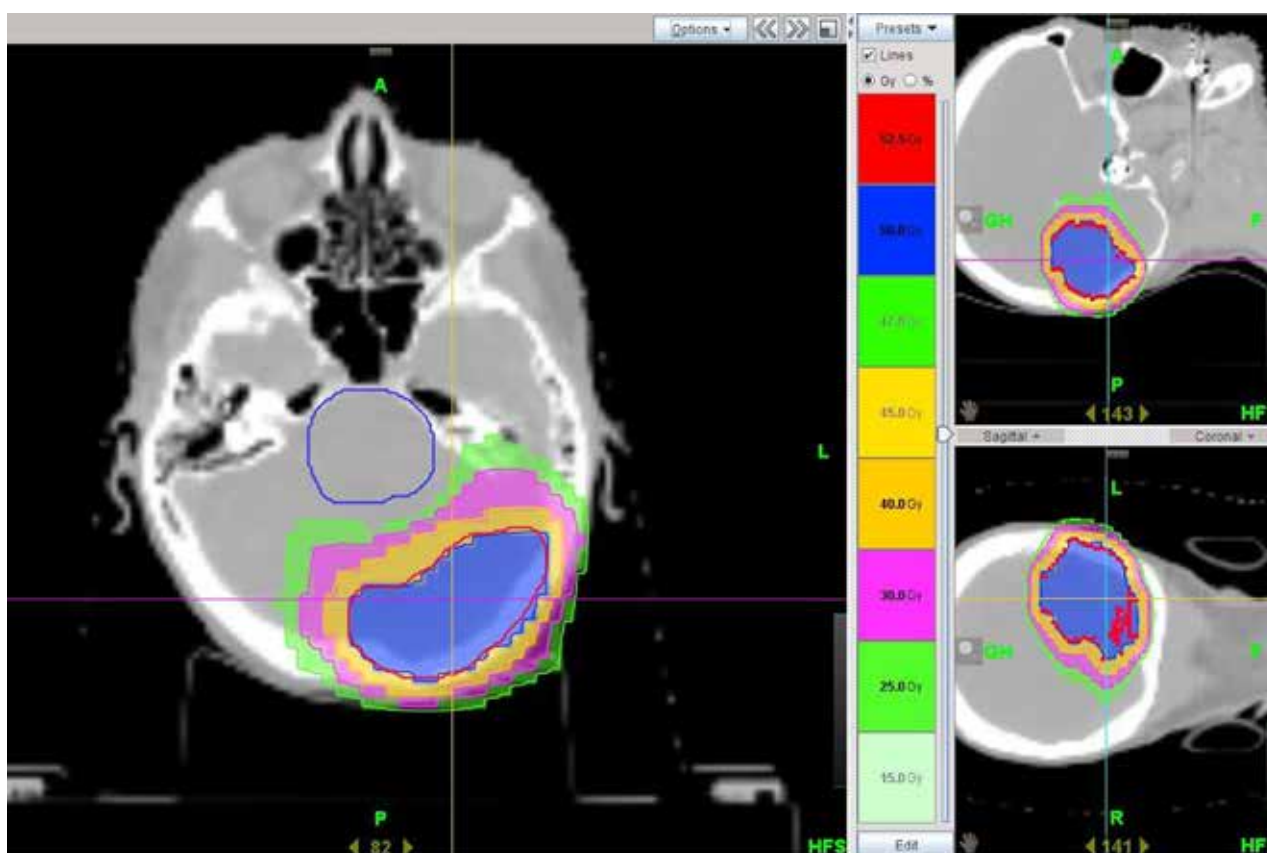
Brain metastasis is uncommon in gastric cancer; recurrence mostly occurs intra-abdominally. Extra-abdominal metastasis, usually involving lung and bone occurs in only about 13% of cases (3). A U.S. study that included over 3,000 gastric cancer cases over a 40-year period reported brain metastasis in only 0.7% of patients (4). In a study from Japan, 2,322 patients were identified to have gastric cancer from 1980 to 1998 and only 11 (0.47%) had metastatic brain lesions (5). Apart from these two large studies, the literature on gastric cancer metastatic to the brain consists mainly of case reports and limited case series.

In gastric cancer, brain metastasis occurring years after the initial diagnosis is rare and almost always accompanied by systemic relapse (4,5). A case series reported an interval period between diagnosis and development of brain metastasis ranging from 1 to 24 months (6). Our case is



**Figure 2** H&E and immunohistochemical staining of the resected brain lesion, indicating gastric origin of the tumor. (A) Invasive adenocarcinoma in cranial resection specimen H&E stain 100× (10× objective × 10× ocular); (B) invasive adenocarcinoma in cranial resection specimen CDX2 stain 400× (40× objective × 10× ocular); (C) invasive adenocarcinoma in cranial resection specimen HER2 IHC stain 200× (20× objective × 10× ocular).





**Figure 3** Axial, sagittal and coronal images from the treatment planning CT, showing prescription doses to tumor bed at 50 Gy (blue), 40 Gy (orange), 30 Gy (purple) and 25 Gy (green) colorwash. Note sparing of dose from the brains.

unique as the patient developed cerebral metastasis 4 years after initial diagnosis with no evidence of other systemic recurrent disease even at autopsy.

Our patient received perioperative chemotherapy for high grade gastric cancer, with a regimen utilized at the Roswell-Park Cancer Institute. She survived 4 years with no systemic recurrence only to relapse in brain with again high grade disease. HER2 positivity is found in 22% of gastric cancer cases (7). In breast cancer, it is associated with a higher incidence of brain metastasis (8), therefore looked for in our case, but negative.

The prognosis of gastric cancer patients who present with brain metastasis is dismal, and treatment is palliative. Response to treatment is poor in this cohort of patients (4,5). Treatment options include surgical resection (SR), brain radiotherapy, steroids, chemotherapy or a combination. The selection of treatment modality for these metastatic brain tumors depends on the number and resectability of the lesion(s) and the general health condition of the patient (9).

York *et al.* reported a median survival of 54 weeks (range, 22–83 weeks) in patients with gastric cancer with brain metastases who underwent SR, whole brain radiotherapy (WBRT) and steroid therapy (4). The median survival among the WBRT-alone group did not differ from patients who received steroid monotherapy (9.0 weeks with WBRT *vs.* 7.0 weeks with steroids,  $P > 0.05$ ). In retrospective analyses, the combination of SR and WBRT was associated with a survival advantage (4,10). A case series from Japan of four patients with cerebral gastric cancer metastases showed an overall survival ranging from 45–94 days post-treatment with SR and/or stereotactic radiosurgery (11). In solid tumors as a group, local brain radiotherapy (LBRT) following surgery was shown retrospectively to be similar to WBRT following surgery in patients with single brain metastasis in terms of local recurrence rate and median survival time (12). Because of this data, we treated our patient with LBRT in conjunction with SR, unfortunately with rapid tumor growth. The best approach to treatment



of these patients remains unclear.

Our case illustrates that gastric cancer cells may lay dormant in the central nervous system for years and recur as virulent resistant disease. As combined modality treatments for initial therapy of aggressive cancers improve outcomes, cancer dormancy may become more apparent and recurrences seen in less common sites like brain. An understanding of cancer dormancy mechanisms and ways to target these small populations of cells is crucial to improving the outcome of these patients.

### Acknowledgements

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Informed Consent:* Written informed consent was obtained from the patient's next of kin for publication of this manuscript and any accompanying images.

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# Diagnostic and therapeutic strategies for gastric cancer in the era of precision medicine

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**Abstract:** Medical concepts are constantly evolving along with the advances in science and technology. In an era of precision medicine, clinicians may precisely classify patients to achieve the tailored treatment of one disease; in return, the accurate diagnosis and classification of patients also have potential impact on subsequent treatment modalities. Precise surgery and minimally invasive surgery aim to reduce the surgical trauma stress, enhanced recovery after surgery (initially known as “fast-track surgery”) tries to accelerate postoperative recovery, whereas multidisciplinary collaborative team aims to use multidisciplinary strategies for the treatment of various diseases. The application of multiple treatment strategies will ultimately improve both prognosis and quality of life.

**Keywords:** Precision medicine; enhanced recovery after surgery; minimally invasive surgery; multidisciplinary collaboration team

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## Introduction

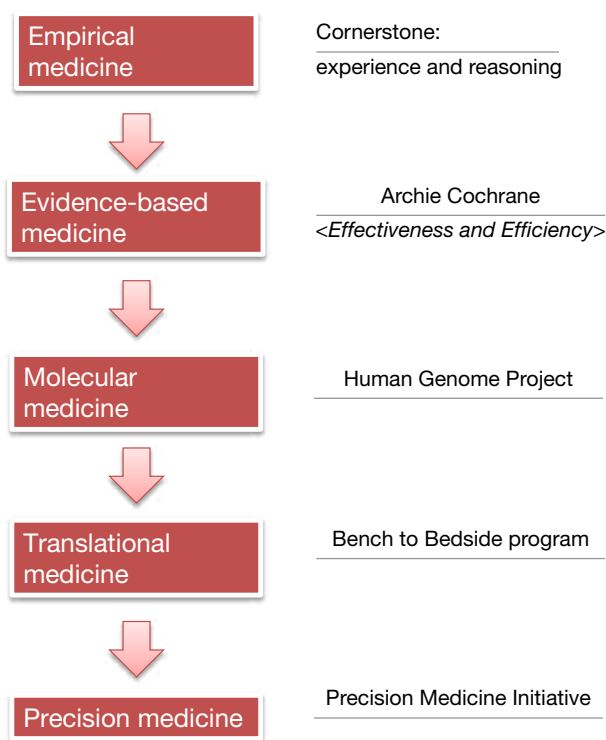
Medical concepts are constantly evolving along with the advances in science and technology. Among them, the “precision medicine” and “precise surgery” are now sweeping the world, the “minimally invasive surgery” strives to limit the size of incisions, the “enhanced recovery after surgery” is designed to achieve the fastest recovery, and the “multidisciplinary cooperative team” emphasizes the important of team work in the treatment of tumors. These ideas will undoubtedly affect the clinical practice and have a profound impact on the diagnosis and treatment strategies of gastric cancer.

## Evolution and existing concepts of medical concepts

Diagnosis and treatment of diseases were mainly based

on the doctors’ experiences decades ago (*Figure 1*). Every day the doctors made key decisions on disease treatment according to textbooks, experiences, and pathophysiological knowledge; this process is known as the empirical medicine, with experience and reasoning being its cornerstones. However, the potential defects of empirical medicine are obvious: it relies too much on the opinions of an individual expert and often lacks knowledge refreshment; as a result, it may neglect the new clinical findings that have substantial impacts on disease management.

In response to the potential defects of the empirical medicine, in 1972 the British epidemiologist Archie Cochrane published an influential book entitled *Effectiveness and Efficiency: Random Reflections on Health Services*, in which he proposed that all the medical professions should sort out the results of all randomized controlled trials and make corresponding evaluations; meanwhile, new findings should



**Figure 1** Evolution of medical concepts.

be continuously collected to update such evaluations, so as to provide reliable evidences for clinical practices, which is known as evidence-based medicine (EBM). This proposal has been widely accepted in the medical community and had a profound influence. EBM centers have been established throughout the world since then; in China, the first EBM center was established in West China Hospital in 1999, which was also the first EBM center in Asia. Currently all the EBM centers are named as Cochrane centers to commemorate his outstanding contribution to the EBM.

Along with the rapid development of science and technology, scientists have been able to explore the mechanisms of pathogenesis at the molecular level and medical research has entered a molecular era. The Human Genome Project was one of the most representative studies. It began in 1990 and costed nearly \$3 billion USD to make a precise determination of all the base pairs that make up the human DNA, with an attempt to decipher the blueprint of life. Although the basic research at molecular level has achieved good results, one of the most serious problems facing the medical profession is: a large number of basic research has not been timely translated into productive

forces to solve the problems encountered during clinical diagnosis and treatment, and many important diseases have not been effectively controlled or still lack effective prevention and control measures.

Therefore, the US National Institutes of Health (NIH) Clinical Center initiated the Bench-to-Bedside project in 1999. Bench and Bedside refer to the basic and clinical research, respectively. This project was designed to promote the translation from the findings of basic research to clinical interventions/treatments, which lead to the rise of translational medicine.

In January 2015, “precision medicine” was formally proposed in US President Obama’s State of the Union address. Since then, the term “precision medicine” quickly swept the world and opened a new horizon for medical science. In fact, early in 2011, the US National Research Council released a report titled *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease*, in which it declared that biology had become a data-intensive science and the traditional taxonomy could not reflect the advances in molecular biology; to better understand the relationship between disease genotype and disease phenotype, a new biomedical research knowledge network should be established based on multidisciplinary efforts and a new system to classify disease should be created. Then, what is precision medicine? Dr. Francis Collins, Director of the NIH, published an article in the *New England Journal of Medicine (NEJM)* in January 2015 and argued that precision medicine was “prevention and treatment strategies that take individual variability into account” (1). The essence of precision medicine is to analyze, identify, verify, and apply the biological markers in large populations and for specific diseases by using omics (e.g., genomics and proteomics) and other sophisticated techniques, so as to accurately find the disease causes and therapeutic targets and perform accurate sub-classification of the different status and processes of a specific disease; by doing so, the clinicians may ultimately achieve the individualized accurate treatment of a disease in a patient and thus improve disease diagnosis, treatment, and prevention. In June 2015, the *NEJM* again arranged a discussion on the issues and perspectives of precision medicine in the decision-making consulting channel and pointed out that the intrinsic goal of the precision medicine is to improve the tailored clinical prognosis and to reduce the unnecessary side effects in non-responsive patients (2). It can therefore be concluded that the precision medicine is a medical model that utilizes a variety of cutting-edge

technology and integrates multi-disciplinary knowledge to achieve the accurate classification of diseases and the individualized prevention and treatment of diseases, so as to ultimately improve the patients' prognosis and minimize the treatment-related adverse reactions.

Despite the constant innovation and evolution of medical concepts, any new medical concept is to augment or enrich the old ones, rather than completely replace them. In addition to precision medicine, many other new medical concepts including precise surgery, minimally invasive surgery, enhanced recovery after surgery, and multidisciplinary cooperative team have also been proposed. All these medical concepts are governed by a common rule: a good doctor should practice should not only practice according to the standardized guidelines but also carry out tailored treatment according to the specific conditions of individual patients.

### **Diagnostic and therapeutic strategies for gastric cancer in the era of precision medicine**

#### ***Disease classification, liquid biopsy, and outcome prediction***

Precision medicine helps us to re-classify the diseases, achieve real-time liquid biopsy, and predict disease outcomes. The US National Cancer Institute and the Human Genome Research Institute jointly launched the Cancer Genome Atlas (TCGA) in 2005, in which the researchers classified the genetic mutations in tumors by using high-throughput sequencing technology and biological information technology; the study was designed to determine the sequences of over 20 common tumors including lung adenocarcinoma, papillary kidney carcinoma, ductal carcinoma of the breast, colon cancer, pancreatic duct cancer, and liver cancer. As part of the research plan, gene sequencing of the gastric cancer had been completed, and the results were published in *Nature* in 2014 (3). Unlike the traditional classification of gastric cancer based on location, etiology, and/or histology, the article proposed a molecular classification dividing gastric cancer into four subtypes: tumours positive for Epstein-Barr virus, microsatellite unstable tumours, genomically stable tumours, and tumours with chromosomal instability. Disease typing at the molecular level may help us to develop drug treatment therapies and may even affect the surgical practices. A 5-cm resection margin is required in the surgery for gastric cancer to minimize the risk of microscopic positive margin (R1 resection) because R1

resection is associated with relapse and shorter survival (4). However, the relationship between R1 resection and recurrence/survival is stage-specific (5). According to the study of the U.S. Gastric Cancer Collaborative, in patients with stage I distal gastric adenocarcinoma, a 3-cm proximal margin (PM) was associated with the same improved OS as a 5.0-cm margin (6); for proximal gastric cancer, the length of PM was not associated with the local relapse and OS, and therefore a specific PM length was not required (7). Thus, for gastric cancer that is conventionally classified according to the locations, the surgical practices will be different. Since gastric cancer can be divided into four types according to molecular types, different types of molecules will certainly have different malignant biological behaviors; it is reasonable to speculate that different molecular types should also have different margin lengths to achieve precision.

Precision medicine has enriched our traditional diagnostic and therapeutic strategies for gastrointestinal tumors. For example, traditionally we rely on blood tumor markers for diagnosis of gastrointestinal tumors and on pathological biopsy of tumor tissues to detect the expression of a specific gene, so as to predict the prognosis and guide the treatment. Fortunately, now we have a new option, that is, liquid biopsy. Unlike tissue biopsy, liquid biopsy detects tumors by determining markers in body fluids. It is less invasive and allows multiple determinations and real-time monitoring. At present, the commonly used liquid biopsy markers include circulating tumor cells (CTC), circulating tumor DNA, and circulating non-coding RNAs.

Patients with advanced colorectal cancer have low 5-year survival rate, and the case-fatality rate can dramatically drop if early diagnosis and treatment can be achieved. According to a prospective multicenter study published in the *Journal of Clinical Oncology* in 2008, if the baseline number of CTCs was  $>3/7.5$  mL in colorectal cancer patients, the OS and PFS were relatively low, along with poor treatment effectiveness; however, if the CTC level dropped after treatment ( $<3/7.5$  mL), a better prognosis could be expected (8). Research has also demonstrated that CTC level is an independent prognostic factor for PFS and OS in patients with metastatic colorectal cancer and can provide more prognostic information before any imaging change occurs (8). As a result, the US FDA has approved the use of CTC as an auxiliary test in clinical laboratories.

Determining the DNA mutations in CTCs can also guide precision treatment. According to a research published in *Nature* in 2012, KRAS mutations could be detected in

the plasma samples of colorectal patients with secondary resistance to cetuximab before radiographic progression. Therefore, testing for ctDNA can help us to judge any drug resistance and guide the further treatment strategy (9).

The circulating non-coding RNAs in the blood can also assist the clinical diagnosis. We have explored the roles of circulating micro RNAs (miRNA) in the diagnosis of gastric cancer and found that miRNA-214 had relatively high diagnostic value (10). Recently, some Japanese authors have explored the diagnostic value of long non-coding RNA (LncRNA) and found that LncRNA H19 had significantly different expression profiles in gastric cancer patients and normal populations, and the area under ROC curve was 0.64 (11).

### *Precise surgery*

Sentinel lymph node navigation surgery offers the possibility of precise surgical treatment. The sentinel lymph node is the first node to receive drainage from the primary tumor and is therefore at the highest risk of tumor metastasis. As seen in literature, the lymph node metastasis rate was 2–18% for stage T<sub>1</sub> gastric cancer and 20% for stage T<sub>2</sub> gastric cancer; over 90% of patients with early gastric cancer survived more than 5 years, in whom the majority of the resected lymph nodes were negative (12,13). Theoretically, if there is no sentinel lymph node metastasis, there is no potential for lymph node metastasis; as a result, the treatment strategies will also be adjusted accordingly. During the sentinel lymph node navigation surgery for T<sub>1-2</sub> gastric cancer without lymph node metastasis and sized <4 cm, tracer is injected around the tumor, followed by lymph node biopsy to identify any metastasis. According to the results of sentinel lymph node biopsy, the corresponding treatment plan will be established to achieve the individualized precise surgical treatment (13).

### *Minimally invasive surgery*

In addition to precision, “minimally invasive” has also long been pursued by surgeons. The concept of minimally invasive surgery was initially proposed by the British surgeon John E. A. Wickham in 1980s, who also established the first minimally invasive surgery center in the United States (14). After nearly 30 years, minimally invasive surgery has been widely used in thoracic surgery, general surgery, urology, and other relevant fields.

For gastric cancer, minimally invasive surgery has two

forms: laparoscopic surgery and robotic surgery. According to the guidelines released by the Japanese Gastric Cancer Association in 2014, laparoscopic surgery for distal gastric cancer is indicated in stage I tumor only; for advanced gastric cancer, laparoscopic gastrectomy for distal gastric cancer and total gastrectomy can only be used for research purpose. As demonstrated in a retrospective study from the CLASS research group in China (published in 2014), laparoscopic-assisted surgery for advanced gastric cancer is safe and technically feasible, with acceptable short-term oncological outcomes: the OS and DFS were 85% and 77% in patients with stage II gastric cancer and 60.5% and 59.3% in those with stage III gastric cancer (15). According to a phase III trial in China that compared the application of laparoscopic and open surgeries in the treatment of advanced gastric cancer, the short-term outcomes showed that D2 radical operation could be safely performed by experienced surgeons (16).

The emergence of the robot has further enriched the connotation of minimally invasive surgery and brought many benefits to both patients and surgeons. Robotic surgery, as another main practice of minimally invasive surgery, has been further studied in the field of gastric cancer. As demonstrated in a multicenter prospective clinical study published in the *Annals of Surgery* in 2015, there was no statistical difference in terms of the postoperative complications and case-fatality rate between the robot-assisted surgery and laparoscopic-assisted surgery for gastric cancer; also, the intraoperative blood loss, rate of conversion to open surgery, and hospital stay were also comparable between these two groups (17). Our team had also retrospectively compared the short-term outcomes of the robotic and laparoscopic gastric cancer surgeries and found that the short-term outcomes were similar between these two techniques (18). In July 2015, a Korean team reported that robotic-assisted radical surgery for distal gastric cancer could dissect more lymph nodes in station 2, especially when dissecting lymph nodes in stations proximal to the splenic artery (19). Thus, the robotic surgery has comparable oncological outcomes with laparoscopic surgery, and meanwhile it also has many advantages such as accurate operation, clear 3D visual field, reduced effect of hand tremor, and feasibility of operation in a small space. Thus, we believe that robotic-assisted minimally invasive surgery will further reduce surgical stress and promote postoperative recovery. However, the majority of the currently available studies were retrospective studies with relatively small sample sizes; therefore, more well-

designed prospective trials are needed to further confirm the potential advantages of robotic surgery in such areas as lymph node dissection.

### *Enhanced recovery after surgery*

In clinical settings, the goal of “minimizing damage and speeding up recovery” also promotes the advances in surgery; as a result, the concept of “Enhanced Recovery After Surgery” (ERAS) occurred. In 2001, Kehlet proposed the concept of fast-track surgery; in 2010, an Enhanced Recovery After Surgery (ERAS) Society was founded in Sweden. Since then, the term ERAS has been widely used. ERAS not only requires optimal surgical approach, fine operation, and sophisticated surgical techniques but also requests optimal perioperative treatment, so as to accelerate postoperative recovery, reduce complications, and shorten the length of hospital stay. The connotation of surgical procedures should be a continuum that is based on the surgical operation but meanwhile also includes the meticulous perioperative management.

In the treatment of tumors, the ERAS Society has developed corresponding surgical procedures based on the different requirements of each surgery. For instance, guidelines for perioperative care in elective colonic surgery, in pancreaticoduodenectomy, and in elective rectal/pelvic surgery were established in 2012 (20–22). In 2014, the ERAS also released the consensus guidelines for enhanced recovery after gastrectomy (23), in which preoperative management of malnutrition, reducing medical procedures such as the placement of nasogastric tube and/or abdominal drainage tube, and early postoperative feeding/artificial nutrition were strongly recommended. It was also strongly recommended to carry out systematic review/evaluation to ensure the compliance of patients (23). Among the minimally invasive techniques used in surgery, laparoscopic surgery for early gastric cancer was also a strong recommendation due to its high evidence level; however, this technique was weakly recommended for advanced gastric cancer and total gastrectomy due to low evidence level (23).

In 2012, the Yamada *et al.* explored the usefulness of ERAS after surgery protocol as compared with conventional perioperative care in gastric surgery and found that the ERAS group had relatively short operative time. In terms of short-term outcomes, the first days of oral intake, oral intake recovery, flatus, and defecation were significantly earlier in the ERAS group than in the conventional care

group. Maximum pain evaluated on a visual analog scale and the number of additional analgesics on demand were also significantly less in the ERAS group. Finally, the postoperative body weight change was smaller in the ERAS group (24).

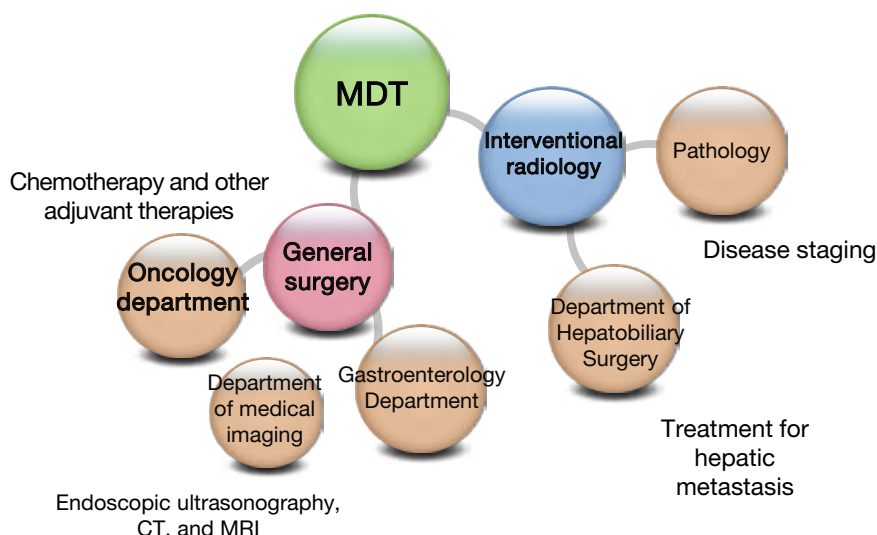
In June 2015, the ERAS group investigated the impact of different levels of compliance on postoperative complications and hospital stay after elective primary colorectal cancer resection and further explored the impact of each ERAS care measure on the short-term outcomes (25). A total of 2,352 patients from 13 centers in 6 countries were enrolled in this study. It was found that the minimally invasive technique (i.e., laparoscopic surgery) in ERAS shortened the hospital stay; increasing ERAS compliance was correlated with shorter hospital stay. Among factors that might affect the postoperative complications, the minimally invasive technique (i.e., laparoscopy) was also a protective factor (OR: 0.68; 95% CI: 0.62–0.74). Increasing ERAS compliance was also correlated with fewer postoperative complications. This analysis has demonstrated that increasing compliance with an ERAS program and the use of laparoscopic surgery is helpful to reduce postoperative complications, shorten hospital stay, and thus accelerate patient recovery (25).

### *Multidisciplinary collaboration team*

The treatment of cancer not only needs surgical operation but also requires the multidisciplinary collaboration among the departments of medical imaging, pathology, and oncology, so as to improve the quality of diagnosis and treatment and thus improve the prognosis (*Figure 2*).

In a multidisciplinary collaboration team, the oncologists shall establish reasonable preoperative and postoperative chemotherapy to improve the disease conditions. Chemotherapy is an important part of multidisciplinary treatment. However, partial resistance to chemotherapy has long been a major clinical problem. Therefore, if we were able to screen out drug-sensitive populations, as we decide the use of antibiotics based on the results of drug susceptibility testing, the treatment mode will undoubtedly meet the idea of precise medication. Patient-derived tumour xenografts may provide such a possibility. The patient-derived tumour xenografts were engrafted into nude mice, and the primary tumors grew in the nude mice were used for drug susceptibility testing. The results of drug susceptibility testing may guide the rational drug use (26). Chip analysis showed that the gene expressions





**Figure 2** Multidisciplinary treatment modalities.

of primary lesions in patients had good correlations with those in tumor xenografts in nude mice; thus, screening patient-sensitive drugs via xenograft tumors in nude mice is molecularly feasible (26).

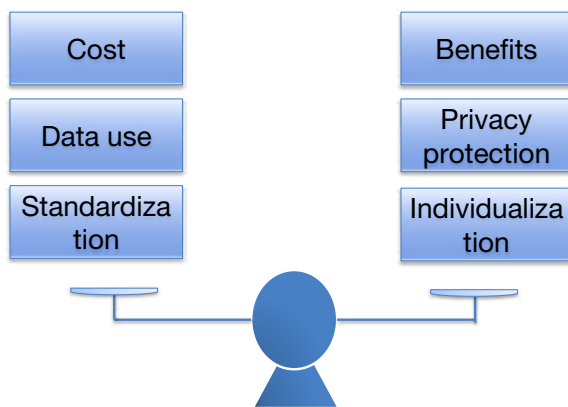
In addition, developing molecular-targeted therapy is another task of a multidisciplinary collaboration team and also a key component of precision medicine. Four key studies have been carried out on the molecular-targeted therapy of gastric cancer: ToGA study, targeting HER2 (27); AVAGAST study, targeting vascular endothelial growth factor (VEGF) (28); EXPAND study, targeting epidermal growth factor receptor (EGFR) (29); REGARD study, targeting vascular endothelial growth factor receptor 2 (VEGFR2) (30). Among these studies, ToGA was quite successful, whereas both EXPAND and AVAGAST failed somehow, which might be because the latter two studies did not include race, pathological type, molecular type, and targets in the study design. The future clinical studies should evaluate multiple molecular mutations based on histological findings and provide tailored treatment according to the results of gene typing. Meanwhile, molecular markers capable of predicting therapeutic efficacy should be screened out to identify drug-sensitive populations.

### Opportunities and challenges

After the US President Obama's Precision Medicine Initiative was unveiled in January 2015, government

authorities and research institutions in China made a quick response. At the end of March, 2015, the National Health and Family Planning Commission (NHFP) of China announced the list of first batch of pilot institutions that will apply the high-throughput gene sequencing technology in tumor diagnosis and treatment. The Ministry of Science and Technology also listed the precision medicine in the "13th Five-Year" national key R&D projects, and decided the funded projects in July 2016. Obviously, the Chinese government has paid special attention on precision medicine, and the corresponding supportive policies will certainly provide development opportunities for the implementation of precision medicine in China.

The era of precision medicine provides us with not only opportunities but also challenges. We need to balance the following three pairs of relationships (*Figure 3*): (A) costs and benefits. Practicing precision medicine will have high costs. For example, while CTC detection can assist diagnosis and prognosis, it is quite expensive. Also, the use of minimally invasive robot in ERAS is costly, not to mention the drugs used in the postoperative molecular targeted therapy. Thus, how to maximizing the benefit of the patients without increasing the economic burden of patients is one of the key issues to be addressed. (B) Data use and privacy protection: It is well known that the popularity of wearable devices provides the possibility to obtain the life parameters of patients in a real-time manner. For example, the information provided by a variety of sports bracelets and apple watches can facilitate decision-



**Figure 3** Three pairs of relationships need to be balanced in the era of precision medicine.

making on disease prevention and control and thus promote health. However, it is equally important to ensure that the patients' health information and privacy will be well protected during the use of these data. (C) Precision medicine undoubtedly enriches our diagnosis and treatment strategies and enables us to provide tailored approaches to the patients. For instance, as mentioned above, the ERAS guidelines on surgeries for gastric cancer, pancreatic cancer, and duodenal cancer had their specific contents. However, standardized diagnosis and treatment is still required when providing individualized precise treatment. Precision and standardization shall be two essential principles of precision medicine.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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# Immunotherapy for advanced gastric and esophageal cancer: preclinical rationale and ongoing clinical investigations

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**Abstract:** Gastric and esophageal cancers represent a major global cancer burden and novel approaches are needed. Despite recent improvements in outcomes with trastuzumab and ramucirumab the prognosis for advanced disease remains poor, with a median overall survival of 1 year. Comprehensive genomic characterization has defined molecular subgroups and potentially actionable genomic alterations, but the majority of patients do not yet benefit from molecularly directed therapies. Breakthroughs in immune checkpoint blockade have provided new therapeutic avenues in melanoma, and continue to expand into other tumor types, with ongoing investigations in gastrointestinal (GI) malignancies. The frequency of programmed death ligand 1 (PD-L1) overexpression, a putative response biomarker, approaches forty percent in gastric cancers. Translational studies and molecular classification suggest gastric and esophageal cancers are candidate malignancies for immune checkpoint inhibition trials and early clinical data is promising. Here we review the mechanisms, preclinical, and early clinical data supporting the role for immune checkpoint blockade in gastric and esophageal cancer.

**Keywords:** Immunotherapy; gastric; esophageal; cancer; programmed death ligand 1 (PD-L1); checkpoint; programmed cell death protein 1 (PD-1)

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## Introduction

Despite therapeutic advances in oncology, the prognosis of late stage gastric and esophageal carcinoma remains exceedingly poor. Gastric cancer is the second leading cause of global cancer-related death, with an estimated 723,000 deaths in 2012 (1). Nearly 1 million new gastric cancers are diagnosed annually making this the fifth most common malignancy overall (1). Esophageal cancer affected an additional 456,000 people in 2012 and caused approximately 400,000 deaths, making it the sixth most common cause of cancer-related death and eighth most common cancer globally (1). While the overall incidence gastric cancer is on the decline, the prevalence of esophageal cancer is rising (2-4).

The majority of gastric and esophageal cancer patients present with advanced disease and evidence-based therapeutic options are limited. First line systemic therapy

for metastatic disease is largely based on a platinum/5-fluoropyrimidine backbone, which produces moderate survival benefits in patients with good performance status (5). The addition of an anthracycline or taxane to platinum/5-fluoropyrimidine regimens may provide additional survival benefit in select patients (5-7). In Her2 amplified adenocarcinoma incorporation of the anti-Her2 monoclonal antibody, trastuzumab, significantly improves survival, and is the first molecularly targeted agent to improve outcomes in advanced gastric and esophageal cancers (8). The recently approved vascular endothelial growth factor receptor 2 (VEGFR-2) antibody ramucirumab has also been shown to improve survival in patients with gastric and gastroesophageal junction (GEJ) adenocarcinoma who progressed on first line therapy (9). While ramucirumab and trastuzumab are meaningful additions to the gastroesophageal armamentarium, overall

survival outcomes remain poor and novel approaches are needed.

Immunotherapy has caused a paradigm shift in the treatment of melanoma and its use continues to expand to include other tumor types (10-12). With increasing clinical experience, biomarker analyses, and improvements in preclinical models, the potential role for immunotherapy in gastric and esophageal cancers is emerging. The major approaches to harnessing immunotherapeutic anticancer effects have come from the development of inhibitory antibodies which modulate immune check points, such as cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed death ligand 1 (PD-L1). Here we review the basic immunotherapeutic mechanisms of CTLA-4 and PD-L1, existing preclinical data, and available clinical results incorporating immunotherapy into the treatment of advanced gastric and esophageal cancers.

### Immunotherapeutic mechanisms

Numerous co-stimulatory and inhibitory molecules interact to form a network of activating and inhibitory pathway “checkpoints” which serve to regulate the human immune system. This molecular interplay allows for uninterrupted pathogen-fighting capabilities while simultaneously preventing autoimmunity and persistent immune response (13). Many of these pathways converge on T lymphocytes, which play a central role in triggering adaptive immune responses to both foreign pathogens as well as neoplastic cells. However, in cases of malignancy, tumor cells frequently escape immune detection by hijacking elements of these checkpoint pathways thereby inhibiting T cell effector function. Ultimately this results in reduced tumor surveillance and tumor recognition (14). The development of antibodies to immune checkpoints, known collectively as immune checkpoint inhibitors, has now translated to improved patient outcomes in several malignancies (11,15).

CTLA-4 is a ubiquitous T-cell receptor belonging to the immunoglobulin superfamily. CTLA-4 shares many similarities with the T-cell co-stimulatory protein CD28, and like CD28, is activated upon binding with CD80 (B7-1) or CD86 (B7-2) (16). In fact, CTLA-4 has been shown to compete with CD28 for CD80 and CD86 binding (17). However, unlike CD28, which stimulates T cells, the effects of CTLA-4 activation differ between T-cell subsets. In CD4<sup>+</sup> helper T cells activated CTLA-4 down modulates activity, whereas in CD4<sup>+</sup>T regulatory cells (T<sub>Reg</sub>) CTLA-4

up-regulates function (18). The net effect of endogenous CTLA4 activation is immune tolerance (19) (*Figure 1*).

Similarly, the T-cell surface receptor PD-1, also a member of the immunoglobulin superfamily, inhibits T cell function upon binding to its ligands PD-L1 (B7-H1) and PD-L2 (B7-DC) (20) (*Figure 1*). The PD-1 ligands are also members of the B7 family, although the inhibitory pathway that PD-1 participates in is thought to be mutually exclusive to that of CTLA-4 (21). PD-L1 is expressed on T cells, B cells, NK cells, dendritic cells, monocytes/macrophages, mast cells, and various tumor types where it is thought to play a role in tumor immune escape (22) (*Figure 1*). It has been suggested that while CTLA-4 may play a significant role in early immune response, primarily occurring in lymphoid tissues, PD-1 whose expression is up regulated after T cell activation in peripheral tissues may be more involved in late immune response (23). Although CTLA-4 inhibition highlighted the power of immune checkpoint modulation, therapeutic focus is shifting towards the use of PD-1 and PD-L1 blockade, which offer benefits of potentially fewer side effects and perhaps improved outcome data.

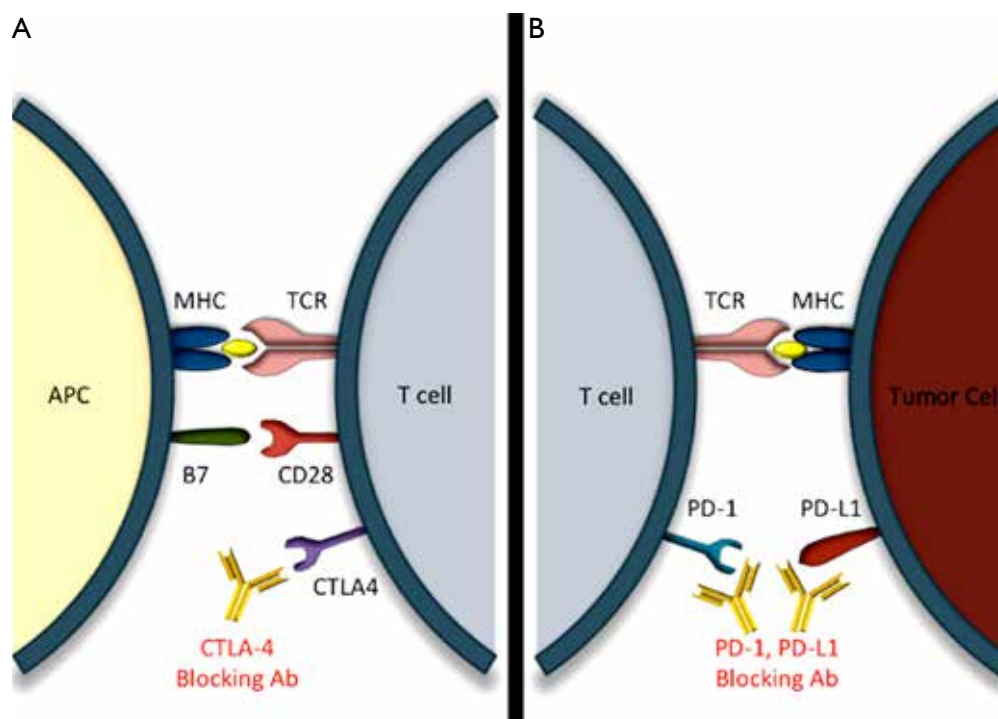
### Preclinical observations in gastric and esophageal cancers

#### *Distribution of PD-L1/PD-L2*

PD-L1 is broadly expressed in many human tissues and organs. In addition to immune cells PD-L1 has been identified on endothelial cells, mesenchymal stem cells, cells of the eye and placenta (22). In contrast, PD-L2 expression is restricted to lymphoid tissues and has only been observed on macrophages and dendritic cells, suggesting non-redundant roles for these two ligands (24). Varying levels of PD-L1 and PD-L2 are expressed on a majority of human cancer cells including: melanoma, renal cell carcinoma (RCC), multiple myeloma, breast, bladder, colon, and lung cancer (22,25,26). Melanoma, RCC, and non-small cell lung cancer (NSCLC) tumor series have shown high levels of PD-L1 expression by both immunohistochemical and RNA analysis, ranging from 66-100% (27-29).

Until recently, few studies had attempted to quantify PD-L1 and PD-L2 expression in gastric and esophageal cancers. Work by Ohigashi *et al.* using immunohistochemical and RT-PCR approaches to examine expression from 41 esophageal squamous cell cancer (ESCC) patients found that 43.9% of samples had either PD-L1 or PD-L2





**Figure 1** Immune checkpoint blockade in central and peripheral immune compartments. (A) Expression of CTLA-4 is up regulated on T cells in lymphoid tissues following activation via MHC/TCR and M7/CD28 mediated signaling. Once activated, CTLA-4 inhibits T cell function leading to immune tolerance. In the presence of blocking antibodies this tolerance can be broken, allowing for enhanced antitumor response; (B) PD-1, also expressed on T lymphocytes, inhibits the action of T lymphocytes upon binding to its ligands PD-L1/2; this process likely occurs in the tumor microenvironment, between PD-L1/2 expressing tumor cells and PD-1 expressing T lymphocytes; (A,B) blocking antibodies to either PD-1 or its ligands allows for T cell activation, enhancing anti-tumor effects peripherally. CTLA-4, cytotoxic T-lymphocyte antigen 4; PD-1, programmed death 1; PD-L1, programmed death ligand 1; APC, antigen presenting cell; MHC, major histocompatibility complex; TCR, T cell receptor.

overexpressing tumor cells (30) (*Table 1*). Similarly, PD-L1 expression was detected in 42.2% of gastric adenocarcinoma samples (n=102) and was undetectable in normal gastric tissue controls and only weakly detectable in gastric adenomas using an IHC approach (31). A recent Chinese series (n=111) suggested PD-L1 positivity in 63% (70/111) of gastric adenocarcinoma resection specimens (32) (*Table 1*). Data from the phase Ib KEYNOTE-012 trial corroborated the above results and found a 40% rate of PD-L1 overexpression in advanced gastric adenocarcinomas (33). Few studies have yet to specifically address rates of PD-1 and PD-L1 positivity in GEJ adenocarcinomas, the predominant location and histology in US patients. Although more studies will be necessary to substantiate these findings in gastric and esophageal cancers, PD-L1 expression levels are comparable to cancers in which anti-PD-L1 directed therapies have demonstrated early success.

#### ***PD-1 expression and tumor infiltrating lymphocytes (TILs)***

The presence of lymphocytes in close tumor proximity has been used as a crude surrogate for immune responsiveness to tumor presence. Multiple large studies in melanoma, colorectal, ovarian, and breast have shown a correlation between increased immune infiltrates and favorable outcomes (34-37). Previous work has also correlated a higher density of TILs with improved outcomes in GI malignancies (38). Recently, work by Turcotte *et al.* defined the presence of endogenous CD8<sup>+</sup> tumor infiltrating T-cells in a small series of patients with advanced gastrointestinal (GI) malignancies, including gastric cancer. They were able to demonstrate that naturally occurring CD8<sup>+</sup> TILs can recognize specific autologous tumor-derived cell lines (39). However, despite the presence of TILs in the tumor microenvironment, tumor regression of late stage gastric



**Table 1** Frequency of PD-L1 expression and correlation with clinical outcomes in gastric and esophageal cancer

Investigational compound	Target	Phase	ClinTrials identifier	Primary endpoint	Secondary endpoints
Ipilimumab	CTLA-4	II	NCT01585987	irPFS	PFS, OS, irBORR
Nivolumab	PD-1	I-II	NCT01928394	ORR	AE
	PD-1	I	NCT00836888	Safety, PK	PD, RR
Lirilumab + nivolumab	KIR, PD-L1	I	NCT01714739	Safety	BOR, irRECIST, PK, PD
MSB0010718C	PD-L1	I	NCT01943461	DLT	irBORR, PD-L1 expression, irPFS, OS
	PD-L1	I	NCT01772004	DLT	irBORR, PD-L1 expression, irPFS, OS
MPDL3280A	PD-L1	I	NCT01375842	DLT	AE
Pembrolizumab	PD-L1	I (KEYNOTE-012)	NCT01848834	ORR, AE	Cohort RR
	PD-L1	II (KEYNOTE-059)	NCT02335411	ORR, AE	PFS, discontinuation
MEDI4736	PD-L1	I-II	NCT01693562	ORR, AE	OS, PFS, DCR, PK

PD-L1, programmed death ligand 1; irPFS, immune related progression free survival; PFS, progression free survival; OS, overall survival; irBORR, immune related best overall response rate; PD-1, programmed cell death protein 1; ORR, overall response rate; AE, adverse events; PK, pharmacokinetics; PD, pharmacodynamics; RR, response rate; irRECIST, immune related response evaluation criteria in solid tumors; DCR, disease control rate.

and esophageal cancers is rarely seen suggesting endogenous mechanisms are likely inadequate. Preclinical models have suggested that there are greater TIL numbers in earlier stage disease, and that advanced GI malignancies are less immunogenic due to selection of the least immunogenic cancer cell clones during disease progression (40,41). Several studies have identified up regulation of PD-1 on TILs in both RCC and hepatocellular carcinoma and correlated increased PD-1 expression with worse prognosis (42,43). In gastric cancer, PD-1 expression on CD8<sup>+</sup> lymphocytes is significantly higher than that of normal gastric mucosa and peripheral blood (44). Further studying the relationship of TIL density to stage and immunotherapy response may help refine the optimal disease setting in which to pursue immune checkpoint inhibition in gastric and esophageal cancer.

#### ***PD-L1/PD-L2 expression and patient outcomes***

In many cancers increased PD-L1 and PD-L2 expression correlate with worse prognosis, and ongoing investigation is needed to determine the prognostic power of PD-L1 expression in gastric and esophageal cancers (45-50). Increased PD-L1 expression in both gastric and esophageal cancer is associated with nodal metastases, advanced stage, and worse outcomes (31,32). Jiang *et al.* demonstrated a positive correlation between expression of B7-H4, another B7

family member, and gastric cancer invasiveness and metastasis. The median overall survival is significantly reduced in gastric cancer patients with higher B7-H4 expression (51). Similarly, higher levels of PD-L1 and PD-L2 expression have been shown to be negative prognostic markers in esophageal cancer, especially in cases in which both ligands are expressed (30). Higher tumor B7-H4 levels, detected by IHC, were associated with worse prognosis and inversely correlated with CD3<sup>+</sup> and CD8<sup>+</sup> T-cells in 112 ESCC samples (52). PD-L1 overexpression, particularly at higher levels, may also serve as a predictive response biomarker in gastric cancer. Updated analysis from the KEYNOTE-012 phase I study suggests a trend toward improved overall response rate (ORR), progression free survival (PFS) with higher levels of PD-L1 overexpression (33). Further support for the predictive power has come from pembrolizumab melanoma and NSCLC cohorts suggesting increased tumor PD-L1 expression correlates with response rate (53,54).

#### **Previous gastroesophageal immunotherapies**

The role for immune modulating therapies in gastric cancer has been a subject of multiple prior investigations, largely in Asian patients. Non-specific immune potentiators such as polysaccharide-K, OK-432, and BCG have been previously investigated dating back to 1975 (55-60). The pleiotropic

immune modulator protein-bound polysaccharide (PSK), derived from the CM-101 strain of the fungus *Coriolus versicolor*, has been shown to increase leukocyte activation, shift the Th1:Th2 balance and inhibit tumor growth in several cancer models (61-63). In Japanese gastric cancer patients undergoing gastrectomy the addition of PSK to mitomycin/5-FU adjuvant therapy improved the five year disease free survival (DFS) (70.7% vs. 59.4%) and 5-year OS (73% vs. 60%) (57). The sclerosant OK-432 (penicillin-killed lyophilized *Streptococcus pyogenes*) induces IL-12, stimulates NK and T-cells favoring a Th1 response, and may improve the function of antigen presenting dendritic cells (64-68). In a small Japanese trial the combination of OK-432 with 5-FU/leucovorin and cisplatin was safe and produced a response rate of 40%, however, a larger adjuvant trial comparing S-1 vs. S-1 and OK-432 failed to demonstrate a survival difference (58,69). Similarly, the non-specific immune upregulation following BCG has translated to some anti-tumor responses without a reliable improvement in overall survival in combination studies (55,70). More recently, a small Chinese trial investigating cytokine-induced natural killer cells given after adjuvant 5-FU based chemotherapy for resected gastric cancer demonstrated a trend toward improved OS and a 6-month improvement in median DFS (34.1 vs. 40.4 months) (71). Retrospective analysis of this data suggested that benefits might be restricted to intestinal type histology (71). The combination of cytotoxic chemotherapy with non-specific immune modulators (chemoimmunotherapy) has largely been restricted to Asian patients and the lack of reproducible survival improvements has limited clinical adoption.

### Early checkpoint inhibitor clinical experience

The first clinical success with immune checkpoint blockade was observed in patients with metastatic melanoma treated with the anti-CTLA-4 monoclonal antibody (mAb) ipilimumab (15). Subsequently, ipilimumab, and another anti-CTLA-4 mAb, tremelimumab, have shown promising results in phase I-III clinical trials in several cancer types including, gastric/GEJ carcinomas (72). Several anti-PD-1 mAbs including nivolumab, pembrolizumab (MK-3475), and pidilizumab have been developed and early data with these agents has shown significant response rates in melanoma, NSCLC, RCC, and diffuse large B-cell lymphoma (73-75). PD-L1 blocking antibodies have also demonstrated favorable outcomes in early trials (12).

Gastric and esophageal cancers have represented a small

minority of patients in early phase immune checkpoint inhibitor trials. In the multicenter phase I trial of the anti-PD-L1 mAb BMS-936559 only 7 of 207 enrolled patients had gastric cancer. The gastric cancer cohort were assigned to the safety arm as opposed to the efficacy arm, and limited efficacy data in gastric cancer is available (12). In a second line gastroesophageal-specific phase II trial (n=18) with tremelimumab (anti-CTLA4 mAb) the observed response rate (RR) was 5%, below the observed response rate to second-line cytotoxic chemotherapy (76). Although this trial failed to meet its pre-specified RR endpoint several patients achieved stable disease (SD) and one patient achieved a partial response (PR), which is quite impressive given the aggressive natural history of advanced gastric and esophageal cancer. Further support comes from the interim analysis of the anti-PD-L1 mAbs MPDL3280A and MEDI4736 (77,78). In the MEDI4736 gastroesophageal cohort (n=16) two heavily pretreated patients remained on study over 24 weeks in the early reporting, beyond the median PFS for second line gastric and esophageal cancer therapies (78). In the most recent ESMO conference preliminary data from the phase IB anti-PD-1 antibody pembrolizumab trial (KEYNOTE-012) in advanced gastric cancer was presented. Patients with PD-L1 positive advanced gastric adenocarcinoma (IHC positive in >1% cells) received pembrolizumab 10 mg/kg every 2 weeks until progression or toxicity. A total of 39 patients were enrolled after screening 162 samples for PD-L1 (65 positive samples, 40% IHC+) (33). An updated analysis of this trial has suggested an ORR of 22% and a median response duration of 24 weeks in this heavily pre-treated population (33). There was a positive correlation with PD-L1 positivity and PFS (P=0.032). Results of this trial have prompted the planned KEYNOTE-059 phase II trial of cisplatin/5-FU in combination with pembrolizumab (33). The toxicity profile and early efficacy signals have prompted expansion of immune checkpoint inhibitors in advanced gastric and esophageal cancers (Table 2).

### Conclusions and future directions

Advanced gastric and esophageal cancers carry a poor prognosis with limited therapeutic options, and few major therapeutic advances. While improving molecular characterization will continue to identify subsets of patients who may benefit from genotype-directed targeted therapies, a majority of patients do not yet benefit and therefore further therapies are needed.

**Table 2** Ongoing clinical investigations targeting immune checkpoint blockade in gastric and esophageal cancer

Study population	Histology	Number of samples	PD-L1 positive (%)	Outcome	Reference
Esophageal	Squamous	41	44.0	Worse outcomes	(30)
Gastric	Adenocarcinoma	102	42.2	Nodal mets, advanced stage	(31)
	Adenocarcinoma	111	63.0	Advanced stage, worse outcome	(32)
	Adenocarcinoma	243	43.6	Improved DFS, lower stage	(49)

PD-L1, programmed death ligand 1; DFS, disease free survival.

The recently published Cancer Genome Atlas (TCGA) gastric cancer analysis has provided molecular rationale for division of gastric adenocarcinoma into four distinct molecular subtypes (79). Interestingly, the EBV-positive gastric cancer subgroup demonstrated high levels of PD-L1/L2 overexpression highlighting a molecularly defined patient population possibly most likely to derive benefit from immune checkpoint blockade (79). Early translational efforts have suggested comparable rates of PD-1 and PD-L1 expression in gastric and esophageal cancers, strengthening the argument that immune checkpoint inhibitors warrant further clinical investigation. Development and validation of predictive biomarkers for response to immune checkpoint blockade will help to refine the optimal location for immunotherapy in gastric and esophageal cancers. Some recent biomarker analyses suggest that PD-L1 directed therapy is most effective in patients with higher pre-treatment CTLA4 expression, absence of fractalkine (CX3CL1) in pre-treatment biopsies, and T-helper type 1 gene expression patterns (80). Interesting preclinical work continues to expand immunotherapy combination approaches including low dose chemosensitization with alkylating agents (81). Irradiation is known to induce antigen presentation and upregulate PD-L1 expression (82-84). The frequent use of adjuvant chemoradiation and high recurrence rates despite adjuvant therapy may make the use of anti-PD-L1 therapies an interesting adjunct to adjuvant therapy, a concept currently under investigation in NSCLC. Here we have presented a review of the current landscape of immunotherapy in gastric and esophageal cancer with attention to translational studies and early clinical investigations.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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# Long-term recurrence-free survival after hepatic resection for metachronous gastric cancer liver metastases

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**Abstract:** We present the case of a man who underwent total gastrectomy and splenectomy at the age of 60 for stage IIIa adenocarcinoma of the stomach. Twenty-two months after surgery abdominal CT scan showed two hepatic metastases in segments V and VI. Because of further progression under palliative chemotherapy and reduced tolerance for this treatment, partial hepatectomy of segments V-VI was performed. Currently 72 years old, he is completely symptom-free without evidence for tumor recurrence. This report shows that long-term recurrence-free survival after hepatic resection for gastric cancer liver metastases (GCLM) is possible even in the presence of several unfavorable prognostic factors.

**Keywords:** Gastric cancer; liver metastasis; hepatectomy

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## Introduction

Gastric cancer is the fifth most common malignancy and the third leading cause of cancer death in both sexes worldwide, with 952,000 new cases (6.8% of the total) and 723,000 deaths (8.8% of the total) in 2012 (1). The liver is one of the most common sites of metastatic spread from malignancies of the stomach, with hepatic metastases [gastric cancer liver metastases (GCLM)] occurring in up to 50% of the patients (2). Three histological subtypes of gastric cancer are likely to give rise to GCLM: differentiated adenocarcinoma, poorly differentiated adenocarcinoma, and the rarer hepatoid carcinoma (2). Metastatic gastric cancer has a dismal prognosis with a median survival of 6 months if untreated and 7–15 months with palliative chemotherapy (3). Survival data for patients with GCLM without further extrahepatic metastases are scarce, with one study reporting 5-year survival of 1.7% for patients with GCLM alone that were treated with systemic therapy (4). In this report we present a rare case of long-term recurrence-free survival of a patient with differentiated adenocarcinoma of the stomach who received curative

surgery with resection of two metachronous GCLM.

## Case presentation

In December 2003, a 60-year-old Caucasian man underwent total gastrectomy and splenectomy for a moderately differentiated intestinal-type pT3N1M0 (stage IIIa) adenocarcinoma of the gastric cardia. In October 2005, twenty-two months after surgery, an abdominal CT scan was performed after routine blood tests had shown chronically elevated alkaline phosphatase (126–137 U/L; normal range, 36–95 U/L) with progressively rising tumor marker carcinoembryonic antigen (CEA) (from 36 to 195 ng/mL; normal range, <3.4 ng/mL for non-smokers) over the last eight months. This investigation revealed two hepatic metastases in segments V and VI (largest lesion: 3.2×2.5 cm<sup>2</sup>) along with multiple hepatic biliary cysts. As the patient was completely symptom-free at this moment, we initially opted for a strategy of watchful waiting, but at re-evaluation three months later there was evidence of progression with confluence of the hepatic metastases on CT scan and

further elevation of CEA (274 ng/mL).

In March 2006, we started palliative chemotherapy with 5-fluorouracil (5-FU) 1,000 mg/m<sup>2</sup>/day for 5 days and cisplatin 100 mg/m<sup>2</sup> on day 1, every 3 weeks. Cisplatin was substituted by carboplatin after one cycle because of mild high-frequency hearing loss. Re-evaluations after two and four cycles respectively showed a partial response accompanied by a decrease in CEA. However, after six cycles of chemotherapy, progression of the hepatic metastases was observed on CT scan and CEA started to increase again. PET scan in July 2006 showed increased FDG uptake in segment V-VI of the liver but no other hepatic metastases. Because of reduced tolerance for the chemotherapy treatment the patient was offered surgical resection of the metastases. Additional preoperative imaging with MRI of the liver confirmed the presence of a voluminous hepatic metastasis in segment VI (9×5.8 cm<sup>2</sup>) and a smaller satellite metastasis located caudally in segment V, but revealed no further active metastatic processes in the other segments. The patient underwent partial hepatectomy of segments V–VI and removal of two lymph nodes, with anatomopathological examination confirming R0 resection. He quickly and fully recovered with complete normalization of CEA and remained in follow-up at our department with clinical examination, routine blood tests and control of CEA every three months and abdominal CT scan every year. Currently 72 years old, he is completely symptom-free without clinical, biochemical or radiological evidence for tumor recurrence or metastases nine years after partial hepatectomy and almost twelve years after resection of the gastric primary.

## Discussion

The position of hepatic resection in the context of GCLM remains controversial and is at present by no means standard of care. This is in part due to the fact that very few patients with GCLM are eligible for curative surgery because of the presence of multiple, scattered, bilobar liver lesions or incurable simultaneous factors such as peritoneal dissemination, widespread lymph nodal metastases, or direct invasion to adjacent structures (3). However, when dealing with liver-confined metastatic gastric cancer, R0 resection of GCLM is the only therapeutic option that can be undertaken with a curative intent. Over the last decade, several retrospective cohort studies have looked at survival after hepatic resection for GCLM compared to other treatment options and have tried to identify favourable

prognostic factors that may permit selection of good candidates for this procedure.

A first systematic review of 19 studies with a total of 436 patients reported median and 5-year overall survival after surgery for GCLM ranging from 9 to 34 months (median: 17 months) and 0–60% (median: 26.5%), respectively (5). A second, more recent systematic review and meta-analysis of 23 studies comprising 870 patients found that median and 5-year overall survival ranged from 8.8 to 48 months and 0–60%, respectively, with a pooled value of 22 months and 24% (30% for metachronous lesions) (6).

As for prognostic factors, synchronous presentation of GCLM, short recurrence-free interval from primary resection (<1 year), the presence of multiple or larger GCLM, bilobar disease, and primary tumor factors such as increased depth of invasion (T-stage), higher degree of lymphatic and venous invasion and moderate or poorly differentiated histological grade were all found to be associated with worse prognosis by some of the studies reviewed by Kerkar *et al.* (5). However, the authors note that based on their analysis, no definitive conclusions can be made regarding negative prognostic factors because no factor was found to be consistently statistically significant across studies (5). The second systematic review by Petrelli *et al.* found that only patients with larger size and number of GCLM were found in at least three studies to carry a worse prognosis (6).

Recently, a working group installed by the guidelines committee of the Japan Gastric Cancer Association reviewed the literature to revisit the treatment of potentially resectable GCLM and listed smaller size (diameter <4–6 cm) and number of GCLM, unilobular distribution, capsular formation, and status of the gastric primary (absence of serosal or lymphatic invasion, lower clinical stage) as potentially relevant favourable prognostic factors (7).

Long-term survivors in a disease as aggressive as metastatic gastric cancer are rare. Our case is even more remarkable because our patient managed to survive for almost twelve years now despite several factors that are reported to possibly adversely affecting prognosis: the presence of more than one hepatic lesion, the large size of one of the lesions (9×5.8 cm<sup>2</sup>) and the high clinical stage and moderate differentiation of the gastric primary (pT3N1M0: stage IIIa). In the systematic review by Kerkar *et al.*, detailed analyses of data for a total of seven patients who survived for ≥10 years showed that all of them had only a single lesion resected, four of six presented with a well-differentiated histological grade and four of five patients had

a T1–T2 primary lesion (5). Furthermore, the progression of the metastases under systemic chemotherapy can also be considered as a sign of the aggressive nature of the tumor (7). On the other hand, factors contributing to the successful outcome in this case presumably are the relatively long recurrence-free interval after gastrectomy (22 months), the absence of extrahepatic disease and the good overall clinical condition of the patient.

### Conclusions

In conclusion, hepatic resection for GCLM seems to be associated with an acceptable 5-year survival in selected patients, while the precise factors on which to base this selection are still under debate. Most literature seems to indicate that patients with a small number of GCLM and without extrahepatic disease, could be offered hepatic resection if this is technically feasible and safe (6). Although guidance in this field should come from properly designed randomized controlled trials, our case report expands the literature on the subject and shows that surgery with curative intent can successfully extend survival even in patients with multiple lesions, lesions with a diameter >5 cm and a high-stage primary tumor.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest

to declare.

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# Quality of life versus survival benefits in patients with HER-2 negative metastatic gastric cancer: exploration of the randomized trials from the patient's perspective

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Despite the significant advances in diagnosis and therapy of gastric cancer (GC), and well developed screening programmes in countries such as Japan and South Korea, this tumor remains the fifth most common malignancy and the third leading cause of cancer mortality worldwide (1,2). Most of the cases are diagnosed in advanced stages with a 5-year survival rate ranging from 20% to 27% (2,3) and median survival of 6–15 months in metastatic cases (4). Moreover, even in patients with early gastric cancer (EGC), aberrant metastatic behaviour and occurrence of skip metastasis are reported (5-7). Other changes related on the GC are the following: increase proportion of cases located in the upper third of the stomach, especially for young patients (1,5), changing spectrum of the histogenetic pathways (8), and progressive augmentation of the poorly-cohesive/diffuse type carcinomas and neuroendocrine variants (1,3,7-10). All of these characteristics and resistance of GC cells upon most of the target chemotherapeutic agents increase the therapeutically difficulty.

In the last years, few clinical trials were performed to identify the best therapeutically approach of patients with HER-2 negative advanced GC with distant metastases. The first randomised controlled trial that examined the survival benefit of additional gastrectomy over chemotherapy alone in incurable GC was published in *Lancet Oncology* in January 2016 (11). Fujitani *et al.* (11) performed an open-label, randomised, multicentric phase 3 trial (REGATTA) that

taken into account patients from 44 centres or hospitals in Japan, South-Korea, and Singapore, diagnosed with HER-2 negative advanced GC with a single non-curable factor. Patients aged 20–75 years with hepatic, peritoneal, or distant lymph node metastases were randomly assigned to chemotherapy alone (oral S-1 and cisplatin) or gastrectomy followed by chemotherapy. No survival benefits were observed between the two groups, the authors concluding that gastrectomy is not justified for these patients, except cases with life-threatening complications such as bleeding, obstruction, etc. (11).

Other ongoing trial is the GYMSSA trial that, based on the studies showing that complete removal of both the gastric primary and peritoneal metastases combined with intraperitoneal chemotherapy associates improved survival, included patients assigned to gastrectomy with metastasectomy plus systemic chemotherapy *vs.* systemic chemotherapy alone with the FOLFOXIRI regimen (4).

The main weak point of the recently trials is the quality of life of the patients that is not usually taken into account to evaluate the success or failure of a certain intervention, as the main point of result. The trials are mostly concentrated upon the overall survival and progression-free survival (4,10), although some of them include patients with short survival rate. In the REGATTA trial the median overall survival was 16.6 for patients assigned to chemotherapy alone and 14.5 months for those that underwent

gastrectomy followed by chemotherapy (11). In the GYMSSA trial the included patients was supposed to have a median survival of 6–11 months (4).

In the REGATTA trial which results have been published in 2016 (11), we performed a statistical analysis of Table 3 and observed that the following chemotherapy induced adverse effects were more frequent in patients assigned to gastrectomy followed by chemotherapy compared with those receiving chemotherapy alone: grade 3–4 leucopenia (29% vs. 12%,  $P=0.0007$ ), grade 3 anorexia (19% vs. 2%,  $P=0.01$ ), grade 3 nausea (15% vs. 5%,  $P=0.02$ ), grade 1–2 diarrhea (45% vs. 22%,  $P=0.03$ ). On the other hand, grade 1–3 sensory neuropathy was slightly more frequent in the patients receiving chemotherapy alone (26% vs. 8%,  $P=0.05$ ). Based on the fact that anorexia, diarrhea, risk for infections, and the perioperative status significantly affect the quality of life (especially for those with upper-third tumors), and also on the previously reported decreased physical function and increased fatigue and poor body image post-gastrectomy (2), the idea of no performing gastrectomy in these patients can be accepted. However, the patient should choose the best therapeutically approach based on its desire (longer life vs. qualitative life). In the REGATTA trial, 41% of the patients refused enrolment and 25% did not receive any explanation of the study (11).

Assessment of the quality of life can be done, in patients with GC, based on the international-validated questionnaires such as the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Stomach (EORTC QLQ-STO22), mostly used in Europe, the Functional Assessment of Cancer therapy-Gastric (FACT-Ga) that is more disposed in Asia and North America, and the Postgastrectomy Syndrome Assessment Scale-45 (PGSAS-45) recently created by the Japanese researchers (2,12). They include evaluation of physical, psychological, and social aspects but few than 20 representative studies were published till January 2016 (2), based on the use of these questionnaires in the clinical trials that included patients with GC. The main evaluated criteria were diarrhea/constipation, dysphagia, dietary restriction, dumping, indigestion, body weight loss, pain, reflux, anxiety, fatigue, iatrogenic-induced effects, and emotional status (dry mouth, body image, taste problems) (2,12).

In summary, in patients with advanced GC and distant metastases the best therapeutically approach should be established based on a specific questionnaire which results should be evaluated after a detailed discussion with the patient. In metastatic cases with a predicted short overall

survival the therapy should be mainly based on the quality of life, not only on the overall survival and progression-free survival. The decision should be based on the Hippocratic Oath principles which paraphrasing can be adapted in the following conclusion: “*Do not harm, do not overtreat, look at the patient in a sympathetic but scientific way, do not play at God, and plan the beginning of a trial conceiving that you can one day be included in your trial*”.

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# Variations in outcome for advanced gastric cancer between Japanese and Western patients: a subgroup analysis of the RAINBOW trial

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Two large, global phase 3 trials have confirmed the efficacy of the vascular endothelial growth factor receptor 2 monoclonal antibody ramucirumab in the second-line treatment of advanced gastric cancer (GC) and gastro-oesophageal junction cancer (GOJ) (1,2). The RAINBOW trial evaluated its use in conjunction with paclitaxel chemotherapy and reported significant improvements in overall survival (OS), progression free survival (PFS) and response rates (RR); however differentials in outcome based on geographical area were noted. For patients from the Asia geographical area (consisting of Japan, South Korea, Hong Kong, Singapore and Taiwan) addition of ramucirumab resulted in improvements in PFS and RR, but no significant improvement in OS (2). The majority of patients from the Asian geographical group were recruited from Japan (140 out of 223). This additional subgroup analysis gives further information about geographical differences in outcome between Japanese patients in comparison to ‘Western’ patients from Australia, Europe, Israel and the USA (3).

Considering the baseline characteristics of the Japanese (n=140) and Western (n=398) patient groups there are some clear and clinically important differences between them. The Japanese group of patients had a better performance status and a shorter time to progression after first line therapy. They also had a higher proportion of diffuse type histology, 0–2 metastatic sites (compared to >3) and a lower incidence of ascites, suggesting a lower burden of metastatic disease compared to the Western patient group. These

findings are consistent with previous subgroup analyses of trials of targeted agents in GC, where Japanese patients have also been found to be comparatively fitter than their Western counterparts (4). The median duration of study therapy was notably longer in the Japanese population compared to the Western population (22.5 *vs.* 16.1 weeks) with less treatment discontinuation due to adverse events (7.4% *vs.* 13.6%). Data was also suggestive of a longer time to deterioration of ECOG performance status in the Japanese group (HR for deterioration 0.64 *vs.* 0.89), although these hazard ratios did not meet significance. This all indicates a generally improved tolerance and longer exposure to treatment among the Japanese patient group. The combination treatment was associated with higher rates of grade  $\geq 3$  neutropaenia across both geographical groups, with a higher incidence amongst the Japanese population (66.2% *vs.* 32.1%). Rates of febrile neutropaenia and serious adverse events however were similar, suggesting that this could be safely managed. Again this finding is consistent with previous studies reporting higher incidences of neutropaenia associated with paclitaxel chemotherapy in Japanese compared to Western patient cohorts (5).

When comparing outcomes, OS, PFS and RR were superior across both arms of the trial in Japanese as compared to Western patients. Within the Japanese group the addition of ramucirumab did not lead to a significant difference in median OS [11.4 *vs.* 11.5 months, HR 0.88 (95% CI: 0.60–1.28)] but did lead to significant

improvements in both PFS and RR. This is in contrast to the Western population where median OS [8.6 *vs.* 5.9 months, HR 0.73 (95% CI: 0.58–0.91)], PFS and RR were all significantly improved. When quantifying the magnitude of benefit seen with the addition of ramucirumab, the improved HR for progression on combination therapy within the Japanese cohort when compared to the Western cohort (0.50 *vs.* 0.63) reflected a greater relative improvement in PFS gained.

A key explanatory factor in the difference in OS benefit found between the two groups is likely to be in the rate of uptake of further lines of post-discontinuation therapy. This was markedly higher in the Japanese population than in the Western population (75.0% *vs.* 37.2%), with a higher proportion of Japanese patients receiving fourth line or beyond therapy. It should also be noted that the median survival of 11.5 months recorded in this unplanned subgroup analysis in the Japanese paclitaxel/placebo group is substantially better than any outcomes previously reported, comparing favourably to the median OS of 9.5 months in the paclitaxel arm of the WJOG trial: so far the best outcome achieved in a second-line chemotherapy trial (6). In a further exploratory analysis included in the paper the magnitude of effect on OS seen with the addition of ramucirumab appeared to be greater across both geographical groups for patients who did not go on to receive any further lines of treatment. The high uptake of further lines of treatment and relatively long survival is likely to have led to a ‘dilution’ of OS benefit seen with the addition of ramucirumab to second-line therapy in the Japanese patient group (7).

It is instructive to compare these findings to other trials of targeted agents in advanced GC. The AVAGAST study compared first line cisplatin/fluoropyrimidine with bevacizumab or placebo (8). Despite significant improvements in PFS and RR with the addition of bevacizumab, the numerically longer median OS seen was not statistically significant. A subgroup analysis revealed patients in the Pan-American subgroup showed a statistically significant benefit in OS whereas those in the European and Asian subgroups did not, with 90% of the Asian subgroup being drawn from Japan and South Korea. In contrast to RAINBOW, the subset of Asian patients in AVAGAST also did not show any improvement in either PFS or RR. There were again differences in this study between the Asian and non-Asian populations that may go some way to explaining these results: the Asian group had fewer GOJ primaries, a lower frequency of liver metastases and received second-

line chemotherapy more often. Such findings are not restricted to anti-angiogenic trials: in a subset analysis of the TOGA study addition of trastuzumab to first-line chemotherapy again did not significantly influence OS in Asia but produced a marked influence in South America where second-line therapies are rarely used (9). There have also been differences in outcome noted within Asian populations. For example in the TYTAN study evaluating the addition of lapatinib to paclitaxel for second-line treatment, there were significant improvements in OS and PFS seen for the Chinese population, but not for the Japanese population (10).

Improved outcomes among Japanese GC patients have been well recognized for a number of years. Whether this reflects differences in cancer epidemiology and biology, or societal and healthcare provision factors such as improved diagnosis and medicines access is a matter of some debate (11). There has been some argument that tumours in Asian populations represent a biologically distinct and less aggressive entity, however studies published to date have failed to find clear genetic or biological differences to support this. In a recent landmark analysis by the Cancer Genome Atlas in which they analysed 295 gastric tumours, no systematic differences in the distribution of the proposed molecular subtypes between East Asian and Western patients was found (12). More specific to the use of anti-angiogenic agents, a biomarker analysis of the AVAGAST study demonstrated that high baseline circulating VEGFA levels and low tumour NRP1 expression appeared to correlate with bevacizumab benefit. In Asian patients however this trend was not seen: this group showed lower levels of VEGFA overall and even those with higher levels still did not gain benefit from bevacizumab (13). These findings have been implicated in the poorer responses to the drug apparently seen in Asian patients, but again it is not clear whether geographic region is a surrogate for differences in disease biology potentially influencing sensitivity to specific anti-angiogenic agents.

Despite a lack of clear evidence of genetic heterogeneity, there are well-recognised differences between Eastern and Western GC populations in terms of epidemiology, histology, and diagnostic and treatment patterns. Western countries have a higher incidence of tumours of the proximal stomach and GOJ, with the incidence of such proximal cancers increasing even whilst the overall incidence of GC in the West declines (14). Proximal tumours are known to be associated with worse outcomes, however even when compared by tumour location survival

differences between East and West persist (15). In Japan mass screening programmes have led to substantial stage-shift, with significantly more cancers being diagnosed and treated at an early stage (16). Even in the context of advanced disease, the earlier diagnosis and treatment in Japanese patients is potentially reflected in the generally lower burden of metastatic or measurable disease found. There are also variations of GC presentation and survival within Europe. Eastern European countries have been found to have higher incidence rates and poorer survival than Western European countries (17). There is also some evidence that the pattern of overall decline in incidence is not being seen in Eastern Europe, perhaps related to epidemiological factors such as high prevalence of *H. Pylori* infection (18).

The lack of demonstration of an OS benefit in Asian patients within RAINBOW is consistent with previous trials of targeted agents in advanced GC. In contrast to AVAGAST however, the PFS and RR improvements seen in the Japanese population do provide evidence for biological effect with the addition of ramucirumab. The use of PFS as an effective surrogate endpoint is a contentious issue in most tumour types and in GC has been questioned, with the results of several large patient and trial-level meta-analyses showing a poor correlation between PFS and OS for chemotherapy in both first and second line treatment settings (19,20). Whether the improvements in PFS seen with Japanese patients in RAINBOW correlate to a more tangible OS benefit remain to be seen. There are a number of ongoing studies looking at ramucirumab use in combinations and sequences that are more standard to Japanese and East Asian practice and which may aid in further clarifying its role in treatment (NCT02359058, NCT02539225).

The advantage of large global studies such as RAINBOW is that nuanced interpretations of geographical differences in outcome can be made, and pre-planned subgroup analyses based on geographical area are important components in the design and interpretation of such trials. This was an unplanned subgroup analysis with relatively small numbers in the Japanese patient group limiting its interpretation; however it does appear to add to the existing evidence of disparity between Eastern and Western GC outcomes. This is likely to be due to a complex mixture of both disease-related, epidemiological, diagnostic and treatment factors. Ramucirumab appears to have a clear benefit in the second-line treatment of GC in Western patients both as monotherapy and in combination with paclitaxel

chemotherapy, reflected in its recent FDA and EMA licensing. The benefit for Japanese and East Asian patients is less pronounced, however this is in the context of a treatment landscape where utilisation of greater numbers of effective therapies is leading to incrementally improved survival outcomes in general. In spite of this the uptake of ramucirumab in Japan has been high, and the results of further trials are awaited with interest. In the emerging era of genomics it is hoped that approaches in GC will start to shift from describing regional differences in treatment to more individualised management based on the molecular profile of the tumour and validated prognostic and treatment biomarkers. Such research may well help to further define the role of ramucirumab and its place amongst other emerging targeted and immunotherapeutic treatments in the future, and that perhaps this more personalized approach will go some way towards overcoming regional variations in outcome seen.

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### Footnote

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# Ethnicity-related differences in tumor immunity: a new possible explanation for gastric cancer prognostic variability?

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Gastric cancer (GC) is a very heterogeneous disease. Despite the decreasing incidence with time, it represents the second most common cause of cancer-related death after lung cancer; however, it is well known that incidence rates are very different throughout the world, with some geographic areas showing much higher rates than other regions (1,2). Subtypes of GC present different and sometimes opposite epidemiological trends, with reference to proximal *vs.* distal tumor locations, or intestinal *vs.* diffuse Lauren histological types (3).

Along with wide variations in epidemiological characteristics, survival probabilities of GC patients are also different between Countries or risk areas in the same country (4). In a report from the EURO CARE Working Group, the improvement in 5-year relative survival of GC during a decade was negligible (4.1% in males and 1.4% in females) (5). Notably, GC exhibited the largest variability in survival rates among European countries, much more than other neoplasms, as breast or colorectal cancer. A recent study from our group also demonstrated strong differences in long-term outcome in GC patients coming from high or low risk areas of Italy, and treated at the same center with a similar surgical approach (6).

The exact reasons of such prognostic variability are still unknown, because differences in tumor (location, histotype) and individual characteristics (age, gender) are not able to completely explain these disparities (7). In general, it seems that a correlation exists between incidence and survival rates. Indeed, the highest is the incidence, the highest seems to be the survival probability (7,8).

We could speculate, as possible explanation of this

phenomenon, that different biological form of GC may be linked to its epidemiology; more aggressive forms may have a uniform incidence throughout the world, whereas less aggressive forms may be more prevalent in high-risk areas. This could lead to better survival probability when the survivals of overall GC cases are analyzed in such areas (8).

Microsatellite instability (MSI) has been reported, in several studies, as an important favourable prognostic factor for GC; we recently confirmed its prognostic value in a large series (9). Furthermore, in our experience we observed a different proportion of MSI cases in patients coming from high-risk or low-risk areas of Italy, being MSI more common in regions with higher GC incidence (manuscript to be submitted). An alarming feature linked to this aspect is that the decreasing incidence of GC, above all in high-risk areas, may be due to the decreasing number of less aggressive forms. As a result, in the future we could observed less GC case, but with more aggressive tumor biology (3).

Two recent important studies which analyzed molecular biological characteristics of GC, the The Cancer Genome Atlas (TCGA) in America and Asian Cancer Research Group (ACRG) in Asian countries, may be helpful to provide possible explanations for these clinical heterogeneities (10,11).

The TCGA proposed molecular division of GC into four subgroups, based on genomic clustering combined to the molecular data: Epstein-Barr virus (EBV)-positive, microsatellite unstable tumors (MSI), genomically stable (GS) and chromosomally unstable (CIN) GC. The ACRG proposed a division into MSI, and three microsatellite

stable subtypes: epithelial—to mesenchymal transition (MSS/EMT), p53 positive (MSS/TP53+), and p53 negative (MSS/TP53-). In our opinion, the most important clinical characteristics of these molecular classifications, revealed to date, are the much better survival of MSI group, and the higher rate of peritoneal metastases in patients with MSS/EMT tumors.

If these molecular classifications may be able to explain heterogeneity in epidemiological features and prognosis of GC in different risk areas should be verified in future clinical studies, many of which are still ongoing.

Another feature linked to GC prognostic variability is patient's ethnicity. It is well known the survival difference between Eastern and Western patients (12-14). Several studies also reported better outcome in Asian Americans when compared with other ethnicities in the US (15,16). Even when adjusting for several tumor and patients' related factors, evaluated by means of validated prognostic scores, survival difference between Eastern and Western series still persisted (17); this may lead to suspect that other biological factors are responsible for these disparities (18).

Recent studies also reported that Asian-American patients have a worse prognosis if born in the USA, whereas those born in Asia exhibited better survival (19), thus suggesting that factors acquired in the youth may have affected the biological characteristics of GC (8).

Other reports from international phase III randomized trials, where the study populations and treatments are standardized across multiple countries, confirmed these differences. In the AVAGAST trial, subgroup analysis revealed a survival benefit in non-Asians but not in Asians. Conversely, in the LOGiC trial, benefit from lapatinib was observed in Asians but not in non-Asians.

In the paper by Lin *et al.*, entitled "Signatures of tumour immunity distinguish Asian and non-Asian gastric adenocarcinomas", considered in the present commentary, gene expression differences between Asian and non-Asian GC, and their potential impact on clinical outcome, were analyzed (20).

The methods adopted in this study are particularly relevant and innovative. First, nine independent GC microarray cohorts comprising 1,016 tumour gene expression profiles—six from Asian localities, and three from non-Asian localities, were assembled. The comparative analysis of patients' characteristics showed no significant differences in most clinical-pathological variables, with the exception of the higher rate of upper third tumors in non-Asian patients, which corresponds to reported data in literature. Importantly,

it was confirmed that Asian patients exhibited a better prognosis with respect to non-Asian patients.

A very interesting methodological tool was the adoption of a novel algorithm, RUV-4, to reduce study-specific effects in gene expression data. This method reduced the impact of unwanted variation between and within cohorts, but preserving locality-specific variation, thus allowing the comparison between the characteristics of different cohorts.

The main result of the present study is the observation that tumor immunity signatures differ significantly between Asian and non-Asian GC. Non-Asian GC were associated with multiple signaling pathways related to T-cell biology. To validate the immune-related gene expression differences between Asian and non-Asian GC, an immunohistochemistry analysis on two independent tissue microarray cohorts was also performed. Results confirmed that the two patients' categories have distinct immune-related components, especially a higher abundance of T-cell infiltration in non-Asian GC. Further statistical adjustments suggested that these tumor immunity differences may contribute to the geographical differences in clinical outcome observed in study cohorts. Although *H. pylori* status information was unavailable for the entire series, precluding a correlative analysis between the immune differences and *H. pylori* exposure, these results are absolutely innovative in GC translational research.

The role of immunological system in GC is still far to be completely explored, and this important paper may provide a crucial step in this field. We are also convinced that immunological status is able to affect the prognosis of GC patients, and when related to patient's ethnicity this could lead to clarify still unexplained clinical features.

We have to also to note that overall survival was the end-point considered in this study. Cancer-related survival may be also interesting to be evaluated, in consideration of the potential impact of postoperative complications and comorbidities on the prognosis of GC patients. Indeed, in this study the divergence in survival curve between Asians and non-Asians cohorts was particularly evident in the first year after surgery, and afterwards the two survival curves appear to run in a parallel way. Potential differences in the pattern of relapse may be also interesting, in order to analyze the impact of immune-related features on hematogenous, local or peritoneal recurrence, in light of possible future therapeutic applications. The observations that chemotherapy outcomes and immune effects may be interdependent, and the emerging role of immunotherapy in GC, are particularly relevant from a therapeutic point of view.



In conclusion, the results of the present study by Lin *et al.* may have important clinical and scientific implications, in a flourishing scientific context of biological and molecular characterization of GC, which is expected to shed more lights on this still enigmatic disease.

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## Footnote

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# Survival in lymph node-negative gastric cancer: the Western experience

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Lymph node status is the strongest prognostic indicator for survival after gastrectomy for gastric adenocarcinoma (GAC) (1). However, for patients who undergo resection and are deemed to be ‘node-negative’ based on pathologic exam, the relevant prognostic indicators and guidelines for adjuvant therapy remain unclear. Our group has recently published the long-term survival results of a large, multi-institutional database of North American patients undergoing gastrectomy for GAC, of which 317 patients were lymph node-negative (2). To date, it is the largest published series of a Western experience with node-negative GAC. The median follow-up time was significant at 68 months, and the overall recurrence rate was 17%. We evaluated endpoints of time to recurrence and overall survival (OS). Our data showed that greater depth of tumor invasion (indicated by T-stage) was independently significant in predicting shorter time to recurrence in a competing risks regression model whereas OS was negatively impacted by higher tumor stage, lymphovascular invasion, signet ring histology, and having less than 15 nodes examined.

In commentary by Hsu *et al.*, the authors contrast the differences between our cohort and two previously published studies of survival in node-negative GAC (3,4). As there are few large Western series in this patient population, the Eastern experience serves as both an educational example as well as a study of contrasts. In a study published in 2013 by Chou *et al.*, recurrence rates for T2–T4 tumors were 8.6%, 12.5%, and 26.5%, respectively (3). In comparison, recurrence rates in our cohort were 9.1%, 29.7% and 35%, respectively (2). In another study published by the same group, the authors

found that extensive lymphadenectomy with >25 lymph nodes examined resulted in better long-term survival than the examination of <15 or 16–25 nodes did, and that greater extent of lymphadenectomy did not increase surgical complication or hospital mortality rates (4). While our data also indicated that having >15 nodes examined did prolong OS, the mean number of nodes examined in our cohort was 16, with interquartile range of 9–22 (2). Both of these differences help to highlight the disparate experiences with GAC in Asia and the West. While the higher recurrence rates seen in our cohort by T stage may very well be related to understaging with fewer total lymph nodes examined, it should also be noted that our overall population was older, had greater comorbidity burden (63% in our cohort *vs.* 27% in Chou *et al.*), and had a much higher perioperative complication rate (40% in our cohort *vs.* 11% in Hsu *et al.*), a risk factor that we have shown to be independently significant for recurrence and survival in gastric cancer (5). Additionally, the cohort presented by Chou *et al.* did not include any patients who received neoadjuvant chemotherapy, whereas 23% of patients in our cohort received neoadjuvant therapy. Despite the known survival advantage of perioperative chemotherapy for GAC, our data showed that while controlling for other clinicopathologic features, patients who received neoadjuvant therapy did worse in terms of recurrence and survival, correlating with a preoperative assessment of more locally advanced and aggressive disease. Furthermore, several factors may be driving the difference in number of lymph nodes retrieved and examined between the Eastern and Western experience, including the greater technical challenge in Western patients with higher BMIs and greater comorbidities as well

as differences in pathology practice, as a recent publication from Memorial Sloan Kettering Cancer Center showed that more extensive *ex-vivo* lymphadenectomy increased the median yield from 21 to 30 lymph-nodes (6). Despite these differences, these data do highlight an opportunity for improvement in the number of lymph nodes both retrieved and examined in North American GAC patients.

While the differences that these studies highlight are an interesting comparison of surgical practice and outcomes, this is not the primary purpose of our analysis. Our aim was to explore what factors can guide clinicians who are choosing adjuvant treatment strategies for patients deemed node-negative after curative resection for GAC. Certainly, the high percentage of patients who were technically understaged in our cohort is concerning and the possibility for stage migration is not trivial. However, as reoperation for adequate staging is unrealistic, data is needed to guide clinicians treating this cohort of node-negative patients. While under-staging in some other solid tumor types is in and of itself an indication for adjuvant therapy, as yet there are no firm guidelines for understaged patients with GAC (7). Our data indicates that patients with higher T stage have significantly increased risk of both recurrence and death, and should strongly be considered for adjuvant chemotherapy and/or radiotherapy, even if they are deemed lymph node-negative.

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# Survivin for chemotherapy efficacy in gastric cancer

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**Abstract:** Survivin belongs to the inhibitor of apoptosis protein family. Its bi-functional role in apoptosis and in cell division makes it an important molecule for the progress of cancer. Survivin is over-expressed in most malignancies but not in normal differentiated tissues. As far as gastric cancer is concerned, survivin is highly expressed in tumor cells and plays a role in the development of carcinogenesis. High rate of survivin influences overall survival of patients and is correlated with poor prognosis in gastric cancer. Moreover, survivin seems to provide gastric cancer cells with chemo and radio-resistance, similar with other type of cancers. The association between over-expression of survivin and resistance to various chemo-drugs and radiation renders this molecule as a significant biomarker. Survivin is considered as an ideal therapeutic target of cancer due to its capacity to inhibit apoptosis and to promote tumor growth and its selective expression in cancer cells. Since survivin expression might be a useful diagnostic, prognostic, and predictive marker in certain malignancies, many studies aim to counteract survivin in order to inhibit tumor growth and to enhance tumor cell response to apoptosis-inducing anticancer agents. Different approaches are used including antisense oligonucleotides (AO), ribozymes and siRNA, gene therapy through dominant negative mutants, synthetic small molecules and immunotherapy.

**Keywords:** Survivin; cancer; gastric cancer; single nucleotide polymorphisms; pharmacogenomics

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## Introduction

Survivin is the smallest member of the inhibitor of apoptosis protein family (IAPs). In contrast to the other IAPs, it contains only a single copy of the 70 amino-domain called baculoviral IAP repeat (BIR) (1,2). Human survivin consists of 142 aminoacids, has a molecular weight of 16.5 kDa and is localized in nucleus, cytoplasm, mitochondria and in extracellular space. Recently, it was found that the multiple function of the protein depends on its subcellular localization (3). The subcellular distribution of survivin seems to be changing through the cell cycle progression and the different pools are modulated independently (4). The gene encoding survivin is 14.5 kb, located at the telomeric region of chromosome 17. Unlike other member of IAPs, it does not contain really interesting new gene (RING) finger motifs or other common structural elements (5,6). Instead of this, it contains an

extended carboxyl-terminal alpha-helical coiled-coil. The human *survivin* gene can give five different transcripts due to alternative splicing (survivin, *survivin 2B*, survivin-3B, survivin-2a and survivin-ΔEx-3) (7).

This protein has a bi-functional role in apoptosis and in cell division. Its anti-apoptotic function occurs via two main apoptosis pathways, the mitochondrial-intrinsic pathway and the death receptor pathway. Survivin blocks the apoptosis pathway either by its binding directly on initiator caspase 9 or indirect by the inhibition of effector caspases 3, 7. Survivin can efficiently protect cells from caspase-dependent apoptosis interacting with other molecules as SMAC/DIABLO and XIAP (8). There is also a caspase-independent inhibition of apoptosis (9). As far as the cellular division is concerned, survivin acts as a mitotic regulator through its association with kinetochores, centrosomes (microtubule-organizing centers), spindle microtubules, central spindle midzone and midbodies. There is a >40

fold up-regulation of the protein during G2/M phase (10,11). Survivin is normally expressed during embryonic development but not in most normal differentiated adult tissues, suggesting its role in pathogenesis when it is expressed in differentiated tissues (12). Survivin's up-regulated expression lies on a variety of molecular mechanisms and epigenetic modifications, including gene amplification, promoter and exon demethylation, and enhanced promoter activity by various transcriptional factors (7,13). However, some studies have revealed the expression of survivin in fast dividing normal cells, such as CD34+ bone marrow derived stem cells, basal epithelial cells, thymocytes and basal epithelial cells of normal uterine cervix, is playing an important role in maturation, survival and proliferation (14-16). Furthermore, survivin has also been detected in the nuclei of mucosal surface epithelial cells and in both nuclei and cytoplasm of chief and parietal cells in human gastric mucosa (17).

### Survivin and cancer

Survivin is highly expressed in the majority of cancers and malignancies suggesting its role in tumorigenesis (12). Survivin, as an antiapoptotic protein, reduces the cell loss rate and promotes both cell proliferation and angiogenesis providing advantage to a rapidly growing tumor and consequently to a neoplastic transformation (4). In addition to its direct role in carcinogenesis, survivin may also play a key role in progression of cancer and tumor angiogenesis because of its high expression in endothelial cells during the remodeling and proliferative phase of angiogenesis (18,19). Both gene and protein expression are evaluated in human malignancies usually by molecular and immunological assays such as semi-quantitative real time PCR and immunohistochemistry, respectively. Up-regulation of survivin has been reported in almost all human cancers including gastric cancer, lung, colon, breast, stomach, esophagus, liver, pancreatic, prostate, ovary cancer, gliomas and in hematopoietic malignancies (20-23). More aggressive behavior of some types of cancer, such as colorectal and gastric carcinomas, can be correlated with overexpression of survivin (24,25). Similar to its expression, survivin promoter activity is largely silent in normal cell types, but is increased in tumor cell lines. A research by Dohi *et al.* showed that mitochondrial survivin promotes tumor growth and inhibits tumor cell apoptosis contrary to cytoplasmic surviving (26). Survivin splice variants expression in tumor samples is related with various clinicopathologic

characteristics in different cancers (27). Kim *et al.* revealed the relationship of survivin and TCF/catenin signaling axis and the increased cell proliferation and survival in colorectal cancer (28). Nuclear localization of survivin has been reported as a favourable prognostic marker for gastric, bladder and breast in contrast to esophageal, hepatocellular, lung and ovarian cancers (29). Many single nucleotide polymorphisms (SNPs) have been identified in survivin gene but mainly -31G/C is thought to participate in carcinogenesis. Two studies have found an association between -31G/C and gastric cancer (30,31). Recently, two different meta-analysis by Srivastava *et al.* and Wang *et al.* have shown that the survivin -31G/C polymorphism is overall correlated with cancer susceptibility especially in Asian population but there is no significant correlation with esophageal or gastric cancer (32,33).

### Survivin and gastric cancer

Gastric cancer is one of the most common malignancies and is probably the second leading cause of cancer death (34). Highly expressed survivin is correlated with poor prognosis (19). Lee *et al.* suggested that survivin triggers tumor angiogenesis in gastric cancer (18). Nuclear localization of survivin does not have a significant impact on overall patients' survival in contrast to its cytoplasmic localization (35). Yu *et al.* supported that survivin might play an important role in the early stage of development of gastric cancer within the members of a family due to the increased survivin expression both in patients with gastric cancers and their first degree relatives (36). At the later-stage of gastric cancer, *survivin 2B* is under-expressed, suggesting its association with tumor progression (37,38). Contrary, *survivin-ΔEX3* was increased in cancer tissues in comparison with para-cancerous tissues (30). A recent study indicates a relationship between PI3K/Akt and survivin in the gastric cancer. In normal gastric mucosa, survivin protein was undetectable and its mRNA was low. In contrast, elevated survivin mRNA and protein levels in biopsy specimens of gastric cancer indicated that alterations in survivin expression are involved in the development of gastric cancer (39). PI3K/Akt pathway regulates survivin and these proteins could possibly be used as markers for the prognosis and the treatment of gastric cancer as they participate in cell proliferation (40). Survivin's interaction with other proteins such as RUNX3 regulates its promoter activity and promotes gastric cancer cells apoptosis (41). Moreover, survivin has a multifunctional role including the



association with STAT3, activated phosphorylated form of signal transducer and activator of transcription 3 (pSTAT3), suppressor of cytokine signaling-1 (SOCS-1) and Bcl2 in gastric cancer. The expression of these molecules and cytoplasmic survivin is associated with poor prognosis and more aggressive cancer. Furthermore, surveys in gastric cancer have shown that as survivin signaling seems to have a major impact on STAT3 downstream targets—MMP-9, MMP-10, cyclin D1, VEGF-C, and VEGFR-3, this molecule may be used for diagnostic and therapeutic purposes in the future (42). A recent meta-analysis study in gastric cancer highlights an association between survivin expression levels and metastatic lymph nodes and overall survival in patients (43). Tu *et al.* confirmed the relationship between survivin and gastric cancer as their experiments resulted that suppression of *survivin* also inhibits *de novo* gastric cancer formation and angiogenesis *in vivo* (44).

### Chemo-resistance

It is widely known that cancer cells develop multiple mechanisms of resistance to therapy. The resistance to conventional cytotoxic drugs and molecular targeted agents share similar mechanisms, including genetic/epigenetic alterations induced and/or constitutive activation of pro-survival pathways to avoid cell death, and increased drug efflux via ATP-binding cassette (ABC) transporters (45). It is clear that resistance to chemotherapy is associated with reduced susceptibility to apoptosis. Evidence shows a relationship between chemo-drugs and expression of survivin in most malignancies. Apart from tumorigenesis, tumor progression and poor prognosis, survivin also seems to increase tumor resistance to various apoptotic stimuli (9). Survivin acts as a strong inhibitor of cell death and protects cells against unfavourable environments antagonizing drug and radiation induced apoptosis (46). Survivin seems to contribute to chemo-resistance by protecting cell survival through two main mechanisms: (I) the inhibition of apoptosis by blocking activated caspases; (II) by stabilizing the microtubule cell network to prevent cell catastrophe. Depending on the cancer type, these two mechanisms contribute in different rate to cancer cell survival (47). Growth factors as VEGF induce the expression of *survivin* through PI3K/PKB pathway and render chemo-protection (48). Chemo-resistance related to survivin has been referred to gastric cancer (49), glioblastoma (50), neuroblastoma (51), chondrosarcoma (46), lung (52), breast (53), pancreatic cancer (54) and thyroid carcinoma (5).

It has been 15 years since Ikeguchi *et al.* noted a connection between survivin expression in gastric cancer cells (cell line MKN-45) and chemotherapy treatment. Their findings showed that both survivin mRNA and protein expression levels at the cells treated with cisplatin were 2 to 6 fold higher than the expression levels of the untreated cells. These results suggested that survivin expression may correlate with the chemo-resistance of malignant gastric cells (55,56). Survivin's splice variants also seem to play a role in chemo-protection of cancer cells and their targeting could result in sensitization to chemotherapy. Survivin 3B is referred as an interesting therapeutic target since it is only present in tumors (57). However, wild-type survivin is mentioned that promote doxorubicin-resistance in gastric cancer (58) and its mRNA level is suggested as a useful tool for evaluating the docetaxel-response in patients with gastric cancer (59). Nevertheless, high expression of nuclear survivin seems to evoke better response to platinum/taxane chemotherapy, so nuclear survivin becomes an independent prognostic factor (52). A recent study demonstrated that lower expression of survivin was associated with better response to paclitaxel in gastric cancer, validating the role of survivin as a biomarker for chemo-sensitivity in this malignancy (49). Moreover, Zheng *et al.* confirmed the association between survivin overexpression and resistance to docetaxel chemotherapy in advanced gastric cancer (60).

Knock down of survivin expression clearly sensitizes gastric cancer cells to chemotherapy both *in vitro* and in nude mice (61). Additionally, Wang *et al.* indicated the synergistic effect of gambogic acid and docetaxel in gastric cancer cell lines via inhibition of survivin (62). Their results are in consistency with previous studies that showed the cytotoxic effect of gambogic acid in human gastric carcinoma MGC-803 cells and BGC-823 inducing apoptosis (63,64).

Survivin appears to be a useful biomarker of resistance to chemotherapeutic drugs or a therapeutic tool through its targeted inhibition in gastric cancer. However, there are only few studies about this cancer type for making safe conclusions. The relationship between chemo-resistance and survivin is confirmed by reports about other type of cancers. An extended study of tumor-associated brain endothelial cells has indicated resistance to multiple classes of drugs as VP-16, paclitaxel, thapsigargin and temozolomide (65). Many studies in breast cancer have been accomplished about the effectiveness of various apoptotic stimuli. Tamoxifen, paclitaxel and trastuzumab seem to be suspended by survivin through caspase inhibitor mechanism



in breast cancer cells (62,66). However, Nestal de Moraes *et al.* have claimed that survivin does not influence the response to doxorubicin and other dox-based drugs (67) and moreover, high levels of cytosolic survivin have been related to advanced chemotherapeutic efficacy by Span *et al.* in breast cancer (53).

Targeted agents, that can silence the *survivin* gene and inhibit DNA repair, increase sensitivity to chemotherapy. These agents, like YM155 and FL118, are used in combination with cytotoxic chemo drugs such as various platinum based drugs in order to increase efficacy and reduce toxicity after their synergistic action (51,68,69). Favarsani *et al.* transcriptionally suppressed survivin through YM155 and this enhanced doxorubicin treatment in breast cancer cells (70). Bortezomib downregulates survivin in many solid and hematological malignancies but, according to a recent study, bortezomib manage therapeutic response to multiple myeloma irrespective the expression of survivin (71).

### Radio-resistance

Radiation, similar to chemotherapy, provokes death of tumor cells by causing irreparable cellular damage and triggering apoptosis. Therefore, inhibitor of apoptosis protein family affects tumor cells inversely and promotes radio-resistance. The relationship between survivin expression and the ability of cancer cells to undergo apoptosis can influence negatively their sensitivity to radiotherapy. It is not clear enough how survivin decreases radio-sensitivity since it is a multifaceted issue. Many mechanisms seem to be involved concluding either caspase-dependent or caspase-independent mechanisms, like impaired DNA repair, altered cell-cycle distribution, mitotic arrest and subsequent cell death (72,73). Studies on colorectal and pancreatic cancer cells have demonstrated that highest level of survivin protein and mRNA are associated with low rate of apoptosis and resistance to radiation. Insensitivity in these cancer cells may rely on the inductive expression of survivin after radiation (54,74). Likewise, a study in glioblastoma have indicated higher survivin expression in radio-resistant cell lines compared with radiosensitive cell lines (75). Overexpression of survivin has been correlated to radio-resistance in breast (76), esophagus (77) and renal cancer cells, as well (78). Different isoforms of survivin have various effects on radio-resistance, wild type and 3b-survivin protects cancer cells against radiation, while the other splice variants seem to have no impact (73). Farnebo *et al.* have claimed that survivin has a converse

effect on head and squamous cancer cells. Highly expressed survivin resulted in better response to radiotherapy and its downregulation leads to increased radio-resistance in this type of carcinoma (79). Recent studies have concentrated in counteracting survivin's expression in order to induce radio-sensitivity in cancer cells. Inhibition of survivin results in radiation-induced apoptosis and enhances radio-treatment. Two researching teams have asserted that targeting survivin leads to inefficient DNA repair exposure in radiation exposed human glioblastoma and colorectal tumor cells (72,75). Correspondingly, Reichert *et al.* have confirmed the protective role of survivin in radio-induced cell death by stimulating DNA double-strand break repair in glioblastoma and suggest targeting survivin as a strategy to increase therapeutic efficacy of radiation (80). Song *et al.* have revealed that targeting *survivin* gene by RNA interference induces apoptosis and promotes radio-sensitization in human cervical carcinoma cells Hela (81). Likewise, silencing of *survivin* gene in gastric cancer cells improves their radio-sensitivity. Gastric cancer colony formation and viability were highly reduced, while apoptosis rate was up-regulated in *survivin*-silenced tumor cells after radiation (61).

### Therapeutic applications

As it is already mentioned above, survivin expression may be a useful diagnostic, prognostic, and predictive marker in certain malignancies. The overexpression of survivin in human cancers and its dual role in malignancy has led to an intense interest in it as a target of therapeutic applications (82). Survivin's unique nodal properties have made its antagonists an attractive potential therapeutic solution to the heterogenous human cancers (83). Inhibition of survivin with molecular genetic approaches additionally to the use of chemotherapeutic drugs or radiotherapy might improve some of the current therapeutic strategies (22). In order to target efficiently survivin, it is necessary the transcriptional and translational modulation of survivin to be well understood. Developing drugs that target survivin might initially seem difficult because survivin is not an enzyme nor it is a cell surface protein. However, advances in understanding of biology and function of this protein, have resulted in a wide spectrum of molecular inhibitors. Different strategies to counteract survivin in cancer cells have been proposed with the double aim to eliminate the tumor growth potential and to enhance tumor cell response to apoptosis-inducing anticancer agents. These approaches

conclude antisense oligonucleotides (AO), ribozymes and siRNA, gene therapy including transfecting with dominant negative mutants, synthetic small molecules inhibiting gene transcription, immunotherapy/vaccines (84-88). Moreover, nonsteroidal anti-inflammatory drugs, like indomethacin, have been mentioned to induce gastric cancer cells apoptosis by counteract survivin and Aurora-B kinase and the simultaneous treatment with siRNA can lead to higher cell injury (89,90).

### Antisense oligonucleotides (AO)

AO are defined as those oligonucleotides that are 8-50 nucleotides in length that bind to RNA through Watson-Crick base pairing and subsequently modulate the function of the targeted RNA (91). The addition of AO against survivin resulted in decreased expression of survivin mRNA and protein, inhibition of proliferation and induction of apoptosis in a dose-dependent manner (92). Suppression of survivin through antisense oligo inhibits *in vivo* tumorigenicity and angiogenesis in gastric cancer cells (93). At first, a study by Yang *et al.* demonstrated that survivin antisense oligonucleotide can inhibit the growth of gastric cancer cell line but cannot induce apoptosis by itself and proposed an AO that is complementary to the initiation codon and five downstream codons which accessed survivin mRNA more efficiently (94). However, a recent study showed that AO targeting survivin could significantly not only inhibit the growth of gastric cancer cells, but also induce their apoptosis and inhibit their telomerase activity (95). Furthermore, AO-mediated downregulation of survivin sensitizes tumors to chemotherapeutic agents as cisplatin (96,97), taxol (98), etoposide (99) and demecitabine (100). Increased sensitivity to radiation treatment has also been reported following AO-mediated downregulation of surviving (101). Nowadays, the second generation AO drug LY2181308 aims to enhance affinity target RNA and decrease toxicity. It has entered phase II of clinical trials.

### SiRNA

SiRNA is a genetic interference technology that is effective for suppressing specific gene expression (102). It involves post-transcriptional gene silencing via a way in which double-stranded RNA (dsRNA) inhibits gene expression in a sequence-based manner through degradation of the corresponding mRNA (103).

In gastric cancer there are few reports of survivin

targeting with siRNA since recently. SiRNA knockdown of the *survivin* gene can induce apoptosis and inhibit the growth of human gastric carcinoma cell (104,105). Li *et al.*, have also shown that siRNA downregulation of survivin promotes gastric cancer cells death and inhibits cell proliferation through decrease in mitochondrial cytochrome C and cytoplasmic cytochrome C and caspase-3 (69). Their findings are consistent to earlier studies in gastric cancer MGC-803 cells and AGS cells (106,107). Moreover, reduction of survivin expression through siRNA leads to increased sensitivity to docetaxel therapy in gastric cancer cell (108). Likewise, studies in other type of cancer cells such as ovarian cancer cells confirmed that siRNA survivin induced high rates of apoptosis when it is combined with chemo-drugs (109). There are several studies on downregulation of survivin by RNAi in many types of cancer such as chondrosarcoma (46), breast (66), liver (110) and pancreatic cancer (54).

### Small molecules inhibitor

YM155 is a small imidazolium-based molecule that inhibits specifically both mRNA and protein survivin expression and provokes tumour regression by activating caspases and inducing apoptosis. YM155 has been mentioned to suspend the growth of a significant number of human cancer cell lines including the cell lines derived from non-Hodgkin's lymphoma, hormone-refractory prostate cancer, ovarian cancer, sarcoma, non-small-cell lung cancer, breast cancer, leukemia and melanoma (111,112). The combination of YM155 plus various chemo-drugs such as platinum-based drugs, doxorubicin, etoposide, results in more effective inhibition of survivin, thus means greater tumor reduction in some cancer types like melanoma, neuroblastoma, non-small cell lung cancer, but not in breast cancer (68,70,113).

Tetra-*o*-methyl nordihydroguaiaretic acid also known as terameprocol, blocks cell cycle progression by inhibiting the expression of the *Cdk1* gene and simultaneously promotes apoptosis by inhibiting the expression of the *survivin* gene (50,114).

Fl118 can target multiple treatment resistant mechanisms. This new small molecule can inhibit not only IAPs but also antiapoptotic protein Mcl-1 and Bcl-2 (45).

### Gene therapy/dominant negative mutants

The use of gene therapy seems to be effective at inhibition of survivin. A dominant negative mutant replacing the

cysteine residue at amino acid 84 with alanine (Cys84Ala) was transfected in gastric and colon cancer cells and provoked apoptosis and mitotic catastrophe and suppressed tumor growth and angiogenesis. Mice expressing dominant-negative survivin showed decreased probabilities of developing tumors or exhibiting tumor-associated angiogenesis. Moreover, survivin dominant-negative therapy increased sensitivity to cisplatin and 5-fluorouracil (43,86,115). A report by Nakamura *et al.* also revealed that inhibition of survivin function by transfection of a dominant-negative mutant of the *survivin* gene augmented susceptibility to cis-diamminedichloroplatinum induced apoptosis in gastric cancer patients (116). A different dominant negative mutation of survivin, characterized by alteration of threonine 34 to alanine was induced to gastric cancer cells by an adeno-associated virus inhibited cell proliferation and cancer growth, induced apoptosis and sensitized gastric cancer cells to 5-Fluorouracil both *in vitro* and *in vivo* (117). Various studies about survivin dominant mutant Thr34Ala in other type of cancers like melanoma, breast, cervical, lung and colorectal cancer cells have shown similar anti-tumor capacity (118).

### Ribozymes

Ribozymes are small RNA molecules that have specific endonucleolytic activity and catalyse the hydrolysis of specific phosphodiester bonds, resulting in the cleavage of the RNA target sequences (119). Pennati *et al.* have found ribozyme-mediated inhibition of *survivin* expression increases spontaneous and drug-induced apoptosis and decreases the tumorigenic potential of human prostate cancer cells, and it also causes chemo-sensitization and radio-sensitization of human melanoma cells (84,120).

### Immunotherapy

Cell-based cancer immunotherapy involves the use of immune cells such as the natural killer cells, dendritic cells, and cytotoxic T lymphocytes, which are isolated from the patient, activated *in vitro* and transfused back to the patient to target cancer cells (86). The main focus of immunotherapy has been on tumor-associated antigen recognition by T lymphocytes. Both CD8+ cytotoxic and CD4+ helper T cells can recognize antigens presented as small peptides in the groove of surface HLA molecules (71,93). The immunologic properties of survivin and the demonstration of HLA class I—restricted cytolytic T cells against survivin peptides in

cancers suggested that survivin peptide-specific cytolytic T-cell immunotherapy might be a new therapeutic way (87,121). Survivin-directed immunotherapeutic strategies have been rapidly moved to the clinical setting: several phase I trials based on the administration of survivin-directed autologous cytotoxic T lymphocytes generated *ex vivo* or survivin peptides have been completed recently and the treatment was proved to be safe, without crucial adverse effects and associated with antigen-specific immunologic responses (84,88). Survivin-based vaccines to experimental animals have been found to induce tumor regression in several types of malignancy including lung cancer, pancreatic cancer, hormone refractory prostate cancer, lymphoma and neuroblastomas (101).

### Conclusions

To summarize, survivin is undoubtedly a molecule that participates in tumorigenesis due to its ability to suppress apoptosis and its role to cell division. Survivin's overexpression in cancer but not in normal differentiated tissues shows the therapeutic potential of this molecule and makes it a promising cancer target. Survivin's inhibitor drugs seem to be the future of cancer treatment. Taking into account that gastric cancer is the second leading cause of cancer death, more studies are needed about its therapy. For more efficacy to cancer therapy, it is obliged to define the molecular pathway through which survivin provokes apoptosis and offer chemo-resistance to gastric cancer cells. Finally therapeutic application targeting this molecule, such as AO, ribozymes, siRNA, immunotherapy and gene therapy, could be an ideal solution to chemo and radio-resistance, but more clinical trials should be performed at various type of cancers concluding gastric cancer.

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### Footnote

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## *Lin Chen*

*Professor, Chief Physician*

Dr. Chen is the Director of the Department of General Surgery, PLA General Hospital, and the Director of PLA Research Institute of General Surgery. He has over 30 years of diverse experience in the clinical management of gastrointestinal cancer and its relevant scientific research. Currently he also serves as the member of the Standing Committee of Chinese Society of Surgery, Chairman of the Committee of Digestive Tract Tumor of Chinese Research Hospital Association, Chairman of the Upper Gastrointestinal Surgical Section of Chinese Medical Doctor Association, vice Chairman of the Medical Equipment Branch of Chinese Medical Equipment Association, and vice Chairman of Beijing Municipal Society of General Surgery.

Dr. Chen was one of the pioneers that introduced the application of minimally invasive treatments (including conventional laparoscopic surgery, robot-assisted surgery, 3D laparoscopic surgery, and gasless laparoscopy) for gastric cancer. His article on endoscopic surgery for gastric cancer published in *Chinese Journal of Gastrointestinal Surgery* in 2005 was rated as one of the top 100 articles of the journal in the past ten years. The relevant results have been presented at the International Gastric Cancer Conference (IGCC) and the Society of American Gastrointestinal and Endoscopic Surgeons. His team had won the PLA Medical Achievement Award (second grade), and his presentation in the 2017 IGCC was rated as the Best Oral Award.

He is actively involved in the promotion of the standardized surgical procedure (radical D2 gastrectomy) and the multidisciplinary treatment of gastric cancer. Since 2008, he has attended and organized a series of tour and promotion work in 13 provinces and cities across the country, which has improved the overall level of standardized surgical treatment of gastric cancer in China. He has won the PLA Medical Achievement Award (first grade) and Chinese Medical Science&Technology Award (first grade) for these efforts.



He has carried out studies on the application of PET and PET/MRI in the diagnosis, staging, and treatment decision of gastric malignant tumors. In 2007, his research in this field won the PLA Medical Achievement Award (second grade), and the relevant research article has been cited by National Comprehensive Cancer Network (NCCN) Guidelines for Gastric Cancer since then.

He instructed the establishment of PLA's first multidisciplinary treatment (MDT) team for gastric cancer, and led the development of China's first *"Expert Consensus on Multidisciplinary Collaborative Treatment Model for Gastrointestinal Tumors"*.

He has carried out clinical and basic research on liver metastasis of gastric cancer. His innovative work on the GTC MDT for liver metastasis of liver cancer has been constantly supported by the Capital Development Health Fund.

He also studies the neoadjuvant chemotherapy for gastric cancer. His research on the "SOX" protocol in the neoadjuvant chemotherapy for gastric cancer is at leading level in China. The relevant research article was included in the 2010 ASCO annual meeting, and Dr. Chen was invited to give a lecture in the meeting. The article has been cited by the *Chinese Anti-cancer Association 2017 Guidelines on the Management of Primary Gastric Cancer*.

He has carried out research on the application of fast-track surgery (FTS) in the elderly populations and participated in the development of expert consensus and path guidelines for FTS in China.

He was the principal investigator of over 20 research projects supported by the "13th Five-Year" Precision Medicine Program, the National Health Industry Special Fund, and the National Natural Science Foundation of China.

The total awarded grant funds reached 20 million RMB yuan. He has published over 60 articles in peer-reviewed journals, with a cumulative impact factor of over 50 points. He is the Editor-in-Chief or Chief Translator of 11 books and also the holder of 10 utility models and invention patents.





# Introduction of

*Department of General Surgery at the General Hospital of the People's Liberation Army (PLAGH)*

The Department of General Surgery of PLA General Hospital has a history of more than 50 years. During its establishment and development, many top clinicians including Zhiqiang Huang, Weishan Lu, Zanming Wen, Guohua Zhang, Yanyong Jiang, Zhuoyun Gu, Shaobai Song, Faqi Liang, Liming Zhou, Rong Li, and Lin Chen have made great contributions. At present, the Department of General Surgery is a base for national key clinical specialty, national key discipline (cultivation), and Beijing municipal key discipline.

The department has many top talents including one "General Logistics Department Famous Teacher", one "General Logistics Department Young and Mid-aged Technical Expert", one "General Logistics Department Science & Technology New Star", two "General Logistics Department Supported Talents", one "PLA Outstanding Doctorate Candidate", one "PLA Excellent Tutor of Doctorate Candidate", 11 "Beijing Science & Technology New Stars", and 5 winners of the titles of "100 Famous Doctors"/ "100 Up-and-coming Stars".

To establish a globally top research department, the Department of General Surgery has actively carried out international exchanges: 1) In 2013, Dr. Chen Lin attended the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) annual meeting and gave a lecture

entitled *A meta-analysis of robotic versus laparoscopic gastrectomy for gastric cancer*. In 2016, he attended the SAGES meeting again and displayed four posters. 2) In 2014, Dr. Chen Lin attended the ASCO-GI conference and displayed a poster titled *Randomized, multicenter, controlled evaluation of S-1 and oxaliplatin (SOX regimen) as neoadjuvant chemotherapy for advanced gastric cancer patients (RESONANCE trial)*. 3) He has served as the member of the Standing Committee of International Association of Surgeons, Gastroenterologists, and Oncologists (IASGO), and he made a keynote report in its 25th annual meeting. 4) He is the co-Chairman of the EAST MEETS WEST Meeting held in Florida Hospital and gave a lecture titled *Surgical Management of Gastric Cancer-Chinese Experience*. 5) In 2015, The PLA General Hospital attended the 11th International Gastric Cancer Congress and gave 7 lectures and displayed 5 posters. As a result, the hospital was granted a "CACA 2015 International Exchange Award" by the Chinese Anti-cancer Association (CACA). 6) In April 2016, the PLA General Hospital attended the Korean Academic Conference on Surgery for Gastric Cancer, during which researchers from the hospital give two lectures and displayed 10 posters.

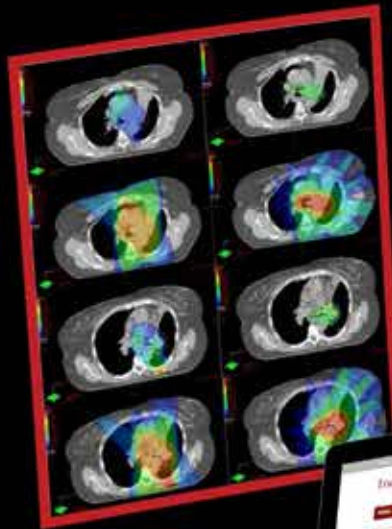


# TRANSLATIONAL CANCER RESEARCH

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