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Rectal Cancer (FIRST EDITION)

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We are pleased to announce that the "AME Research Time Medical Book Series" co-launched by AME Publishing Company, Central South University Press and DXY.cn will be published as scheduled.

Finishing my medical degree after 4 years and 3 months of study, I decided to quit going on to become a doctor only after 3 months of training. After that, I had been muddling through days and nights until I started engaging in medical academic publishing. Even 10 years after graduation, I had not totally lost the affection for being a doctor. Occasionally, that subconscious feeling would inadvertently arise from the bottom of my heart.

In April 2011, Mr. Tiantian Li, the founder of DXY.cn, and I had a business trip to Philadelphia, where we visited the Mütter Museum. As part of The College of Physicians of Philadelphia, the museum was founded in 1858 and has now become an exhibition hall of various diseases, injuries, deformities, as well as ancient medical instruments and the development of biology. It displays more than 20,000 pieces of items including pictures of wounded bodies at sites of battle, remains of conjoined twins, skeletons of dwarfs, and colons with pathological changes. They even exhibited several exclusive collections such as a soap-like female body and the skull of a two-headed child. This museum is widely known as "BIRTHPLACE OF AMERICAN MEDICINE". Entering an auditorium, we were introduced by the narrator that the inauguration ceremony of the Perelman School of Medicine at the University of Pennsylvania would take place there every year. I asked Mr. Li, "If it was at this auditorium that you had the inauguration ceremony, would you give up being a doctor?" "No," he answered.

In May 2013, we attended a meeting of British Medical Journal (BMJ) and afterwards a gala dinner was held to present awards to a number of outstanding medical teams. The event was hosted annually by the Editor-in-Chief of BMJ and a famous BBC host. Surprisingly, during the award presentation, the speeches made by BMJ never mentioned any high impact papers the teams had published in whichever prestigious journals over the past years. Instead, they laid emphasis on the contributions they had made on improving medical services in certain fields, alleviating the suffering of patients, and reducing the medical expenses.

Many friends of mine wondered what AME means.

AME is an acronym of "Academic Made Easy, Excellent and Enthusiastic". On September 3, 2014, I posted three pictures to social media feeds and asked my friends to select their favourite version of the AME promotional leaflet. Unexpectedly we obtained a perfect translation of "AME" from Dr. Yaxing Shen, Department of Thoracic Surgery, Zhongshan Hospital, Shanghai, who wrote: enjoy a grander sight by devoting to academia (in Chinese, it was adapted from the verse of a famous Chinese poem).

AME is a young company with a pure dream. Whilst having a clear focus on research, we have been adhering to the core value "Patients come first". On April 24, 2014, we developed a public account on WeChat (a popular Chinese social media) and named it "Research Time". With a passion for clinical work, scientific research and the stories of science, "Research Time" disseminates cutting-edge breakthroughs in scientific research, provides moment-to-moment coverage of academic activities and shares rarely known behind-the-scene stories. With global vision, together we keep abreast of the advances in clinical research; together we meet and join our hands at the Research Time. We are committed to continue developing the AME platform to aid in the continual forward development and dissemination of medical science.

It is said that how one tastes wine indicates one's personality. We would say how one reads gives a better insight to it. The "AME Research Time Medical Books Series" brings together clinical work, scientific research and humanism. Like making a fine dinner, we hope to cook the most delicate cuisine with all the great tastes and aromas that everyone will enjoy.

Stephen Wang
Founder & CEO,
AME Publishing Company

This is a comprehensive textbook, covering all aspects of the diagnosis and multidisciplinary management of rectal cancer. The book includes in-depth discussions of topics ranging from surgical treatment, chemotherapy, radiotherapy and immunotherapy of rectal cancer. Each chapter is written by world-renowned, international radiologists, surgeons, radiation oncologists, and medical oncologists who address the key, practice-changing, scientific data on therapy for rectal cancer as well as how to apply these approaches in real-world management of this disease.

We hope that this very comprehensive edition will provide the trainees and practicing oncologists with fresh new insights into the multidisciplinary approach to rectal cancer.

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The abdominoperineal resection for rectal cancer, which was performed in the late 90's of the 19th century by Quénu and Hartmann marked the beginning of modern rectal cancer surgery. In those days, without flexible endoscopy and without any reliable imaging methods, most rectal tumors would be regarded as late stage locally advanced cancers nowadays. Without modern combination treatment still most of the patients would die from a recurrence. Still, for the first time in history, some patients could be cured and survive and not all would die of local recurrence with or without progressive systemic disease. Only a couple years earlier, Billroth the founding father of gastro-intestinal surgery had proclaimed, that rectal cancer could not be cured by surgery. The publication of Miles on abdomino-perineal resection in the Lancet in 1907 is considered one of the most important milestones for rectal cancer surgery. Since then, several technical advances have been made. It became possible to perform anastomoses, in the beginning mostly above the peritoneal reflection, after the introduction of mechanical staplers it became possible to construct anastomoses below the peritoneal reflection and even to the level of the anorectal canal. However, even at the end of the 20th century survival rates were poor, local recurrence rates were high up to 40% and many of the patients died after developing metastatic disease, if they did not develop local recurrence, which would kill them.

Surgery of rectal cancer received an enormous boost by the ground breaking work of Heald, who introduced the concept of total mesorectal excision. The concept was not new, and was already known from many other tumours, however the understanding of the exact anatomy of the rectum, its enveloping mesorectal fascia and the bordering parietal pelvine fascias, which had already been described by Waldeyer around the turn of the century in 1900, made it possible to develop a new surgical technique, which respects these fascias. An important paradigm shift was the realization that it is not the tumor, which determines the outcome of rectal cancer surgery, but it is the quality of surgery itself. By doing better surgery local recurrence rates could be dropped below 10%, and even lower, below 5%. However this was not the only change that took place. More potent magnetic resonance imaging devices (MRI) were developed, and they made it possible to delineate fascial layers within the soft tissue. For the first time the surgeon was not blind, but could anticipate on the extension of the tumour, and could realise where a resection would be troublesome, and could lead to a positive resection margin, which is still a very poor prognostic sign. No longer the final pathologic specimen guided additional therapy, but instead, the preoperative image, which corresponds very well with the final pathology, made it possible to make treatment decisions beforehand. Preoperative treatment on the basis of preoperative imaging is now generally accepted.

Preoperative radiotherapy did enable to shrink the tumour to such an extent that even in tumours, which were thought to be irresectable a resection could be performed. No longer rectal cancer treatment was the domain of the surgeon alone. Preoperative radiotherapy and intensification of preoperative radiotherapy with concomitant chemotherapy became an important part of the treatment. Postoperative radiotherapy has been discarded almost completely in the management of rectal cancer, and probably the same will be true for postoperative adjuvant chemotherapy.

New approaches to systemic treatment in rectal cancer are being investigated. Administering preoperative systemic treatment seems very promising as a down-staging modality, almost comparable to preoperative radio-chemotherapy. However, a possible advantage of preoperative chemotherapy could be that not only there will be a local effect on the tumour, but may be also microscopic metastases can be treated, before any surgery is being performed.

In this highly recommendable book, new trends in research and developments in management on rectal cancer are being discussed.

Optimal use of the available imaging modalities like MRI, CT and PET are reviewed in the first chapter. These modalities are truly complimentary displaying their strengths in local and distant staging of patients with rectal cancer. In the next section on treatment overview, eminent authors stress that modern rectal cancer treatment is unthinkable without a multidisciplinary approach and corresponding multidisciplinary team working in "concert" to decide on the best sequence and combinations of treatment.

In the next part of this book, it is pointed out that surgery still plays a major role. New surgical techniques are still being developed looking for less traumatic surgery and fewer complications. Laparoscopic and even robotic surgery have found their way to the operating theatre. The next section raises an important issue regarding the use of systemic therapy. In a later chapter an overview of all studies on adjuvant chemotherapy is provided, but in these chapters it is discussed if in the era of neo-adjuvant treatment the use of preoperative chemotherapy is much more effective than postoperative chemotherapy? The same fate as is shown for postoperative systemic treatment has already become true for postoperative radiotherapy, which has been replaced by preoperative radiotherapy. Nowadays, it is not possible to talk about neoadjuvant treatment

without radiotherapy. In small rectal cancers, high doses of local radiotherapy may replace surgery. Further intensification of radiotherapy by means of an intraoperative boost or the use of proton beam radiotherapy may also help to optimize outcome in more locally advanced or even locally irresectable tumors. It is accepted that radiotherapy with concomitant chemotherapy results in downsizing and downstaging of a rectal tumor. The work of Habr-Gama has brought this concept to a higher a level. She has shown that after complete response after chemo-radiation even in advanced cases organ preservation has become a realistic option for a substantial number of patients. Many questions regarding prediction of response and optimal selection of patients for a possible organ preserving approach remain open, but they also demonstrate how far we have come since the first successful abdomino-perineal resection at the end of the 19th century.

Concluding:

In order to achieve an optimal treatment of rectal cancer patients many specialties have to collaborate. The sequence of different treatments will become an important issue and these patients best can be discussed in the multidisciplinary tumour board. A good registry is necessary to combine data of best practices within countries and to combine data from international institutes. These data will enable to produce guidelines from which everyone can benefit. The authors of the chapters in this book demonstrate state of the art research and help to identify future questions, which still remain to be resolved.

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With the researchers' efforts and their exploration into the mechanisms of rectal cancer, the horizon of scientific knowledge in this field has widened remarkably with dramatic improvements. The management of rectal cancer has witnessed enormous and significant changes since the first recorded surgical resection in 1826. We are really honor to be the Editor and Associate Editor of this textbook that mainly focuses on the treatment of rectal cancer.

Distinguished experts from 10 countries all around the world are gathered to give their insights into the current and future management of rectal cancer, especially in the section "Treatment overview of Rectal Cancer". This text is comprehensive and fascinating in its consideration for the treatment overview of rectal cancer, including surgical treatment, chemotherapy, radiotherapy, neoadjuvant chemoradiation therapy and immunotherapy in the remaining sections.

As the Professors of department of colorectal surgery at Sun Yat-sen University Cancer Center (SYSUCC), the largest integrated cancer center in the southern China for cancer care, research and prevention, we have managed colorectal tumors with surgery, as well as preoperative chemoradiation, intraoperative and postoperative chemotherapy. The multidisciplinary comprehensive treatment mode has been recommended and extensively used at the colorectal surgery department. As one of the four earliest tumor hospitals in China and one of the affiliated hospitals of the Sun Yat-sen University, SYSUCC provides a comprehensive range of healthcare services for cancer diagnosis and treatment including surgery, radiotherapy, chemotherapy, interventional therapy, immunotherapy, gene therapy and Traditional Chinese Medicine.

Drawing on the experience of international leading experts in the field, this book is designed to provide a summary of state-of-the-art developments of rectal cancer treatment and to provide a valuable reference for practicing clinicians in identifying the most appropriate clinical therapy for rectal cancer patients. There is no doubt that current therapies mentioned above will point us in the direction of future improvements.

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The management of rectal cancer is evolving fast and becoming more complex. It is timely that AME has put some efforts into complying the hot topics on the standard of care and controversial aspects in their book on management of rectal cancer. It covers a broad spectrum of subjects from diagnosis to treatment which will help with our discussions at the multidisciplinary meetings (MDT). These regular MDTs has been the corner stone in improving the outcomes for patients with rectal cancer. This book will certainly help to update our knowledge in various aspects of rectal cancer management and I recommend this book to all clinicians and health care professionals involve in the care of rectal cancer patients.

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Even though the management of rectal cancer has seen several milestones over the last 100 years, the quest for the optimal management of rectal cancer is far from over. It is now well recognised that the increasing expertise with local staging and the use of neoadjuvant therapy combined with refined surgical technique involving total mesorectal excision have markedly improved the outcomes of surgical management of rectal cancer. However, these milestones have failed to address one of the major issues associated with rectal cancer treatment which is the morbidity associated with surgical resection that has not improved despite the use of, and increasing experience with, the various minimally invasive approaches in rectal cancer surgery. Consequently, there has been increasing interest in the studies reporting the outcomes of patients who have had complete response to neoadjuvant therapy with close 'watch and wait' management. Nevertheless, it is still too early to adopt this as a standard treatment approach.

It is increasingly evident that an individualised treatment approach is needed for patients with rectal cancer. This approach would take into consideration the patient's wishes, tumour staging, and suitable treatment options in the light of the available local expertise.

The authors of this book have attempted to address some of the dilemmas that clinicians face while treating patients with rectal cancer which include challenges in imaging, chemotherapy, radiotherapy, surgical approach, and non-operative management.

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It is with great enthusiasm that the editors present the first edition of *Rectal Cancer* by AME Publishing Company. This collection of manuscripts has been specifically compiled to provide a comprehensive guide to understanding the complex management of rectal cancer. Thought leaders and researchers world-wide, in the fields of radiology, nuclear medicine, pathology, gastroenterology, surgical oncology, medical oncology, and radiation oncology have come together to contribute their expertise to this text. The aim of this project is to provide a useful, practical, high-quality, evidence-based tool that providers will readily reference when managing patients with rectal carcinoma.

This comprehensive book is divided into 9 sections, building from diagnosis, through treatment overview, to specific treatments, ultimately to prognosis. In section one, *Imaging of rectal cancer*, authors Raman *et al.*, evaluate the evolution of imaging in rectal cancer specifically how advancing imaging modalities have impacted diagnosis, staging, treatment, and response to treatment. In the second section, *Treatment Overview of Rectal Cancer*, authors discuss topics relating to a treatment overview for rectal cancer. Dr. Fung-Kee-Fung details a broad look at rectal cancer while Dr. Minsky provides a glimpse to the future of rectal cancer management detailing advances in staging and comprehensive management

In section three, *Surgical Treatment of Rectal Cancer*, a collection of 8 manuscripts breakdown the various intricacies of surgical treatment for rectal cancer. Innovative minimally invasive surgical modalities like robotic and laparoscopic resection are reviewed in closer detail in a series of 3 articles detailing their current and future use in rectal cancer surgery. Other topics include analysis of value, surgical margin delineation, and the influence of anastomotic leakage on patients' outcomes. Section four, *Chemotherapy of Rectal Cancer*, features a detailed discussion on chemotherapy. From the optimal timing for chemotherapy in locally advanced rectal cancer to the emerging role of neoadjuvant chemotherapy in resectable disease, the authors outline recommended strategies for systemic therapy delivery.

Section 5, *Radiotherapy for Rectal Cancer*, includes a collection of papers evaluating the evolving field of radiation therapy in rectal cancer treatment. Dr. Myint reviews novel radiation techniques such as high-dose-rate brachytherapy. Dinapoli *et al.* introduce the concept of radiomics for rectal cancer, while Holman *et al.* present the results of intraoperative electron beam radiation as a component of multimodality treatment. Dr. Das completes the Radiation section with a review of the latest in proton beam therapy for rectal cancer.

In section 6, *Radiotherapy and Chemotherapy for Rectal Cancer*, the combination of concurrent chemotherapy and radiation are analyzed in further detail. Araujo *et al.* describe the current state of neoadjuvant therapy and the impact on the surgeon while Noh *et al.*, review genomic predictors for treatment response. Yang *et al.* investigate whether there is a role for definitive chemoradiation in certain complete responders. In the next section, *Immunotherapy*, Dr. Glimelius reviews the current and future role for immunotherapy specifically regarding the impact of immunoscoring in rectal cancer patients.

Yaffee *et al.* provide a comprehensive assessment of the current state of systemic therapy in the locally advanced and metastatic settings in section eight, *Comprehensive Treatment of Rectal Cancer*. Van Eeghen *et al.* then review outcomes after radiotherapy with long or short intervals prior to surgery. Additionally, Mitin *et al.* review the management of oligometastatic rectal cancer, with specific attention to the liver. In the final section, *Prognosis of Rectal Cancer*, Petrelli *et al.* review 22 randomized trials and discuss the limitations of potential surrogate end points for 5-year survival.

The editors are very proud of the first edition of *Rectal Cancer* by AME Publishing Company. We wish to extend our sincere gratitude to all of the contributors for lending their experience, vision and expertise to this book. It is our hope that this manuscript will serve as an invaluable resources for providers in their care of rectal cancer patients.

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Evolution of imaging in rectal cancer: multimodality imaging with MDCT, MRI, and PET

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Abstract: Magnetic resonance imaging (MRI), multidetector computed tomography (MDCT), and positron emission tomography (PET) are complementary imaging modalities in the preoperative staging of patients with rectal cancer, and each offers their own individual strengths and weaknesses. MRI is the best available radiologic modality for the local staging of rectal cancers, and can play an important role in accurately distinguishing which patients should receive preoperative chemoradiation prior to total mesorectal excision. Alternatively, both MDCT and PET are considered primary modalities when performing preoperative distant staging, but are limited in their ability to locally stage rectal malignancies. This review details the role of each of these three modalities in rectal cancer staging, and how the three imaging modalities can be used in conjunction.

Keywords: Rectal cancer; staging; magnetic resonance imaging (MRI); computed tomography (CT); positron emission tomography (PET)

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Introduction

Colorectal cancer is incredibly common, representing the 4th leading cause of cancer mortality and the 2nd most common malignancy worldwide, with nearly 1 million newly diagnosed colorectal cancers each year (1,2). Of all colorectal cancers, rectal cancer comprises over 1/3 of cases, with over 40% arising within 6 cm of the anal verge (1,3). While there is little doubt that colonoscopy and biopsy are, and will remain for the foreseeable future, the gold standard modalities for the initial diagnosis of rectal cancer, traditional radiologic imaging modalities are of vital importance with regard to the local staging of patients with a known diagnosis and the identification of distant metastatic disease (i.e., distant staging).

The importance of diagnostic imaging in accurate distant staging is beyond doubt, with multidetector computed tomography (MDCT), magnetic resonance imaging (MRI), and positron emission tomography (PET) all offering valuable means of identifying tumor spread to the liver, lungs, and distant lymph nodes; the three most common sites of distant metastatic disease (2,4). Traditionally, metastatic colorectal cancer at presentation has been treated solely with chemotherapy, although it is increasingly thought that this patient population might also benefit from local resection of their tumor, with associated increased quality of life measures and longer survival (even despite the presence of distant metastases), and in some cases, resection of metastases (particularly to the liver or lungs) may also be a feasible option. Accordingly, the identification of distant metastatic disease has a profound impact on the management algorithm employed for this group of patients, making accurate distant radiologic staging vital (4,5). However, local staging has become equally critical in patient management, particularly given the increasing incorporation of neoadjuvant chemoradiation into treatment protocols. More specifically, while the increasing adoption of total mesorectal excision (i.e., 'en-bloc' resection of the mesorectum) has significantly reduced the incidence of post-operative local recurrence within the surgical bed

(once as high as 38%), locally advanced tumors are still far more likely to recur, and these locally advanced tumors are increasingly being treated with preoperative radiation and chemotherapy prior to total mesorectal excision, requiring radiology to be accurate in determining the local extension of tumors (T-stage), the relationship of a tumor to the mesorectal fascia, and the presence of suspicious locoregional lymph nodes (N-stage) (6). This review will describe the role of the three most important radiologic modalities in the local and distant staging of rectal cancer, namely MDCT, MRI, and PET or PET-CT, all of which serve complementary roles in the initial accurate staging of patients.

Magnetic resonance imaging (MRI)

Local staging

Technique

From a technique standpoint, while the protocols utilized in rectal MRI will vary slightly from institution to institution, high resolution T2 weighted images (with a slice thickness of 3 mm) with a small field of view (FOV) focusing on the rectum are the most critical to accurate diagnosis, as they provide the best means of evaluating the rectal wall and perirectal fat (allowing optimal discrimination of T2 from T3 tumors), and should be acquired in the axial, sagittal, and coronal planes. While the radiologist may choose to primarily focus on the axial images, the coronal and sagittal images become increasingly important when confronted by an infiltrative tumor involving larger portions of the rectum, or an excessively tortuous rectum. In addition, the coronal plane tends to be the most useful for establishing the relationship of a tumor with the internal and external anal sphincters, as tumoral involvement of the sphincter complex could potentially necessitate the performance of an abdominoperineal resection with en bloc resection of the sphincter complex. While the small FOV high-resolution T2 weighted images are the most important imaging sequences, most protocols will incorporate larger FOV T2 weighted images of the pelvis and pre- and post-gadolinium 3-dimensional fast spoiled gradient echo sequence (FSPGR) images to evaluate for the presence of pelvic lymphadenopathy (outside of the mesorectum) and to identify other salient pelvic abnormalities. Moreover, while the T2 weighted images are the most important to evaluate the tumor itself and its relationship with the rectal wall and mesorectal fat, the post-gadolinium images may be helpful in some select cases. In addition, diffusion weighting imaging (DWI) has increasingly been incorporated into these protocols, and can serve as a means for accentuating the primary tumor and locoregional lymph nodes. While DWI and post-gadolinium images are not absolutely critical for evaluation of the primary tumor, most rectal cancers will enhance avidly and demonstrate restricted diffusion (3,6).

Typically, the rectum will be 'cleansed' prior to the study using a standard preparation of sodium bisphosphonate or a sodium phosphate enema, in order to avoid fecal material interfering with study interpretation. Subsequently, many practices will administer a small volume (usually 60 cc) of a rectal contrast agent, which can either be ultrasound gel (a 'positive' contrast agent that is T2 hyperintense) or a mixture of barium sulfate and ferumoxsil (a 'negative' contrast agent that is T2 hypointense). These agents can help accentuate small or polyploid tumors that might be difficult to identify without adequate rectal distension, particularly in tumors that are higher in the rectum. Some, but not all, practices utilize a bowel paralytic such as glucagon, which can reduce artifacts related to bowel motion (3,6). The utilization of an endorectal coil has increasingly decreased, particularly as positioning of the coil can be problematic in higher rectal tumors, as well as those lesions that cause significant narrowing of the rectum, and moreover, it places limits on the field of view that may hinder complete assessment of a tumor's involvement of the mesorectal fascia and slightly more distant mesorectal lymph nodes (7). While the use of an endorectal coil was originally advocated in the belief that it offered improved image quality and signal to noise ratio (SNR), there is very little evidence that the endorectal coil offers any substantial benefit over a standard phased array coil in terms of diagnostic quality.

T-stage and local tumor extension

A T1 tumor extends through the muscularis mucosa and into the submucosa, while a T2 tumor extends through the submucosa into the muscularis propria. In most cases, these two T-stages are treated equivalently, without the addition of preoperative chemotherapy or radiation, and distinguishing T1 and T2 tumors is not possible on MRI with a high degree of accuracy given that the submucosa and muscularis propria of the rectal wall cannot be consistently differentiated on MRI (8). However, T3 tumors (which extend beyond the muscularis propria) have been shown to have better outcomes (with a lesser risk of local recurrence) when treated with preoperative chemoradiation and these lesions can be distinguished from

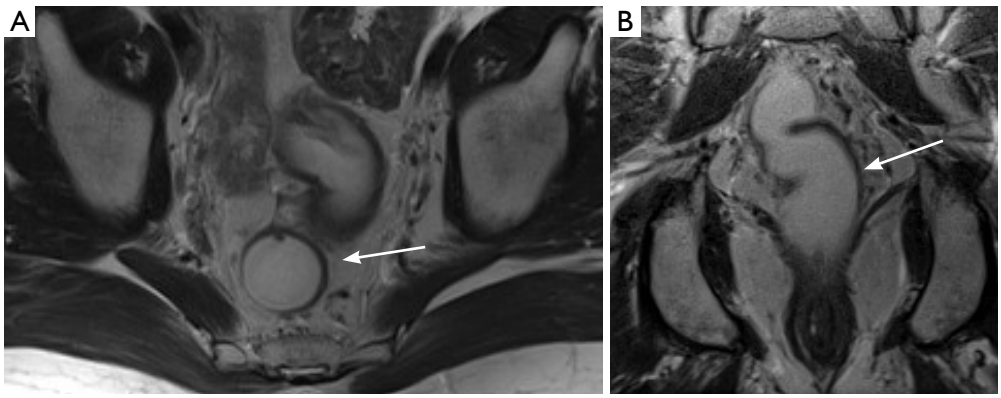

Figure 1 Normal appearance of the rectum on T2 weighted images. In both images, there is a clearly defined, T2 hypointense line (arrow) around the margins of the rectum, representing the intact muscularis propria.

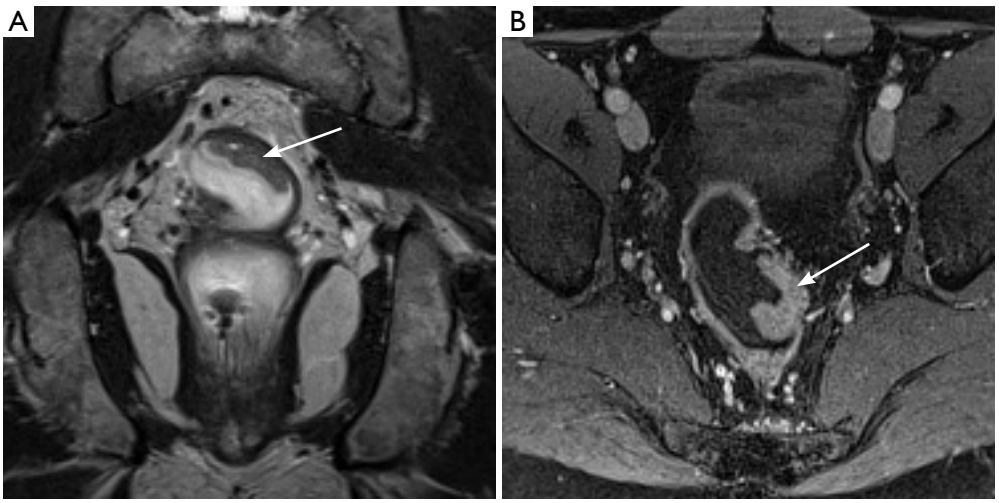

Figure 2 Example of a T2N0 rectal cancer. Coronal (A) T2 weighted image demonstrates a small polyploid mass (arrow) arising from the wall of the rectum. Importantly, the overlying hypointense line demarcating the muscularis propria remains intact, suggesting this is not a T3 lesion. Axial post-gadolinium image (B) nicely demarcates the mass (arrow), although evaluating extension through the muscularis is not possible on this sequence.

T1 and T2 tumors on MRI. T4 tumors are characterized by their spread into the visceral peritoneum, adjacent organs, or the levator musculature (3,6). On MRI, the three layers of the rectal wall are usually clearly discernible on T2-weighted images, with the mucosa and submucosa appearing relatively hyperintense, the muscularis appearing relatively hypointense in the middle of the wall, and a layer of hyperintense perirectal fat on the outside of the wall. Careful evaluation of the T2 hypointense muscularis throughout the areas abutting the rectal cancer is critical, and this thin hypointense line should be intact and clearly visible throughout the rectum for a tumor to be described as a T1 or T2 lesion. A tumor that has breached the T2 hypointense layer of the rectal wall (i.e., the muscularis is not clearly visualized adjacent to the tumor) can be considered to be at least a T3 tumor, necessitating preoperative chemoradiation (*Figures 1-4*) (3,6).

Once a tumor is characterized as either a T1/T2 or T3 lesion, the extent of involvement of the surrounding mesorectum and the adjacent pelvic structures can also have an important impact on patient prognosis. T3 tumors can be further subdivided into T3a (<5 mm extension beyond the muscularis) and T3b (>5 mm extension beyond the muscularis), and MRI has been shown to be relatively accurate in distinguishing these small differences in involvement. Such a distinction between T3a and T3b

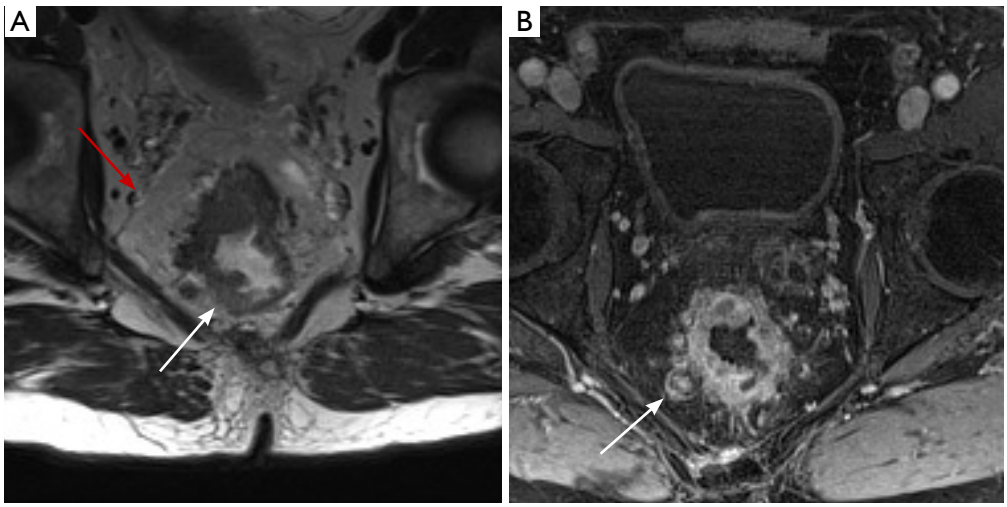

Figure 3 Axial high-resolution T2 weighted image (A) demonstrates circumferential thickening (white arrow) around the entirety of the rectum, in keeping with the patient's malignancy. In this case, the T2 hypointense muscularis is absent underlying the mass, suggesting this represents a T3 malignancy. Red arrow illustrates the intact mesorectal fascia or circumferential resection margin (CRM). Axial post-gadolinium axial image (B) demonstrates a heterogeneously enhancing malignant lymph node (arrow) in the 7 o'clock position.

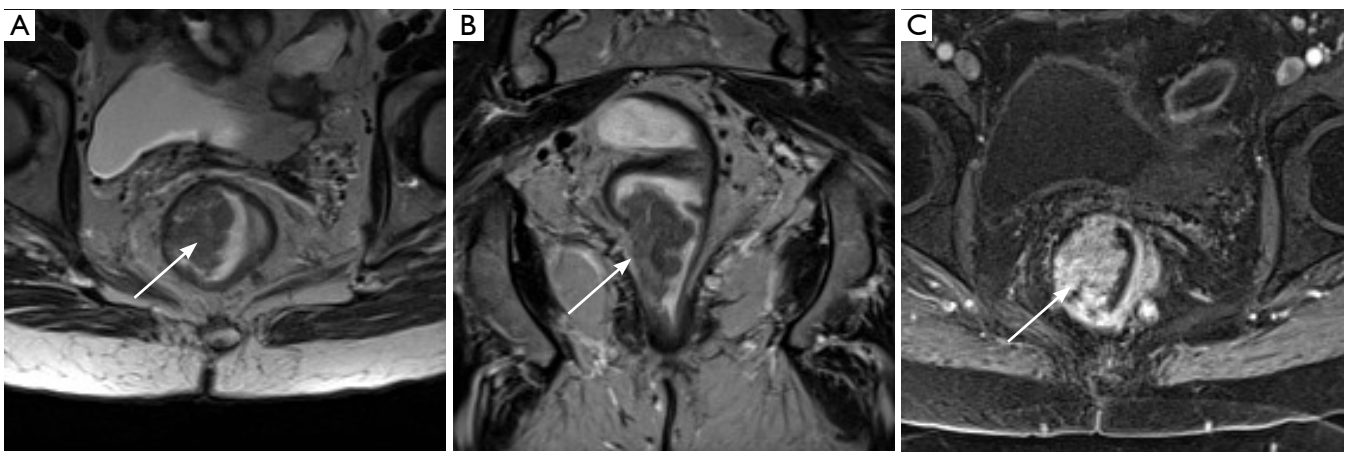

Figure 4 Axial (A) and coronal (B) T2 weighted images demonstrate a polyploid mass (arrow) arising from the right lateral aspect of the rectum, with complete loss of the underlying T2 hypointense muscularis (best visualized on the coronal image), in keeping with a T3 lesion. The mass (arrow) (C) demonstrates avid enhancement on the post-gadolinium image.

tumors may be of clinical importance, as >5 mm extension into the mesorectum has been found to be associated with a significantly lower 5-year survival rate (54% *vs.* 85%) (9). Just as important as the tumor's T-stage, however, is the proximity of the tumor to the margins of the mesorectal fascia (also described as the 'circumferential resection margin' or 'CRM'), as tumors that are 1 mm or less from the mesorectal fascia are at substantially higher risk of local recurrence (*Figure 5*) (8). A tumor's relationship to the fascia is relatively easy to perceive on MRI, but is not usually possible to delineate with endoscopic ultrasound (EUS). Finally, particularly for advanced tumors, MRI offers an accurate means of assessing involvement of adjacent pelvic organs (including the prostate, seminal vesicles, uterus, vagina, etc.), the sacrum, the anal sphincters, the pelvic sidewalls, and adjacent vasculature (*Figure 6*) (3,6).

Locoregional lymph node staging

While the superior soft tissue resolution of MRI does facilitate the identification of local lymph nodes (both in the

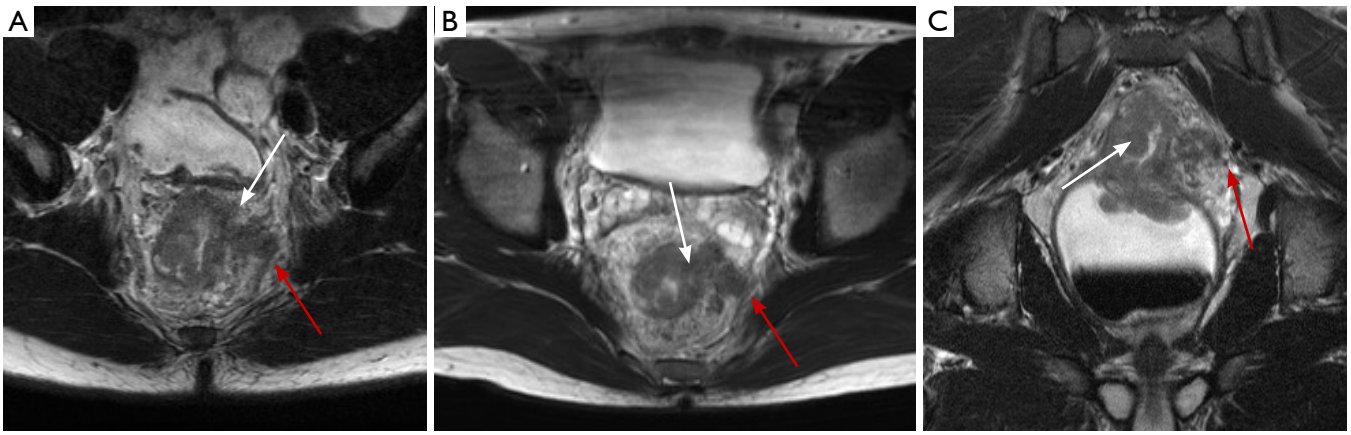

Figure 5 Axial (A,B) and coronal (C) T2 weighted images demonstrate a rectal mass (white arrows) extending through the rectal wall at the 3 o'clock position into the mesorectal fat. In this case, the mass involves the CRM at this position (red arrow).

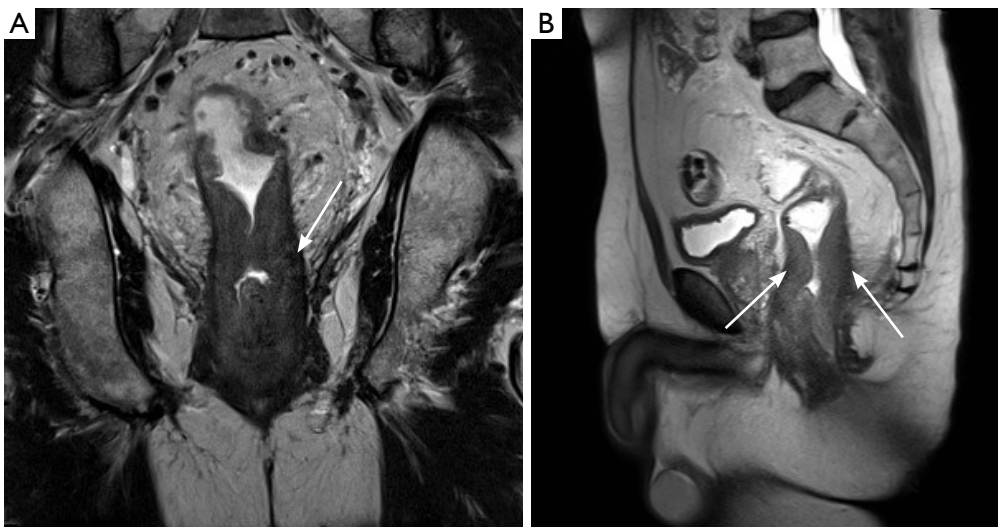

Figure 6 T4 low rectal cancer (arrows) with involvement of both the internal and external sphincters illustrated on coronal (A) and sagittal (B) T2 weighted images.

mesorectum and the pelvis), the ability to discern a benign from a malignant lymph node is still partially based upon size criteria, inherently limiting sensitivity and specificity. The most commonly used size criteria, particularly in the mesorectum, is 5 mm, which provides a sensitivity of only 68% and a specificity of only 78%, as a sizeable number of ultimately metastatic nodes at histopathology measure under 5 mm in size. Morphologic data, including irregular lymph node margins and abnormal signal or enhancement may also be useful ancillary features. The presence of suspicious nodes is important for treatment planning, as mesorectal lymph nodes (which are typically resected with the surgical excision) close to the mesorectal fascia may necessitate wider surgical margins at that site, while lymph nodes outside of the mesorectum (which are not usually resected with the surgical specimen) may necessitate wider radiation, an extended surgical resection, or even upstaging to M1 disease (lymph nodes in the external iliac chains, obdurator chains, or the retroperitoneum) (3,6).

Accuracy of MRI for local staging

There is little doubt that MRI is an accurate modality for establishing the T-stage of a tumor and delineating its relationship with the mesorectal fascia (CRM). A meta-analysis by Al-Sukhni *et al.* in 2012 (10) encompassing 21 different studies found excellent

sensitivities and specificities for establishing involvement of the CRM (up to 77% and 94% respectively), with a slightly lower performance for determining T-stage (87% and 75% respectively). The excellent performance of MRI in evaluating CRM involvement has been consistent across multiple studies in the literature, including a study by the MERCURY study group that found 92% specificity in predicting a negative surgical margin (11-13). However, as one would expect given the limitations of any anatomic imaging modality in evaluating lymph nodes, sensitivities and specificities for lymph node involvement in the study by Al-Sukhni *et al.* were only 77% and 71% respectively (10). While some had hoped that the inclusion of DWI into imaging protocols might help distinguish benign from malignant lymph nodes, this has not turned out to be the case: Metastatic lymph nodes do demonstrate lower mean ADC values, but ADC values have not proven particularly sensitive or specific for metastatic lymphadenopathy (14,15).

When compared to EUS, another modality commonly utilized for local staging, there is little doubt that EUS is superior in distinguishing T0, T1, and T2 tumors, a distinction that is not possible on MRI, and that may be clinically important in a small group of patients who might undergo local resection (T0 or T1 tumor) rather than total mesorectal excision (with a T2 tumor). In general, both modalities are probably relatively similar in their ability to distinguish T1 or T2 tumors from T3 tumors, and both modalities have similar limitations in distinguishing metastatic from benign lymph nodes in the mesorectum (although EUS can likely identify more lymph nodes than MRI given its spatial resolution). MRI can clearly better identify lymph nodes distant from the tumor (including the upper rectum), and the ability to evaluate CRM involvement is clearly an advantage of MRI (8).

Distant staging

In most cases, MDCT represents the best primary option for distant staging of rectal cancer, particularly given the propensity for tumors to metastasize to the lungs (where MRI is highly limited). Moreover, even with regards to evaluation of the liver (usually considered the greatest strength of MRI), in the vast majority of cases the routine preoperative addition of MRI to MDCT is likely to be of little benefit, as a study by Wiggans *et al.* found that the addition of MRI did not make a significant difference in patients with colorectal cancer to lesion detection, recurrence rates, or patient survival (16).

Nevertheless, the primary role of MRI in distant staging is as a trouble-shooting modality when confronted with an indeterminate lesion on MDCT, particularly in the liver. It is not at all uncommon to be confronted with a 'too-small-to characterize' lesion on MDCT measuring under 1 cm in size, which cannot be definitively characterized as either benign (i.e., cyst or hemangiomas) or malignant (i.e., metastasis) (17). Given the superior soft tissue resolution of MRI, as well as the ability to use several imaging sequences in conjunction to arrive at a diagnosis, the specificity of MRI for small liver lesions is superior to MDCT (18). In most cases, metastases will be T1 hypointense and T2 hyperintense (although lower in signal compared to cysts or hemangiomas) and will demonstrate peripheral enhancement. Moreover, the increasing utilization of diffusion weighted images in liver protocols offers another means of both identifying lesions which might not be conspicuous on either CT or standard MRI pulse sequences, as well as the risk stratification of liver lesions (as liver metastases will tend to have lower ADC values) (19,20).

Multidetector computed tomography (MDCT)

Technique

In cases with a known primary rectal malignancy, most institutions employ a single-phase technique, with the acquisition of venous phase images at roughly 60-70 s after the rapid injection of intravenous contrast (3-5 cc/s). In some instances, when seeking to better define subtle abnormal enhancement or delineate a subtle bowel lesion, the incorporation of arterial phase images may have some value in certain select cases (typically at 25-30 s after the injection of IV contrast). Particularly in those cases when the primary tumor has not yet been resected, and there is the intention to evaluate local tumor extension and mesorectal lymphadenopathy, neutral contrast agents (such as VoLumen) are utilized to distend the bowel without creating unnecessary streak or beam-hardening artifacts. Accordingly, positive oral contrast is usually avoided in these cases, as the dense contrast material may obscure subtle abnormalities in the adjacent bowel wall, and streak artifact may preclude accurate identification of small mesorectal lymph nodes (17,21). Given that MDCT is almost never utilized for local tumor staging, rectal contrast administration is not a common component of these imaging protocols, and no attempt is usually made to

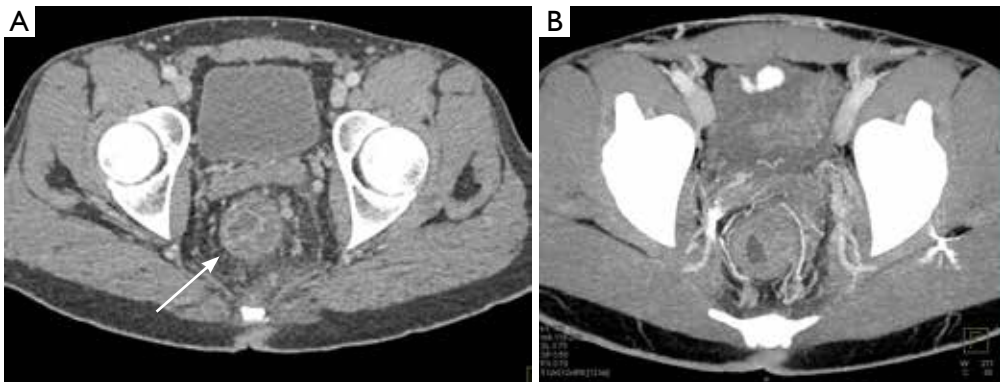

Figure 7 Rectal cancer on MDCT. Axial (A) contrast-enhanced and axial volume rendered (B) images demonstrate severe circumferential wall thickening of the rectum, with neovascularity nicely illustrated on the volume rendered 3-D image. While there is stranding and edema in the mesorectal fat, it is not possible to distinguish tumor invasion into the mesorectum from edema and inflammation. MDCT, multidetector computed tomography.

distend the rectum with contrast material.

The latest generation of MDCT scanners allows the acquisition of thin-section isotropic images, with identical resolutions in the x, y, and z-axes, at 0.5-0.75 mm collimation. These images are reconstructed to 3 mm for routine axial image review, as well as to 0.75 mm for the further generation of multiplanar reformations (coronal and sagittal) and 3-D images. The 3-D reconstructions typically include maximum intensity projection (MIP) images, which highlight the highest attenuation voxels in a dataset and project them into a 2-dimensional (2-D) representation, and volume rendered (VR) images, which utilize a complex computer algorithm to assign colors and transparencies to each voxel in a study based on its attenuation and relationship to other nearby voxels, thus creating a 3-D representation of the data set. These two 3-D techniques can be of great value in allowing the identification of lesions that might otherwise not be visualized on the standard 2-D images, as well as potentially highlight lesion features that might allow a more specific diagnosis (17,21-24).

Local staging

The MDCT appearance of rectal tumors can vary, including circumferential wall thickening, focal mural wall thickening, or a discrete polyploid mass (*Figure* 7). The conspicuity of these tumors can vary significantly depending on rectal distension, and the degree of enhancement can also vary widely. Even with the last generation of MDCT scanners, which have offered dramatic improvements in both spatial and temporal resolution compared to prior generations of technology, the layers of the rectal wall cannot be clearly differentiated in any phase of imaging (whether arterial, venous, or delayed). As such, like MRI, it is impossible to differentiate T0, T1, or T2 tumors. However, the mesorectal fat surrounding a tumor can be clearly visualized on CT, and in those cases where the tumor is seen to directly extend into the perirectal fat, a T3 tumor can be diagnosed. However, this is often confounded by the fact that perirectal fat stranding or induration secondary to rectal inflammation or peritumoral fibrosis cannot be definitively differentiated from tumor extension. Unfortunately, diagnosis of T4 tumors can be difficult in some cases as a result of MDCT's general lack of soft tissue resolution in the pelvis, and it can be quite difficult in the more subtle cases to clearly delineate tumoral involvement of adjacent organs, the pelvic sidewalls, or the adjacent vasculature. Diagnosis in these cases is contingent on loss of fat planes between a tumor and the adjacent organ or structure (*Figures 8*,*9*).

Unfortunately, despite multiple studies over the last 15 years seeking to establish MDCT as a tool for local rectal cancer staging, the results have been mixed (1). In a study by Juchems *et al.* in 2009 MDCT was unable to correctly differentiate lesions requiring neoadjuvant therapy from those lesions that could directly undergo surgical resection (25). Another study by Vliegen *et al.* in 2007 found that MDCT had a relatively poor accuracy in determining tumor involvement of the mesorectal fascia (26). However, in a study by Kanamoto *et al.* in 2007 the sensitivity/specificity for T1 and T2 tumors was 93.9%/94.3%, while the sensitivity/specificity for T3 tumors was 93.8%/94.3%,

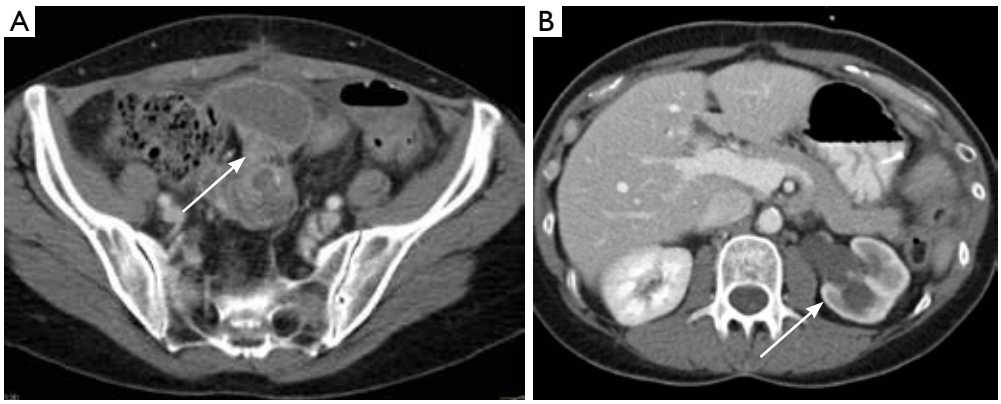

Figure 8 T4 rectal cancer on MDCT. In this case, a high rectal cancer (arrow in A) directly invades the bladder, resulting in severe left-sided hydronephrosis (arrow in B). The loss of fat plane between the bladder and rectum, as well as an appearance suggesting direct invasion, allow the diagnosis of a T4 tumor. MDCT, multidetector computed tomography.

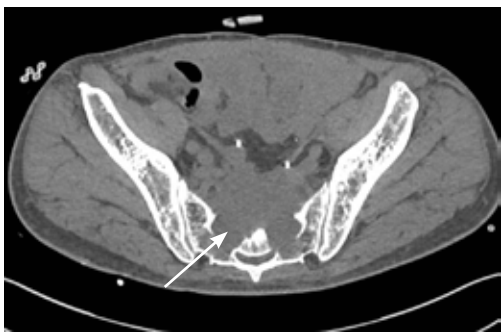

Figure 9 T4 rectal cancer with destruction of the sacrum on MDCT. A large bulky mass directly invades, and destroys, the adjacent sacrum. MDCT, multidetector computed tomography.

while another study by Taylor *et al.* in 2007 found that MDCT and MRI were relatively similar in their accuracies for CRM involvement (27,28). Overall, while individual studies dating back over several years have shown variable results, with some studies demonstrating T-staging and CRM involvement accuracies that are acceptable, a large meta-analysis by Kwok *et al.* examining close to 500 patients found that MDCT had a sensitivity of only 78% for extension of tumor through the rectal wall (with an accuracy of only 73%), as well as a sensitivity and specificity for mesorectal lymph node metastasis of only 52% and 78% respectively (29-31). Overall, there is little doubt that MDCT should not be utilized as a 1st line modality for the local staging of rectal cancer, particularly with regard to T-staging and assessment of the CRM (32). However, in those cases with clear tumor extension outside the rectum, the radiologist should not hesitate to make the diagnosis of a T3 or T4 tumor, even given the limitations of MDCT.

Distant staging

The American College of Radiology recommends that all patients with colorectal cancer undergo a preoperative staging MDCT not only because of its proven efficacy in the identification of metastatic disease, but also because of its ability to identify complications that might alter a patient's management (perforation, obstruction, abscess, pulmonary embolus, etc.) (2).

The most common site of distant metastases for colorectal cancer patients as a whole is the liver. These metastatic lesions tend to be most conspicuous on venous phase images, and will typically appear as hypoenhancing solid nodules that are easily juxtaposed against the avidly enhancing surrounding liver parenchyma (*Figure 10*). In some cases, the arterial phase images may be of benefit, as small liver metastases may demonstrate a rim of surrounding hyperemia, prominent peripheral enhancement or a surrounding perfusion abnormality that might increase lesion conspicuity. There is a wealth of data in the literature supporting the efficacy of MDCT in identifying colorectal cancer liver metastases: The overall sensitivity of MDCT for liver metastases is very good, with sensitivities ranging from 77-94% (33-35). Particularly with larger lesions (i.e., lesions measuring over 1 cm), MDCT is relatively specific as well, as most lesions measuring over 1 cm in size can be reliably differentiated from benign liver lesions (such as cysts or hemangiomas). However, while MDCT

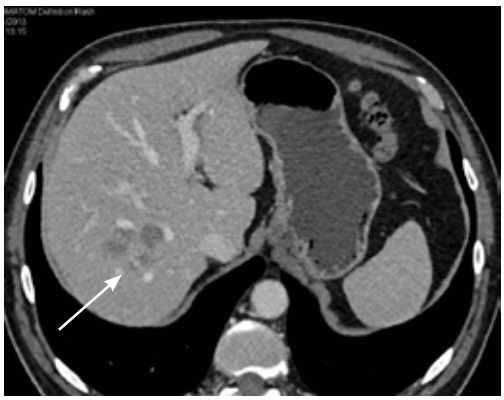

Figure 10 Typical MDCT appearance of colon cancer metastases to the liver. Axial contrast-enhanced MDCT image demonstrates small, ill-defined hypodense lesions (arrow) in the right hepatic lobe. MDCT, multidetector computed tomography.

is excellent in identifying larger metastases, it struggles with smaller lesions measuring under 1 cm in size, with reported sensitivities dropping to as low as 41.9% (18). The specificity of MDCT is also suboptimal for lesions under 1 cm, as it can be difficult to differentiate a tiny cyst or hemangioma from an early liver metastasis with confidence. Unfortunately, this can be quite problematic, as these small, nonspecific hypodensities measuring <1 cm (also known as 'too small to characterize' hypodensities) are very common, perhaps present in as many as 17% of all patients (36). Nevertheless, in the vast majority of cases, even in those patients with a known underlying malignancy, these small hypodensities in the liver are overwhelmingly likely to be benign (~90%), and can be safely followed over time. As a result, the relative lack of specificity of MDCT for smaller lesion is not clinically important in the vast majority of cases. It should be noted that many of these studies judging the efficacy of MDCT in identifying and characterizing liver metastases were performed on older generation scanners with inferior spatial and temporal resolutions to the last generation of technology. Accordingly, it is quite likely that these studies underestimate the efficacy of MDCT, which is likely to be substantially higher than the numbers reported in these studies.

Evaluation of lung metastases is also an important component of MDCT distant staging, and it is important that a chest CT be included when a patient undergoes their initial staging examination. In a study by Kirke *et al.*, 17.9% of patients with rectal cancer had evidence of at least one pulmonary metastasis on MDCT, with an increasing risk of pulmonary metastasis with rising tumor grade (37). Just as importantly, rectal cancers seem more likely than other colon cancers to present with pulmonary metastases without liver metastases, likely reflecting the unique systemic venous drainage of the rectum compared to the remainder of the colon (2). Accordingly, the ACR guidelines recommend that a patient's initial staging MDCT include images through the chest (2).

Unfortunately, as with MRI, MDCT has significant limitations in establishing a patient's nodal status, largely because the diagnosis of a malignant lymph node is contingent on enlargement and size criteria. This is particularly a problem when evaluating mesorectal lymph nodes, where 95% of all malignant lymph nodes measure under 5 mm, and 50% of all malignant lymph nodes measure under 3 mm, making any size cut-off inaccurate (38). Although at least one study has suggested utilizing a size cut-off of 4.5 mm in the mesorectum, such a cut-off would clearly miss a sizeable number of positive lymph nodes (38). Not surprisingly, a study by Ju *et al.* found that MDCT had an accuracy of only 61.5% when evaluating perirectal lymph nodes (39).

Positron emission tomography (PET)

Technique

PET is a nuclear medicine examination utilizing ^{18}F-fluoro-2-deoxy-D-glucose (FDG) as a primary tracer. This tracer, which acts glucose analog in the body, is transported into cells, phosphorylated, and subsequently accumulated, without entering the glycolytic cycle. Accordingly, given that many tumors demonstrate increased metabolism of glucose, FDG-PET utilizes the degree of FDG uptake as a surrogate measure of a tumor's metabolic activity, and this uptake can be assessed both qualitatively (via visual examination of the degree of uptake of a tumor relative to other tissues) and quantitatively (via a SUV value). Not only is FDG taken up by tumors, but also there is also some degree of physiologic uptake by normal tissues and organs, including the bowel, renal collecting systems, muscle, fat, and brain. This places great importance on proper patient preparation prior to a study, as a patient's blood glucose level, activity levels, ambient temperature, medications (particularly G-CSF), and food ingestion can all have a dramatic impact on the degree of uptake of FDG by not only by the tumor itself, but normal physiologic uptake as well. While PET was traditionally performed as a stand-

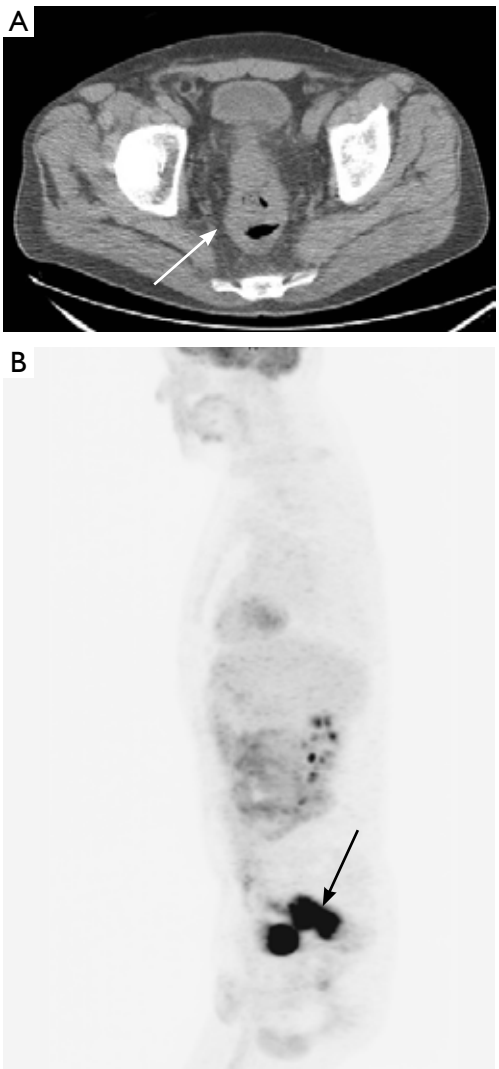

Figure 11 Axial non-contrast, non-diagnostic CT image (A) acquired as part of a PET-CT examination demonstrates severe mass-like thickening (arrow) of the rectum, corresponding to the patient's known rectal cancer. PET image (B) demonstrates marked FDG uptake associated with the mass (arrow). Notably, the spatial resolution of PET does not allow local T staging of the lesion.

alone examination, these studies are now almost always performed in conjunction with a CT (in dedicated PET-CT scanners), with acquisition of either a non-diagnostic non-contrast CT intended only for accurate localization of lesions or abnormalities seen on the PET portion of the study, or alternatively, a dedicated diagnostic quality intravenous contrast-enhanced CT meant to both serve both as a localizer for abnormalities on the PET, as well as a stand-alone diagnostic-quality MDCT examination (40,41).

Local staging

PET has a relatively low spatial resolution of only 5 mm, and as a result, is highly limited in its ability to locally stage tumors (*Figure 11*). Specifically, T-staging is not possible with PET-CT, as it has neither the anatomic detail (in terms of the layers of the rectal wall) or the spatial resolution to accurately judge the degree to which a tumor extends through the rectal wall (42). Moreover, PET is not particularly useful for evaluating locoregional lymph nodes in the mesorectum, as many of these perirectal or mesorectal lymph nodes measure 5 mm or less (below the resolution of PET), and moreover, 'blooming' (i.e., significant radiotracer uptake in a lesion artifactually appearing to extend into the adjacent soft tissues) from the primary lesion in the rectum can obscure uptake in small mesorectal lymph nodes (42). Nevertheless, while PET may not be of value in traditional TNM staging, it may have some value in terms of establishing a tumor's ultimate prognosis based on examinations performed before and during a patient's preoperative chemoradiation, although the data is certainly not conclusive. In a study by Lee *et al.*, a formula utilizing the total lesion glycolysis (TLG) (a PET parameter) of the primary tumor was found to be predictive of a patient's survival after neoadjuvant chemoradiation, a finding also confirmed elsewhere (43-47). Similarly, a meta-analysis by de Geus-Oei *et al.* suggested that PET-CT performed before and during a patient's chemoradiation regimen was able to predict which patients would respond to the treatment (48). In addition, as some groups have begun to advocate for a "watch and wait" approach after chemoradiation for rectal cancer, choosing to defer surgery in those patients who have a clinical complete response (cCR) based on imaging, it is conceivable that pre- and post-therapy PET might offer a better correlation with "true pathologic response" compared to digital rectal examination, sigmoidoscopy, or other imaging studies (CT, MRI), although this will certainly require far more rigorous study if this treatment algorithm becomes more widely utilized (49).

Distant staging

PET-CT serves as a very important modality in the distant staging of patients with colorectal cancer, potentially identifying 30% more distant metastases compared to MDCT (*Figure 12*) (42). In a study by Llamas-Elvira *et al.* PET showed an excellent diagnostic accuracy of 92%

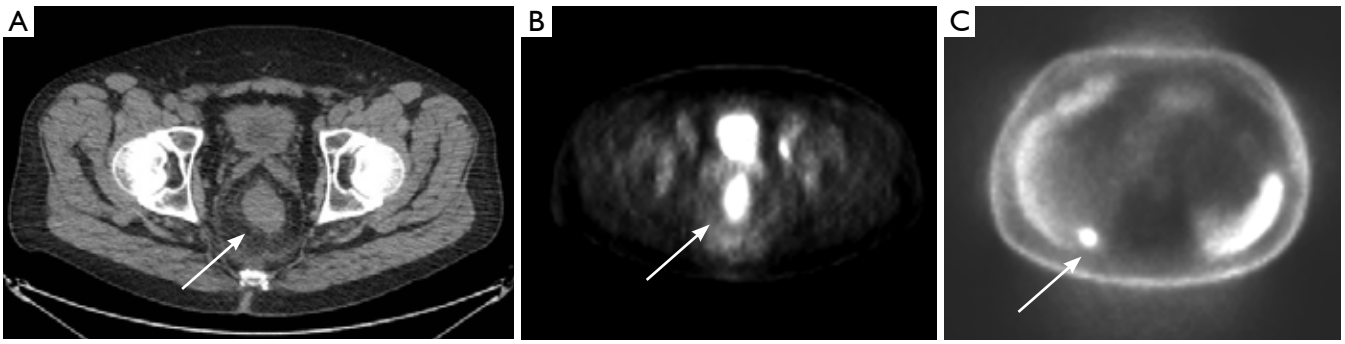

Figure 12 Axial non-contrast, non-diagnostic CT image (A) demonstrates mass-like thickening (arrow) of the rectum, corresponding to the patient's known rectal cancer. PET image (B) at the same level demonstrates marked FDG uptake associated with the mass. PET image (C) though the liver demonstrates an occult metastasis (arrow), which was not identifiable on the patient's formal contrast-enhanced MDCT. MDCT, multidetector computed tomography.

(as opposed to 87% for MDCT), changed the patient's stage in 13.5% of cases, identified previously unknown disease in 19.2% of cases, changed the patient's planned surgery in 11.5% of cases, and changed the patient's therapy in 17.8% of cases (50). Another study by Abdel-Nabi *et al.* found PET-CT to be superior to MDCT in identifying liver metastases (51), while a study by Gearhart *et al.* found that PET-CT upstaged 50% of patients, downstaged 21% of patients, and changed the patient's treatment plan in 27% of patients (52). This study noted that PET-CT was particularly likely to identify 'discordant' findings (i.e., findings not identified on MDCT) in patients with low rectal cancers due to the propensity of this group of lesions to metastasize to local lymph nodes in the pelvis (particularly nodes in the inguinal, femoral, or iliac chains), as PET-CT identified metastatic lymphadenopathy in 13.5% of patients in this study which were not diagnosed on MDCT (52).

Conclusions

MRI, MDCT, and PET are complementary imaging modalities in the preoperative staging of patients with rectal cancer, and each offers their own individual strengths and weaknesses. MRI is clearly the best available radiologic modality for the local staging of patients with rectal cancer, and has the potential to play an important role in accurately distinguishing which patients should receive preoperative chemoradiation prior to total mesorectal excision. Alternatively, while MDCT and PET are both quite limited in local staging, both should be considered primary modalities when performing preoperative distant staging. In particular, every patient with a newly diagnosed rectal cancer should undergo a preoperative staging MDCT which includes the chest, abdomen, and pelvis, as MDCT can not only accurately stage distant metastatic disease, but it can also identify acute complications which may change a patient's treatment algorithm. Alternatively, PET may offer a valuable diagnostic adjunct for identifying distant metastatic disease, changing a patient's management in a sizeable percentage of cases.

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Footnote

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References

1. Samee A, Selvasekar CR. Current trends in staging rectal cancer. World J Gastroenterol 2011;17:828-834.
2. Dewhurst C, Rosen MP, Blake MA, et al. ACR Appropriateness Criteria pretreatment staging of colorectal cancer. J Am Coll Radiol 2012;9:775-781.
3. Dewhurst CE, Mortele KJ. Magnetic resonance imaging of rectal cancer. Radiol Clin North Am 2013;51:121-131.
4. McKeown E, Nelson DW, Johnson EK, et al. Current approaches and challenges for monitoring treatment response in colon and rectal cancer. J Cancer 2014;5:31-43.
5. Glimelius B, Tiret E, Cervantes A, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis,

treatment and follow-up. Ann Oncol 2013;24 Suppl 6:vi81-vi88.
6. Kaur H, Choi H, You YN, et al. MR imaging for preoperative evaluation of primary rectal cancer: practical considerations. Radiographics 2012;32:389-409.
7. Gowdra Halappa V, Corona Villalobos CP, Bonekamp S, et al. Rectal imaging: part 1, High-resolution MRI of carcinoma of the rectum at 3 T. AJR Am J Roentgenol 2012;199:W35-42.
8. Samdani T, Garcia-Aguilar J. Imaging in rectal cancer: magnetic resonance imaging versus endorectal ultrasonography. Surg Oncol Clin N Am 2014;23:59-77.
9. Merkel S, Mansmann U, Siassi M, et al. The prognostic inhomogeneity in pT3 rectal carcinomas. Int J Colorectal Dis 2001;16:298-304.
10. Al-Sukhni E, Milot L, Fruitman M, et al. Diagnostic accuracy of MRI for assessment of T category, lymph node metastases, and circumferential resection margin involvement in patients with rectal cancer: a systematic review and meta-analysis. Ann Surg Oncol 2012;19:2212-2223.
11. Videhult P, Smedh K, Lundin P, et al. Magnetic resonance imaging for preoperative staging of rectal cancer in clinical practice: high accuracy in predicting circumferential margin with clinical benefit. Colorectal Dis 2007;9:412-419.
12. Purkayastha S, Tekkis PP, Athanasiou T, et al. Diagnostic precision of magnetic resonance imaging for preoperative prediction of the circumferential margin involvement in patients with rectal cancer. Colorectal Dis 2007;9:402-411.
13. MERCURY Study Group. Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. BMJ 2006;333:779.
14. Cho EY, Kim SH, Yoon JH, et al. Apparent diffusion coefficient for discriminating metastatic from non-metastatic lymph nodes in primary rectal cancer. Eur J Radiol 2013;82:e662-e668.
15. Heijnen LA, Lambregts DM, Mondal D, et al. Diffusion-weighted MR imaging in primary rectal cancer staging demonstrates but does not characterise lymph nodes. Eur Radiol 2013;23:3354-3360.
16. Wiggans MG, Shahtahmassebi G, Aroori S, et al. Assessment of the value of MRI scan in addition to CT in the pre-operative staging of colorectal liver metastases. J Gastrointest Cancer 2014;45:146-153.
17. Raman SP, Horton KM, Fishman EK. Multimodality imaging of pancreatic cancer-computed tomography, magnetic resonance imaging, and positron emission tomography. Cancer J 2012;18:511-522.
18. Berger-Kulemann V, Schima W, Baroud S, et al. Gadoxetic acid-enhanced 3.0 T MR imaging versus multidetector-row CT in the detection of colorectal metastases in fatty liver using intraoperative ultrasound and histopathology as a standard of reference. Eur J Surg Oncol 2012;38:670-676.
19. Holzapfel K, Reiser-Erkan C, Fingerle AA, et al. Comparison of diffusion-weighted MR imaging and multidetector-row CT in the detection of liver metastases in patients operated for pancreatic cancer. Abdom Imaging 2011;36:179-184.
20. Malayeri AA, El Khouli RH, Zaheer A, et al. Principles and applications of diffusion-weighted imaging in cancer detection, staging, and treatment follow-up. Radiographics 2011;31:1773-1791.
21. Raman SP, Horton KM, Fishman EK. MDCT and CT angiography evaluation of rectal bleeding: the role of volume visualization. AJR Am J Roentgenol 2013;201:589-597.
22. Raman SP, Horton KM, Fishman EK. Transitional cell carcinoma of the upper urinary tract: optimizing image interpretation with 3D reconstructions. Abdom Imaging 2012;37:1129-1140.
23. Raman SP, Horton KM, Fishman EK. MDCT evaluation of ureteral tumors: advantages of 3D reconstruction and volume visualization. AJR Am J Roentgenol 2013;201:1239-1247.
24. Raman SP, Horton KM, Fishman EK. Computed tomography of Crohn's disease: The role of three dimensional technique. World J Radiol 2013;5:193-201.
25. Juchems MS, Ernst AS, Kornmann M, et al. Value of MDCT in preoperative local staging of rectal cancer for predicting the necessity for neoadjuvant radiochemotherapy. Rofo 2009;181:1168-1174.
26. Vliegen R, Dresen R, Beets G, et al. The accuracy of Multi-detector row CT for the assessment of tumor invasion of the mesorectal fascia in primary rectal cancer. Abdom Imaging 2008;33:604-610.
27. Kanamoto T, Matsuki M, Okuda J, et al. Preoperative evaluation of local invasion and metastatic lymph nodes of colorectal cancer and mesenteric vascular variations using multidetector-row computed tomography before laparoscopic surgery. J Comput Assist Tomogr 2007;31:831-839.
28. Taylor A, Slater A, Mapstone N, et al. Staging rectal cancer: MRI compared to MDCT. Abdom Imaging 2007;32:323-327.
29. Sinha R, Verma R, Rajesh A, et al. Diagnostic value of multidetector row CT in rectal cancer staging: comparison of multiplanar and axial images with histopathology. Clin

Radiol 2006;61:924-931.
30. Matsuoka H, Nakamura A, Masaki T, et al. Preoperative staging by multidetector-row computed tomography in patients with rectal carcinoma. Am J Surg 2002;184:131-135.
31. Kwok H, Bissett IP, Hill GL. Preoperative staging of rectal cancer. Int J Colorectal Dis 2000;15:9-20.
32. Beets-Tan RG, Beets GL, Borstlap AC, et al. Preoperative assessment of local tumor extent in advanced rectal cancer: CT or high-resolution MRI? Abdom Imaging 2000;25:533-541.
33. Larsen LP, Rosenkilde M, Christensen H, et al. Can contrast-enhanced ultrasonography replace multidetector-computed tomography in the detection of liver metastases from colorectal cancer? Eur J Radiol 2009;69:308-313.
34. Wicherts DA, de Haas RJ, van Kessel CS, et al. Incremental value of arterial and equilibrium phase compared to hepatic venous phase CT in the preoperative staging of colorectal liver metastases: an evaluation with different reference standards. Eur J Radiol 2011;77:305-311.
35. Mainenti PP, Mancini M, Mainolfi C, et al. Detection of colo-rectal liver metastases: prospective comparison of contrast enhanced US, multidetector CT, PET/CT, and 1.5 Tesla MR with extracellular and reticulo-endothelial cell specific contrast agents. Abdom Imaging 2010;35:511-521.
36. Jones EC, Chezmar JL, Nelson RC, et al. The frequency and significance of small (less than or equal to 15 mm) hepatic lesions detected by CT. AJR Am J Roentgenol 1992;158:535-539.
37. Kirke R, Rajesh A, Verma R, et al. Rectal cancer: incidence of pulmonary metastases on thoracic CT and correlation with T staging. J Comput Assist Tomogr 2007;31:569-571.
38. Perez RO, Pereira DD, Proscurshim I, et al. Lymph node size in rectal cancer following neoadjuvant chemoradiation--can we rely on radiologic nodal staging after chemoradiation? Dis Colon Rectum 2009;52:1278-1284.
39. Ju H, Xu D, Li D, et al. Comparison between endoluminal ultrasonography and spiral computerized tomography for the preoperative local staging of rectal carcinoma. Biosci Trends 2009;3:73-76.
40. Dibble EH, Karantanis D, Mercier G, et al. PET/CT of cancer patients: part 1, pancreatic neoplasms. AJR Am J Roentgenol 2012;199:952-967.
41. Shrikhande SV, Barreto SG, Goel M, et al. Multimodality imaging of pancreatic ductal adenocarcinoma: a review of the literature. HPB (Oxford) 2012;14:658-668.
42. Grassetto G, Marzola MC, Minicozzi A, et al. F-18 FDG PET/CT in rectal carcinoma: where are we now? Clin Nucl Med 2011;36:884-888.
43. Lee SJ, Kim JG, Lee SW, et al. Clinical implications of initial FDG-PET/CT in locally advanced rectal cancer treated with neoadjuvant chemoradiotherapy. Cancer Chemother Pharmacol 2013;71:1201-1207.
44. Gulec SA, Suthar RR, Barot TC, et al. The prognostic value of functional tumor volume and total lesion glycolysis in patients with colorectal cancer liver metastases undergoing 90Y selective internal radiation therapy plus chemotherapy. Eur J Nucl Med Mol Imaging 2011;38:1289-1295.
45. Grassetto G, Capirci C, Marzola MC, et al. Colorectal cancer: prognostic role of 18F-FDG-PET/CT. Abdom Imaging 2012;37:575-579.
46. Murcia Duréndez MJ, Frutos Esteban L, Luján J, et al. The value of 18F-FDG PET/CT for assessing the response to neoadjuvant therapy in locally advanced rectal cancer. Eur J Nucl Med Mol Imaging 2013;40:91-97.
47. Sun W, Xu J, Hu W, et al. The role of sequential 18(F) -FDG PET/CT in predicting tumour response after preoperative chemoradiation for rectal cancer. Colorectal Dis 2013;15:e231-e238.
48. de Geus-Oei LF, Vriens D, van Laarhoven HW, et al. Monitoring and predicting response to therapy with 18F-FDG PET in colorectal cancer: a systematic review. J Nucl Med 2009;50 Suppl 1:43S-54S.
49. Park IJ, Yu CS. Current issues in locally advanced colorectal cancer treated by preoperative chemoradiotherapy. World J Gastroenterol 2014;20:2023-2029.
50. Llamas-Elvira JM, Rodríguez-Fernández A, Gutiérrez-Sáinz J, et al. Fluorine-18 fluorodeoxyglucose PET in the preoperative staging of colorectal cancer. Eur J Nucl Med Mol Imaging 2007;34:859-867.
51. Abdel-Nabi H, Doerr RJ, Lamonica DM, et al. Staging of primary colorectal carcinomas with fluorine-18 fluorodeoxyglucose whole-body PET: correlation with histopathologic and CT findings. Radiology 1998;206:755-760.
52. Gearhart SL, Frassica D, Rosen R, et al. Improved staging with pretreatment positron emission tomography/computed tomography in low rectal cancer. Ann Surg Oncol 2006;13:397-404.

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Focusing the management of rectal cancer

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Provenance: This is a Guest Perspective commissioned by Section Editor Hongcheng Zhu, MD, PhD (Department of Radiation Oncology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China).

Comment on: Sebio A, Salazar J, Páez D, *et al*. EGFR ligands and DNA repair genes: genomic predictors of complete response after capecitabine-based chemoradiotherapy in locally advanced rectal cancer. Pharmacogenomics J 2015;15:77-83.

Abstract: Rectal cancer treatment has undergone major changes over the last 15 years with a focus on individualized care based around MRI assessment of the relationship of the tumour to the mesorectal fascia, improved surgical techniques and targeted use of pre-operative oncological therapies in patients with locally advanced disease. The recognition that some tumours responded completely to pre-operative chemoradiotherapy, and the selective use of a non-operative policy has led to a quest to further identify those patients and their tumour in whom this approach could be used, irrespective of MRI stage. With no clear patient factors identified, the tumour and its gene expression has become a target for research to identify individual single-nucleotide polymorphisms, which may indicate a response to specific treatment, or not. To date some agents have been identified and trialed, such as cetuximab, with individual tumours being assessed for response allowing directed treatment. The reviewed paper by Sebio and colleagues report a study that links polymorphisms in the DNA repair gene XRCC1 with response to neoadjuvant 5-Fluorouracil treatment in rectal cancer patients. However, genetic heterogeneity alone may not explain the variations of drug response and environmental factors may lead to epigenetic effects and therefore alter responses. Therefore whilst this study demonstrates the impact of different single nucleotide polymorphisms (SNPs), it is only one step forward, but perhaps a step in the right direction.

Keywords: Rectal cancer; genomics; tumor heterogeneity; single nucleotide polymorphisms (SNPs)

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Over the last 15 years, there has been a change in the focus of therapy for rectal cancer. Traditionally surgery was the mainstay of treatment, either with removal of the rectum and restoration of bowel continuity (anterior resection) or removal of the rectum and anus and formation of a colostomy (abdominoperineal excision). Prior to the introduction of MRI staging of rectal cancer and the planning of individualised care through the multidisciplinary team (MDT), the principle concern was the avoidance of an incomplete resection, technically an involved circumferential resection margin (CRM +ve) as this is associated with high levels of local recurrence (1-3).

The recognition that pre-operative chemoradiotherapy in selected cases and the resultant down-staging of disease through MRI-directed care has led to improvements in overall survival and a reduction in CRM +ve rates (4). However, the morbidity of surgery remains and the potential for lifelong alteration of bowel function, through low anterior resection syndrome (LARS) or a permanent colostomy persists following surgery and impairs quality of life (5).

It was the recognition of the work of Dr. Habr-Gama in Brazil and the non-operative management of rectal cancer following chemoradiotherapy that has led to a

desire to identify patients who may respond completely to chemoradiotherapy and hence avoid surgery, known as "*Watch and Wait*" (6). Rates of complete clinical response (cCR) (and radiological response) have been reported as high as 15% in selected series of advanced disease in the UK and across cancer networks, however, there is also a group of patients who undergo resection and there is no evidence of tumour remaining in the specimen—a pathological complete response (pCR) (7,8). Together these may make up 25% of tumours selected for CRT based upon MRI-stage. The challenge currently is to identify these patients, as no characteristics or biochemical markers have been identified for cCR/pCR. In many centres around the world for early stage tumours CRT is avoided if there is no evidence of a potentially involved CRM and surgery is offered. This contrasts with the Habr-Gama group who offered CRT to all low rectal tumours, and achieved higher rates of cCR. The question is who best to treat with CRT irrespective of MRI stage?

There are no current biomarkers to predict the response of patients to this highly variable treatment. An accurate method for predicting the response to CRT would therefore allow for improved treatment choice with avoidance of unnecessary side effects: patients with chemoradiation-resistant disease would be spared the morbidity of this treatment. Equally, patients with a prediction of pCR may be spared radical surgery and its complications. Individualised genomic sequencing assessing for genetic mutations that could act as predictive biomarkers to cancer treatment offers a future potential for individualised therapy. Single nucleotide polymorphisms (SNPs), which are variations of one nucleotide occurring across the genome, are the most frequently identified mutations (9). In their recent paper, Sebio *et al*. explored specific SNPs in epidermal growth factor receptor (EGFR) ligands and DNA repair genes in rectal cancer patients with the aim of identifying potential biomarkers of treatment response (10).

EGFR, which is a trans membrane tyrosine kinase receptor, has been extensively studied as a biomarker in several malignancies. Activation of EGFR leads to a cascade of cellular events that promote cell proliferation, invasion and metastatic spread. Aberrant activation of EGFR may be achieved by several mechanisms including SNPs. The work of Khambata-Ford and colleagues established that the expression levels of EGFR ligands (AREG and EREG) can be predictive for cetuximab efficacy in patients with colorectal cancer (11). Further studies were able to confirm the predictive value of the ligands in cetuximab treated patients in colorectal cancer. Yet, the role of EGFR ligands in rectal cancer under different chemotherapeutic regimens, as the authors point out, has not been studied.

Additionally, CRT exerts its effects through generating DNA damage. Therefore, genetic variants of DNA repair genes in the form of SNPs could modulate treatment response. A recent large pharmacogenetic analysis examining 66 SNPs showed that there is an association between SNPs in DNA repair genes and response to neoadjuvant CRT in patients with locally advanced rectal cancer (12). Sebio *et al*. report studies that link polymorphisms in DNA repair gene XRCC1 with response to neoadjuvant 5-Fluorouracil treatment in rectal cancer patients (10).

The best regimen for neoadjuvant treatment in rectal cancer however, is not yet fully established, due to lack of consistent differences in terms of local recurrence between different regimes (13). Whilst short course radiotherapy (SRT-5 Gy per day for 5 days) has been adopted as the standard neoadjuvant treatment in some countries, in others long-course CRT (45–50.4 Gy over 5 weeks with concomitant chemotherapy) is preferred. Other regimes have used induction chemotherapy prior to CRT, for example the expert trial and added cetuximab in follow-up arms (Expert-C) (14,15). However, DNA repair gene pathways and EGFR alterations differ depending on the treatment chosen. Additionally, literature on SNPs in EGFR ligands in the context of treatment of rectal cancer with capecitabine only, is lacking. Sebio *et al*. address this by selecting SNPs in previously unexplored ligands in patients treated with neoadjuvant capecitabine for rectal cancer, making this a novel study (10).

The authors analysed 28 known polymorphisms in 84 patients with locally advanced rectal cancer. They found an association between three SNPs and pCR after neoadjuvant CRT with capecitabine (10). The associations were tested in both uni-variate and multi-variate regression models. Two SNPs retained their significance, one located in DNA repair gene (ERCC1) and one in EGFR ligand (AREG). The identification of the rs11942466 C>A polymorphism in the AREG gene region, previously found to be correlated with outcome in metastatic CRC, is a novel finding in rectal cancer studies. Previous studies looking at SNPs in ERCC1 in rectal cancer failed to establish any associations, yet, the authors have established a significant association between RCC1 rs11615 C>T and pCR. They attribute this to the effect of the capecitabine on DNA repair pathways that differs from other chemotherapy agents used in previous studies.

There are, however, limitations to this paper. The study was under-powered to show significant differences in association and important outcomes. The short follow-up period also affected association links with recurrence rates and overall survival outcomes. The authors acknowledge these limitations. Patient related factors such as sex, age and comorbidities, may influence response to targeted therapies. Patients in the study were not stratified into different age groups and potential gender differences were not explored. These factors should be considered as important predictive biomarkers. Nevertheless, the authors succeed in shedding a light at new associations between SNPs in rectal cancer and treatment response. The SNPs identified could potentially be explored further as biomarkers of treatment response and would benefit from replication in large cohorts, or through tissue banks of rectal cancer specimens who have outcome data for recurrence and survival, particularly the pCR group and those in whom there is disease progression despite CRT.

Moreover, the molecular heterogeneity of rectal cancer is believed to be one of the factors responsible for the variability in treatment response among patients with the same stage of cancer (16). Tumour heterogeneity refers to the differences between tumours of the same type in different patients, or between cancer cells within the same tumour. Both can lead to different responses to therapy, even targeted therapy. This may explain why some tumour cells remain present in the patient after completion of cancer treatment. Therefore, single biopsy specimens of primary tumours may not represent the full genetically diverse malignant picture. Similarly, analysis techniques may not be sensitive enough to detect the lower frequency changes in tumour sub clones.

Finally, there is an increasing consensus that genetic heterogeneity alone is not enough to explain variations in drug response between different individuals. The influence of the environment and interaction of genes with environmental variables, represented by the field of epigenetics, has been the focus of research in the last decade. Epigenetic mechanisms modify gene expression independently of DNA sequence (17,18). They can be environmentally induced, tissue specific and can have similar effects to pathogenic mutations: they can silence, increase or decrease the expression of a gene. Epigenetic mechanisms currently play an important role in development, prognosis and treatment response of colorectal cancer and are becoming more prominent in rectal cancer research. With that, an emerging need to combine genetic and epigenetic data is arising.

Current selection of CRT is based upon MRI-staging, which is attempting to ask the question for the surgeon, "if I operate will I achieve a CRM negative specimen?" This is a crude tool, CRT being used in advanced stage cases or those with poor MRI-prognostic features; however, Habr-Gama has demonstrated that CRT in all low rectal tumours achieves a higher rate of cCR, yet at the expense of increased use of CRT. Therefore the improved understanding of the biology within an individual tumour within an individual patient remains the goal for treatment selection. No crude biomarkers, such as NLR ratio, CEA, age, sex, etc. have offered an accurate selection, perhaps identification of SNPs will offer the way?

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Footnote

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

References

1. Burton S, Brown G, Daniels IR, et al. MRI directed multidisciplinary team preoperative treatment strategy: the way to eliminate positive circumferential margins? Br J Cancer 2006;94:351-357.
2. MERCURY Study Group. Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. BMJ 2006;333:779.
3. Quirke P, Durdey P, Dixon MF, et al. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. Lancet 1986;2:996-999.
4. Taylor FG, Quirke P, Heald RJ, et al. Preoperative magnetic resonance imaging assessment of circumferential resection margin predicts disease-free survival and local recurrence: 5-year follow-up results of the MERCURY study. J Clin Oncol 2014;32:34-43.
5. Emmertsen KJ, Laurberg S. Low anterior resection syndrome score: development and validation of a symptom-based scoring system for bowel dysfunction after low anterior resection for rectal cancer. Ann Surg 2012;255:922-928.

6. Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg 2004;240:711-717.
7. Dalton RS, Velineni R, Osborne ME, et al. A single-centre experience of chemoradiotherapy for rectal cancer: is there potential for nonoperative management? Colorectal Dis 2012;14:567-571.
8. Renehan AG, Malcomson L, Emsley R, et al. Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. Lancet Oncol 2016;17:174-183.
9. Preskill C, Weidhaas JB. SNPs in microRNA binding sites as prognostic and predictive cancer biomarkers. Crit Rev Oncog 2013;18:327-340.
10. Sebio A, Salazar J, Páez D, et al. EGFR ligands and DNA repair genes: genomic predictors of complete response after capecitabine-based chemoradiotherapy in locally advanced rectal cancer. Pharmacogenomics J 2015;15:77-83.
11. Khambata-Ford S, Garrett CR, Meropol NJ, et al. Expression of epiregulin and amphiregulin and K-ras mutation status predict disease control in metastatic colorectal cancer patients treated with cetuximab. J Clin Oncol 2007;25:3230-3237.
12. Boige V, Vincent M, Alexandre P, et al. DPYD Genotyping to Predict Adverse Events Following Treatment With Flourouracil-Based Adjuvant Chemotherapy in Patients With Stage III Colon Cancer: A Secondary Analysis of the PETACC-8 Randomized Clinical Trial. JAMA Oncol 2016. [Epub ahead of print].
13. Biondo S, Fraccalvieri D, Golda T, et al. Update on advances and controversy in rectal cancer treatment. Tech Coloproctol 2016;20:145-152.
14. Chua YJ, Barbachano Y, Cunningham D, et al. Neoadjuvant capecitabine and oxaliplatin before chemoradiotherapy and total mesorectal excision in MRI-defined poor-risk rectal cancer: a phase 2 trial. Lancet Oncol 2010;11:241-248.
15. Dewdney A, Cunningham D, Tabernero J, et al. Multicenter randomized phase II clinical trial comparing neoadjuvant oxaliplatin, capecitabine, and preoperative radiotherapy with or without cetuximab followed by total mesorectal excision in patients with high-risk rectal cancer (EXPERT-C). J Clin Oncol 2012;30:1620-1627.
16. Bettoni F, Masotti C, Habr-Gama A, et al. Intratumoral Genetic Heterogeneity in Rectal Cancer: Are Single Biopsies representative of the entirety of the tumor? Ann Surg 2017;265:e4-e6.
17. Virani S, Bellile E, Bradford CR, et al. NDN and CD1A are novel prognostic methylation markers in patients with head and neck squamous carcinomas. BMC Cancer 2015;15:825.
18. Goel A, Boland CR. Epigenetics of colorectal cancer. Gastroenterology 2012;143:1442-1460.e1.

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Future of therapy for rectal cancer

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Abstract: Since 2004, the standard of care for patients with cT3 and/or N+ rectal cancer has been preoperative chemoradiation followed by surgery and postoperative adjuvant chemotherapy. A number of advances have occurred and are defining the future of rectal cancer therapy. Among these are short course radiation, the impact of postoperative adjuvant chemotherapy, selective radiation and selective surgery, and new chemoradiation regimens with novel agents. This review will examine these developments and assess their impact on the future therapy of rectal cancer.

Keywords: Rectal Cancer; Adjuvant therapy; chemoradiation

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Chemoradiation is the standard treatment for locally advanced, clinically resectable (T3 and/or N+) rectal cancer (1). When 5-FU is used concurrently with radiation, continuous infusion (CI) is the conventional regimen (2,3). The NSABP R-04 trial compared preoperative chemoradiation with CI 5-FU *vs.* capecitabine (with or without oxaliplatin). Compared with CI 5-FU, capecitabine had similar rates of pCR (22% *vs.* 19%), sphincter-sparing surgery (63% *vs.* 61%), and grade 3+ diarrhea (11%) (4). Hofheinz *et al.* randomized 401 patients with CI 5-FU-based chemoradiation *vs.* capecitabine-based chemoradiation. Patients who received capecitabine had equivalent pCR rates (6% *vs.* 7%) and their 5-year survival was non-inferior (76% *vs.* 66%, P=0.0004) compared with CI 5-FU (5). Therefore, CI 5-FU and capecitabine-based chemoradiation regimens are equivalent. The addition of oxaliplatin to preoperative radiation is not standard of care and the results of the randomized trials are discussed below.

Advances in clinical staging and the selection of patients for preoperative therapy

Transrectal ultrasound and high resolution MRI are the most common methods to determine T stage. Historically, ultrasound was used most commonly in North America and most European investigators have preferred high resolution MRI. The advantage of MRI is its ability to identify patients likely to have close or positive radial (circumferential) margins if they underwent initial surgery and therefore, would be better treated with preoperative therapy (6). It is gaining wider acceptance in North America.

The overall accuracy in predicting T stage is approximately 50-90% with ultrasound (7) or high resolution MRI (8) and 50-70% with CT or conventional MRI (9). Although FDG-PET may be more accurate compared with CT for identification of metastatic disease (10), its use to restage patients following preoperative chemoradiation remains controversial (11-14).

Overstaging is common, especially when there is a fibrotic thickening of the rectal wall following preoperative chemoradiation. A reasonably high level of accuracy has been observed by phased array MRI for differentiating ypT0-2 *vs.* ypT3 disease (15). Both diffusion-weighted MRI and FDG-PET have been used to monitor therapy response and to predict outcome to preoperative therapy. With FDG-PET there is a decrease in SUV on post-radiation in responders compared to non-responders, but the clinical value of this information remains unclear (16).

Identification of positive lymph nodes is more difficult. Overall, the accuracy in detecting positive pelvic lymph

Table 1 Short course radiation *vs.* long course chemoradiation: randomized trials

Trial	Polish (27,28)	TROG (29)
# Patients	316	326
Clinical stage	T3-4	T3Nany
Chemoradiation	50.4 + 5-FU/LV	50.4 Gy + CI 5-FU
Short course radiation	5 Gy ×5	5 Gy ×5
Postop chemo	Optional	4-6 cycles of 5-FU/LV
Local failure		
- Short course radiation	9%	8%
- Chemoradiation	14% (4-yr)	6% (5-yr)
Survival		
- Short rourse radiation	67%	74%
- Chemoradiation	66% (4-yr)	70% (3-yr)

LV, leucovorin; 5-FU, fluorouracil; CI, continuous infusion

nodes with the above techniques is approximately 50-75%. The accuracy of MRI is similar to CT, however, it is improved with the use of external and/or endorectal coils. Both CT and MRI can identify lymph nodes measuring >1 cm, although enlarged lymph nodes are not pathognomonic of tumor involvement. The accuracy of ultrasound for the detection of involved perirectal lymph nodes may be augmented when combined with fine needle aspiration (17). Despite these advances, the ability to accurately predict the pathologic stage following preoperative chemoradiation with MRI (18,19), ultrasound (20), FDG-PET (11-13,21) or physical exam (22) remains suboptimal.

Advances in radiation fractionation: 5 Gy ×5 *vs.* chemoradiation

Adjuvant preoperative therapy for rectal cancer is delivered by two fractionation schedules: short course radiation and long course chemoradiation. Patients selected for treatment with short course radiation included those with cT1-3 disease, whereas those selected for chemoradiation include T3 and/or N+ disease. Therefore, retrospective comparisons of trials are not feasible. There are two randomized trials which have included patients with cT3 and/or N+ disease also delivered sequential or postoperative chemotherapy, thereby allowing a more relevant comparison with chemoradiation. New trials of short course radiation have included patients with stages cT3 and/or N+ also delivered sequential or chemotherapy.

Short course radiation: standard approaches

There are 12 modern randomized trials of preoperative short course radiation (23). The only trial which mandated total mesorectal excision (TME) was the Dutch CKVO 95-04 trial. Patients with cT1-3 disease were randomized to TME alone or 25 Gy in 5 fractions followed by TME (24). With a 12-year median follow-up, 5-year local failure was higher with TME (11%); however, it was significantly decreased to 5% with preoperative radiation (25). The acute toxicity in the Dutch CKVO 95-04 trial was substantial, including 10% neurotoxicity, 29% perineal wound complications, and 12% postoperative leaks (26). In the patients who developed postoperative leaks, 80% required surgery resulting in 11% mortality. In contrast to the earlier randomized trials of short course radiation, multiple field radiation techniques were used. Whether the increases in morbidity and mortality were due to the learning curve associated with a new surgical technique, the 1 week interval between the completion of radiation and surgery, or both is not known.

Short course radiation is used in the SCRIPTS (Simply Capecitabine in Rectal cancer after Irradiation Plus TME surgery) trial from the Dutch Colorectal Group (CKTO 2003-16). The trial opened in 2007. Patients with clinical stage II (T3-T4, N0) or III (any T, N+) rectal adenocarcinoma (below the level of S1/S2 or inf. margin within 15 cm of the anal verge) received preoperative 5 Gy ×5 followed by TME. Patients are then randomized postoperatively to either capecitabine or observation. This trial tests the role of adjuvant chemotherapy after short course radiation.

Randomized trials

There are 2 randomized trials of short course radiation *vs.* chemoradiation. The Polish trial from Bujko *et al.* and the Intergroup TROG, AGITG, CSSANZ, RACS Trial reported by Ngan *et al.* (*Table 1*).

Polish trial

Bujko and colleagues randomized 316 patients with cT3 rectal cancer (27,28). All tumors were above the anorectal ring, TME was performed for distal tumors only. Postoperative chemotherapy was at the discretion of the investigator. There was no radiation quality control review.

Compared with short course radiation patients who received chemoradiation had a higher pCR rate (16% *vs.* 1%) and a lower incidence of CRM+ (4% *vs.* 13%, P=0.017). There were no significant differences in sphincter preservation (58% *vs.* 61%), crude local recurrence (14% *vs.* 9%), disease-free survival (56% *vs.* 58%) and 4-year survival (66% *vs.* 67%). Although acute toxicity was significantly higher with chemoradiation (18% *vs.* 3%, P<0.001) there was no difference in postoperative complications.

TROG, AGITG, CSSANZ, RACS intergroup trial

A similar trial from Australia and New Zealand was reported from the Tasman Radiation Oncology Group (TROG) (29). A total of 326 patients with ultrasound or MRI staged cT3Nany adenocarcinoma located in the lower 2/3rds of the rectum were randomized to short course radiation versus long course chemoradiation. All patients received 6 months of postoperative adjuvant chemotherapy. The median potential follow-up time was 5.9 years and the primary endpoint was 3-year local recurrence.

Compared with short course radiation, patients who received long course chemoradiation had a 3% lower cumulative local recurrence rate at 3 years (4.4% *vs.* 7.5%), and 2% at 5-year (5.7% *vs.* 7.5%). Neither was statistically significant. Likewise, there were no significant differences in distant failure, overall survival, or late radiation toxicity. A subset analysis of the 79 patients with distal tumors revealed a cumulative incidence of local recurrence of 12.5% for short course radiation and there were no failures with long course chemoradiation.

Although a well-designed and performed trial, there were two criticisms of the trial. First, the numbers of patients were relatively small. Second, rather than powered to show equivalence it was designed to have an 80% power to detect a difference in the projected 3-year local recurrence rate of 15% for short course radiation compared with 5% for long course chemoradiation. Although the 3% lower incidence of local recurrence with long course chemoradiation *vs.* short course radiation did not reach statistical significance (P=0.24) the 95% CI for the difference included an 8% difference in favor of long course (i.e. 10% *vs.* 2%). Overall, the data suggest a small local control advantage for long course chemoradiation, especially for distal tumors. There are two additional considerations. Neither trial was limited to patients with N+ disease and both require longer follow-up.

Late local recurrences can occur in patients with rectal cancer. The incidence of local recurrence for all patients in the preoperative radiation arm of the Dutch CKVO trial increased from 3% at a median follow-up of 3.5 years to 6% at a median follow-up of 6 years (30). In the German CAO/ARO/AIO 94 trial, patients who received preoperative chemoradiation had an increase in local recurrence (7% *vs.* 5%) and decrease in survival (60% *vs.* 74%) at 10 *vs.* 5 years, respectively (31). Therefore, long term follow-up, regardless of which preoperative approach is used, is needed to determine the ultimate local control rates.

Advances in chemoradiation regimens

Four randomized trials examined the role of adding oxaliplatin to 5-FU or capecitabine based preoperative chemoradiation (4,32-35). Three reported higher acute toxicity and no significant benefit in the pCR rate (4,32-34), The German trial reported the opposite results (35). The ACCORD 12 trial revealed no improvement with the addition of oxaliplatin in 3-year local control (4% *vs.* 5%) or survival (88% *vs.* 85%) (34).

Targeted biological agents are being added to preoperative chemoradiation regimens. In the adjuvant setting, preliminary results from the EXPERT-C phase II trial (50.4 Gy/CAPOX/Cetuximab) suggest a survival benefit in patients whose tumors were KRAS wild type *vs.* mutant (36). Early trials using preoperative chemoradiation with CAPOX + bevacizumab revealed pCR rates of 18-24% (37,38). Unfortunately, more recent trials report increased acute toxicity and have been closed early (39,40).

Selective use of radiation

Node negative rectal cancer

In general, the risks of chemoradiation in patients with pT3N0 disease outweigh the potential benefits (41,42). Patients who undergo a TME, have at least 12 nodes examined, and have stage pT3N0 disease likely do not need the radiation component of chemoradiation. The approximately 3-4% benefit in local control with radiation is not be worth the risks, especially in women of reproductive age. However, patients with pT3N0 tumors with adverse pathologic features, resected without a TME, or when fewer than 12 nodes are examined should still receive postoperative chemoradiation.

The risk/benefit ratio in patients seen preoperatively with cT3N0 disease is more complex. Neither preoperative

imaging, molecular markers, or clinicopathologic factors can reproducibly identify patients with LN+ disease (43). The development of more accurate methods to identify LN+ disease is essential.

In the German CAO/ARO/AIO-94 trial, 18% of patients clinically staged as cT3N0 and underwent initial surgery without preoperative therapy had pT1-2N0 disease. Therefore, those patients would have been over-treated if they had received preoperative therapy. Although not ideal, preoperative therapy is still preferred to performing surgery first in this subset of patients. Even after preoperative chemoradiation which downstages tumors, Guillem *et al.* reported that 22% of patients have ypN+ disease at the time of surgery (44). In patients who undergo surgery alone this number is as high as 40% (45). These patients will then require postoperative chemoradiation which, compared with preoperative chemoradiation, has higher local recurrence, acute and chronic toxicity and, if a low anastomosis is performed, inferior functional results.

Furthermore, the incidence of positive nodes is not dependent on the distance from the anal verge (44). In his series, of the 103 patients with tumors from 0-5 cm from the anal verge, 23% were ypN+, whereas of the 85 with tumors 6-12 cm from the anal verge the incidence was 20%. These data suggest that up to 12 cm from the anal verge, the risk of positive nodes, and likely local recurrence, is similar.

Node positive rectal cancer

Given the improvements in systemic chemotherapy there may be an opportunity to use preoperative radiation more selectively. In a prospective trial reported in abstract form, Cercek *et al.* treated 32 patients with uT2N1 or uT3N0-1 rectal cancer who by preoperative assessment with neoadjuvant FOLFOX + bevacizumab (46). Only patients who did not require an abdominoperineal resection were eligible. Pelvic radiation was reserved for patients who progressed preoperatively or, following surgery had either pT4, pN2, or positive margins. Of the 30 patients who underwent surgery none required radiation, the pCR rate was 27%, and 2 required postoperative radiation. This approach remains investigational and is being prospectively tested in the phase II/III Alliance N1048 trial.

Upper rectal cancer

The limited data examining the impact of the distance from the anal verge on local recurrence are subset analysis not stratified by distance. There are no prospective randomized data. Furthermore, there are additional variables which may have contributed to differences in local recurrence. For example, TME was standard in the Dutch CVKO and German trials and not in the Swedish trial. All 3 trials included patients with tumors >12 cm from the anal verge in the "upper or high" category. Since the peritoneal reflection varies from 12-16 cm some patients with tumors above the peritoneal reflection (colon cancer) were included in the 3 trials. Most investigators now limit preoperative treatment to tumors <12 cm from the anal verge (44). Lastly, distance measurements using a flexible proctoscope are less accurate than a straight proctoscope. Flexible scopes were used in the Dutch CKVO trial. The German trial used a straight scope. In the Swedish trial proctoscopic information was not mentioned and eligibility was limited to tumors "below the promontory as identified by barium enema." The Polish trial is not included since all tumors were within reach by digital examination (28).

Tumors defined as "high" in both the Dutch CKVO and Swedish trials (defined as >10.1 cm and 11 cm, respectively) had a lower incidence of local recurrence compared with mid and lower tumors. Short course radiation did not significantly decrease local recurrence. By multivariate analysis, tumor location was an independent prognostic variable in the Dutch CKVO trial. It is interesting to note that radiation did significantly decrease local recurrence for mid tumors in both trials whereas for lower tumors it was helpful in the Swedish trial.

In contrast, there was no significant difference in local recurrence between mid and upper tumors in the German trial (47). However, data were not provided. In a subset analysis, patients with tumors above 6 cm had a lower local recurrence rate.

Nash and colleagues reported that in a retrospective analysis of 627 patients with stage I-IV rectal cancer treated with either surgery alone or chemoradiation, the pelvic recurrence rate was lower in tumors 7-12 cm from the anal verge *vs.* 0-6 cm (3% *vs.* 7%, P=0.009) (48). However, mucosal, distant, and overall recurrences were not significantly different.

Given the conflicting data combined with the report from Guillem *et al.* confirming that the incidence of positive nodes is the same from 0-12 cm from the anal verge, treatment decisions based on the current definitions of low *vs.* mid *vs.* high should not be used.

Advances in chemoradiation plus conservative surgery

Experience with preoperative chemoradiation followed by local excision is limited. Borschitz *et al.* reported local recurrence rates by pathologic stage: ypT1: 2%; ypT2: 6-20% (49). The incidence was 43% in ypT3 tumors which did not respond. Kundel *et al.* examined 320 patients with T2-4N0-1 rectal cancer and reported a subset of 14 patients who underwent a local excision for ypT0 disease (50). With a median follow-up of 48 months none developed local recurrence or distant failure. In a compilation of 100 patients reported in 11 series, 7% had local recurrence and 8% had distant failure.

This approach has been examined prospectively in the ACOSOG Z6031 trial (51). Patients with uT2N0 disease received preoperative CAPOX and radiation therapy. Those with stage ypT0-2 and negative margins following a local excision had observation only. Patients with stage ypT3 and/or positive margins underwent radical surgery. A total of 77 patients were enrolled and the pCR rate was 43%. Local recurrence and survival results are pending. A similar trial (GRECCAR 2) will accrue 300 patients with cT2-3 disease.

Advances in the non-operative approach (watch and wait)

Although the conventional adjuvant treatment for rectal cancer is preoperative chemoradiation there are clinical settings where surgery has not been performed. These include patients early stage tumors, those with medically inoperable disease, and patients who have refused surgery following a favorable response to preoperative chemoradiation. In these settings, radiation has been delivered by a variety of techniques including endocavitary (contact) treatment, brachytherapy, and pelvic external beam.

Retrospective series

Treatment of rectal cancer without surgery is not a new concept. Although patients can be cured, the results are inferior to surgery. A number of modern retrospective series report the use of radiation alone or chemoradiation, most commonly for patients who are medically inoperable or refuse surgery.

In general, patients received pelvic radiation followed by a boost with either external beam and/or brachytherapy. Brierley *et al.* from the Princess Margaret Hospital reported the results of pelvic radiation alone (40-60 Gy) in patients who refused surgery or had unresectable or medically inoperable disease (52). The overall 5-year survival was 27% and by the mobility of the primary tumor was: mobile, 47%; partially fixed, 27%; and fixed, 4%.

Gerard and associates reported the combination of pelvic radiation, endocavitary, and brachytherapy in 63 patients with uT2-3 tumors (53). For patients with uT3 disease the 5-year local failure and survival rates were 20% and 35%, respectively.

A total of 48 patients with cT3 disease who received radiation or chemoradiation alone due to medical inoperability or patient refusal was reported by Lim *et al.* (54). The clinical CR rate was 56% and, with a median follow-up of 49 months, 37% had progression of disease.

Prospective series

There are four series which advocate the watch and wait approach following preoperative chemoradiation (*Table 2*). The first was initially reported by Habr-Gama and colleagues in 2004 (59). A total of 265 patients were treated with preoperative 50.4 Gy plus 5-FU and leucovorin. Of those, 27% achieved a clinical CR and were selected for observation only. Close follow-up was required including frequent exams, biopsy, and abdominal/pelvic CT scans every 6 months.

With a mean follow-up of 57 months there was a 3% luminal recurrence rate, 4% distant metastasis rate, and 100% 5-year survival. In an update of 361 patients, the local recurrence rate was 5% and 5-year overall survival was 93% in the 28% who achieved a clinical CR (55). It should be emphasized that patients with cT1-3 disease were included and those who developed a local recurrence in the first year were excluded from analysis.

Mass *et al.* reported their experience of 192 patients with locally advanced rectal cancer (60). Patients were staged with diffusion weighted MRI and had either cT4, cT3 with threatened margins, or node positive disease. They received 50.4 Gy plus capecitabine and 6-8 weeks later underwent MRI restaging. A strict definition of clinical CR was used which included meeting all of the following criteria: (I) substantial downsizing with no residual tumor or residual fibrosis only, (II) no lymph nodes, and (III) endoscopy revealing no tumor or a small residual erythematous ulcer or scar, (IV) negative biopsy, and (V) no palpable tumor.

Table 2 Non-operative treatment of rectal cancer with the watch and wait approach

Series	# Patients treated	# Patients observed	Outcome
Sao Paulo (55)	265	28	5% luminal recurrence
			93% 5-yr survival
Maastricht (56)	192	21	89% 2-yr DFS
			100 2-yr survival
Exeter (57)	49	12	Biopsy-: all NED
			Biopsy+: 2/6 distant failure
MSKCC (58)	-	32	21% 2-yr local failure
			9% 2-yr distant failure

DFS, disease free survival; NED, no evidence of disease

A subset of 21 patients had a clinical CR and, based on patient preference, were included in a wait-and-see policy. Of the 21, 10 had distal tumors which would have required an abdominoperineal resection. The mean follow-up was 25 months. One patient developed an endoluminal local recurrence without nodal recurrence at 22 months and was salvaged with TEM surgery. The cumulative probability of 2-year disease free survival was 89% and overall survival was 100%.

Dalton and colleagues from Exeter treated 49 patients with 45 Gy plus capecitabine (57). Twelve achieved a cCR by MRI and underwent biopsy 6-8 weeks later. They were then followed closely by PET, CT, MRI, and endoscopy. The 6 who were biopsy negative were all without evidence of disease with a median follow-up of 26 months and 2 of the 6 who were biopsy positive developed distant failure.

The series from Smith *et al.* reported 32 patients with uT2-4 and/or N+ disease who received 50.4 Gy (45-56 Gy) + 5-FU or Capecitabine (58). A clinical CR was defined as a negative endoscopy at 4-10 weeks. Biopsy and imaging were optional. The local failure rate was 19% crude and 21% 2-yr actuarial. The median time to local failure was 11 months and all were salvaged and without evidence of disease at 17 months. Of note, 5 of the 6 local failures were endoluminal. The incidence of distant failure was 9%.

Their current recommendation for follow-up following chemoradiation is a 2-stage process. At 6-7 weeks patients undergo and exam and endoscopy. If they have a cCR they are followed. If < cCR then it is repeated at 10-12 wks. Patients who have a cCR at 14 months will likely remain in cCR.

Most series suggest an improved outcome in patients who achieve a pathologic CR following preoperative chemoradiation. Patients who are downstaged to ypT0 following chemoradiation have a 5% incidence of positive nodes and a corresponding low nodal recurrence rate (50). Mass and colleagues reported a pooled analysis of 27 series reporting patients who underwent preoperative chemoradiation and achieved a pathologic CR (61). There was a significant increase in 5-year disease free survival compared to those who did not achieve a pCR (83% *vs.* 63%, P=0.0001).

Selecting patients for a non-operative approach based on response is reasonable. The challenge is identifying a surrogate method to surgery for the identification of a pathologic CR. Current methods include endoscopy and physical exam, ultrasound, CT, MRI, and PET either alone or in combination. With the exception of the rigorous approach used by Mass *et al.* in their wait- and-see series (60), most have not been consistently successful. Glynne-Jones and associates reviewed 218 phase II and 28 phase III trials of preoperative radiation or chemoradiation and confirmed that clinical and/or radiologic response does not sufficiently correlate with pathologic response and do not recommend a "wait and see' approach to surgery following preoperative therapy (62). However, further refinements in imaging may improve the selection process.

In summary, surgery remains a standard component of the treatment of rectal cancer. The wait-and-see approach is encouraging but remains investigational. More accurate methods for post-chemoradiation assessment are needed.

Advances in chemoradiation regimens

Both cytotoxic and targeted chemotherapeutic agents have been incorporated into preoperative chemoradiation regimens. Most of the phase I/II regimens report higher pCR rates compared with historical rates seen with 5-FU

Table 3 Oxaliplatin based preoperative chemoradiation: randomized trials

Author/regimen	#	RT (Gy)	% pCR	% LF
Aschele (32) (STAR)				
CI 5-FU	295	50.3/1.8	16	-
CI 5-FU/oxaliplatin	291	50.4/1.8	15	-
Gerard (33,34) (ACCORD 12/0405 PRODIGIE)				
Capecitibine	379	4.5/1.8	14	6 (3-yr)
Capecitibine/oxaliplatin	368	50/1.8	19	4
Roedel (35) (CAO/ARO/AIO-94)				
CI 5-FU	637	50.4/1.8	13	-
CI 5-FU/oxaliplatin	628	50.4/1.8	18	-
Roh (4) (NSABP R-04)				
CI 5-FU or capecitabine	622	50.4/1.8	19	-
CI 5-FU or capecitabine + oxaliplatin	631	50.5/1.8	21	-

R, randomized phase II trial; RT, radiation dose/fraction size; pCR, pathologic complete response rate; LF, local failure; A, second primary failure

alone. The RTOG 0247 randomized phase II trial of CAPEIRI *vs.* CAPOX based chemoradiation revealed a higher pCR with the irinotecan based regimen (21% *vs.* 10%) with no difference in grade 3+ acute toxicity (63).

Four randomized trials have examined the impact of addition of oxaliplatin to 5-FU or capecitabine based chemoradiation on response rates and acute toxicity in patients with cT3-4 and/N+ rectal cancer (*Table 3*). The STAR-01 trial randomized 747 patients to preoperative chemoradiation with 50.4 Gy + CI 5-FU +/- oxaliplatin (60 mg/m^2 weekly) (32). There was a significant increase in grade 3+ toxicity with oxaliplatin (24% *vs.* 8%, P<0.001) with no improvement in the pCR rate (15% *vs.* 16%). In the ACCORD 12/0405 PRODIGIE trial, 598 patients were randomized to preoperative chemoradiation with 50 Gy plus capecitabine + oxaliplatin (CAPOX) *vs.* 45 Gy plus capecitabine (33). There was a similar significant increase in grade 3+ toxicity with oxaliplatin (25% *vs.* 11%, P<0.001) with no improvement in the pCR rate (19% *vs.* 14%). Oxaliplatin did not improve 3-year local recurrence (6% *vs.* 4%) or survival (88% *vs.* 83%) (34).

The NSABP R-04 trial was a 4 arm trial (2×2 comparison) of CI 5-FU *vs.* capecitabine based preoperative chemoradiation (50.4 Gy) with or without oxaliplatin (4). A total of 1,606 patients with cT3 and or N+ disease were randomized. The addition of oxaliplatin (to either 5-FU or capecitabine) was associated with a significantly higher incidence of grade 3+ diarrhea (15% *vs.* 7%, P=0.0001) with no improvement in the incidence of pCR (21% *vs.* 19%) or sphincter-sparing surgery (60% *vs.* 64%).

The German CAO/ARO/AIO-04 randomized 1,265 patients with cT3-4 and or N+ disease to the preoperative arm of CAO/ARO/AIO-94 (50.4 Gy + 5-FU) versus 50.4 Gy/5-FU+ oxaliplatin (50 mg/m^2 weekly) (35). In contrast with the STAR-01, ACCORD, and NSABP R-04 trials, patient who received oxaliplatin based CMT had a significant improvement in pCR (17% *vs.* 13%, P=0.045) with no corresponding increase in acute grade 3+ toxicity (23% *vs.* 22%). The results of the 5th trial (PETACC-6) are pending.

Since 3 of 4 randomized trials reveal an increase in acute toxicity with no benefit in the pCR rate the current standard is not to include oxaliplatin to preoperative chemoradiation regimens. However, local control and survival data are not available and this recommendation may need to be modified once these data are reported.

The role of targeted biological agents such as bevacizumab and cetuximab are being tested. Phase I/II trials using preoperative chemoradiation with CAPOX + bevacizumab reveal pCR rates of 18-24% (37,38). Two recent trials combining bevacizumab to preoperative FOLFOX (56) or capecitabine (40) based chemoradiation were stopped early due to excessive toxicity.

Although the report from Heidelberg of CAPEIRI based chemoradiation reported a pCR rate of 25% (64) other trials with 5-FU, capecitabine, or CAPOX have more limited rates of 5-12% (65,66).

Patient selection based on KRAS expression is useful in patients with metastatic disease (38). Preliminary results

from the phase II EXPERT-C trial (50.4 Gy/CAPOX/Cetuximab) suggest a survival benefit in patients whose tumors were KRAS wild type *vs.* mutant (36).

Advances in chemotherapy sequencing

The Spanish GCR-3 randomized phase II trial compared neoadjuvant chemotherapy followed by chemoradiation with conventional preoperative chemoradiation followed by surgery and postoperative chemotherapy (67). A total of 108 patients received preoperative 50.4 Gy plus CAPOX and were randomized to receive 4 months of CAPOX either by induction or adjuvant (postoperative). Although the pCR rates were not different (14% *vs.* 13%) both grade 3+ toxicity was lower (17% *vs.* 51%, P=0.00004) and the ability to receive all 4 chemotherapy cycles was higher (93% *vs.* 51%, P=0.0001) with the induction approach.

Advances in predictors of response

Most series suggest that there is improved outcome with increasing pathologic response to preoperative therapy (68-70). A retrospective review of 566 patients who achieved a pCR after receiving a variety of preoperative chemoradiation regimens at multiple European centers was reported by Capirci and associates (69). With a median follow-up of 46 months the local recurrence rate was only 1.6% and the 5-year disease-free and overall survival rates were 85% and 90% respectively. A pooled analysis 3,105 patients from 14 studies confirmed a significant improvement in local recurrence, distant failure, disease free, and overall survival for the 16% of patients who achieved a pCR (ypT0N0M0) compared to those without a pCR (61). Acellular mucin pools are seen in 15% of tumors following chemoradiation and do not have a significant impact on outcome (71).

Although a number of molecular markers are predictive of outcome in colorectal cancer (38,72,73), they have had varying success in identifying patients who may respond to preoperative therapy (74-76). Kuremsky *et al.* reviewed 1,204 studies examining a total of 36 molecular biomarkers which may have predictive value (77). Restricting the analysis to patients treated with preoperative chemoradiation and to gene products examined by 5 or more studies, only p53, epidermal growth factor receptor (EGFR), thymidylate synthase, Ki-67, p21, and bax/bcl-2 met these criteria. Of these, quantitatively evaluated EGFR or EGFR polymorphisms, thymidylate synthase polymorphisms, and p21 have been identified as promising candidates that should be evaluated in larger prospective trials for their ability to guide preoperative therapy. Since the studies are limited retrospective trials and most do not examined multiple markers, the need for adjuvant therapy should still be based on T and N stage.

Konski and associates performed pre and post-treatment 18-FDG PET scans on 53 patients receiving preoperative chemoradiation (78). By multivariate analysis the percent decrease in SUV trended marginally in predicting pCR (P=0.07).

Advances in radiation techniques and dose

The clinical utility of routine 3-D and IMRT treatment planning techniques are being investigated (79,80). The most important contributions of 3-D treatment planning are the ability to plan and localize the target and normal tissues at all levels of the treatment volume and to obtain dose volume histogram data. An analysis of 3-D treatment planning techniques suggests that the volume of small bowel in the radiation field is decreased with protons as compared with photons (81). IMRT treatment planning techniques can further decrease the volume of small bowel in the field (82). However, the clinical benefit of IMRT compared to 3-D or conventional treatment delivery for rectal cancer remains to be determined (80). Guidelines for the definition and delineation of the clinical target volumes (CTV) are available from a number of investigators (83,84).

The RTOG R-0012 phase II randomized trial compared twice a day preoperative chemoradiation up to 60 Gy (1.2 Gy to 45.6 Gy, with a boost of 9.6-14.4 Gy) with conventional fractionation (1.8 Gy to 45 Gy, with a boost of 5.4-9.0 Gy) plus 5-FU/irinotecan (85). Both regimens resulted in a 28% pCR rate, but were also associated with a >40% rate of grade 3-4 acute toxicity.

Summary

The therapy of rectal cancer continues to evolve. Both diagnostic and therapeutic advances are challenging historical approaches and have opened new directions for the future and are areas of clinical investigation.

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Footnote

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References

1. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731-1740.
2. Krook JE, Moertel CG, Gunderson LL, et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. N Engl J Med 1991;324:709-715.
3. Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med 2005;352:2696-2704.
4. Roh MS, Yothers GA, O'Connell MJ, et al. The impact of capecitabine and oxaliplatin in the preoperative multimodality treatment in patients with carcinoma of the rectum: NSABP R-04. J Clin Oncol 2011;29:abstr 3503.
5. Hofheinz R, Wenz FK, Post S, et al. Capecitabine (Cape) versus 5-fluorouracil (5-FU)–based (neo)adjuvant chemoradiotherapy (CRT) for locally advanced rectal cancer (LARC): Long-term results of a randomized, phase III trial. J Clin Oncol 2011;29:abstr 3504.
6. Salerno GV, Daniels IR, Moran BJ, et al. Magnetic resonance imaging prediction of an involved surgical resection margin in low rectal cancer. Dis Colon Rectum 2009;52:632-639.
7. Barbaro B, Valentini V, Coco C, et al. Tumor vascularity evaluated by transrectal color Doppler US in predicting therapy outcome for low-lying rectal cancer. Int J Radiat Oncol Biol Phys 2005;63:1304-1308.
8. Valentini V, DePaoli A, Gambacorta MA, et al. Chemoradiation with infusional 5-FU and ZD1839 (Gefitinib-Iressa) in patients with locally advanced rectal cancer: a phase II trial. Int J Radiat Oncol Biol Phys 2006;66:s168.
9. Kim NK, Kim MJ, Park JK, et al. Preoperative staging of rectal cancer with MRI: accuracy and clinical usefulness. Ann Surg Oncol 2000;7:732-737.
10. Nahas CS, Akhurst T, Yeung H, et al. Positron emission tomography detection of distant metastatic or synchronous disease in patients with locally advanced rectal cancer receiving preoperative chemoradiation. Ann Surg Oncol 2008;15:704-711.
11. Buijsen J, van den Bogaard J, Janssen MH, et al. FDG-PET provides the best correlation with the tumor specimen compared to MRI and CT in rectal cancer. Radiother Oncol 2011;98:270-276.
12. Everaert H, Hoorens A, Vanhove C, et al. Prediction of response to neoadjuvant radiotherapy in patients with locally advanced rectal cancer by means of sequential 18FDG-PET. Int J Radiat Oncol Biol Phys 2011;80:91-96.
13. Mak D, Joon DL, Chao M, et al. The use of PET in assessing tumor response after neoadjuvant chemoradiation for rectal cancer. Radiother Oncol 2010;97:205-211.
14. Shanmugan S, Arrangoiz R, Nitzkorski JR, et al. Predicting pathological response to neoadjuvant chemoradiotherapy in locally advanced rectal cancer using 18FDG-PET/CT. Ann Surg Oncol 2012;19:2178-2185.
15. Barbaro B, Fiorucci C, Tebala C, et al. Locally advanced rectal cancer: MR imaging in prediction of response after preoperative chemotherapy and radiation therapy. Radiology 2009;250:730-739.
16. Calvo FA, Domper M, Matute R, et al. 18F-FDG positron emission tomography staging and restaging in rectal cancer treated with preoperative chemoradiation. Int J Radiat Oncol Biol Phys 2004;58:528-535.
17. Shami VM, Parmar KS, Waxman I. Clinical impact of endoscopic ultrasound and endoscopic ultrasound-guided fine-needle aspiration in the management of rectal carcinoma. Dis Colon Rectum 2004;47:59-65.
18. Kim YH, Kim DY, Kim TH, et al. Usefulness of magnetic resonance volumetric evaluation in predicting response to preoperative concurrent chemoradiotherapy in patients with resectable rectal cancer. Int J Radiat Oncol Biol Phys 2005;62:761-768.
19. Kuo LJ, Chern MC, Tsou MH, et al. Interpretation of magnetic resonance imaging for locally advanced rectal carcinoma after preoperative chemoradiation therapy. Dis Colon Rectum 2005;48:23-28.
20. Barbaro B, Schulsinger A, Valentini V, et al. The accuracy of transrectal ultrasound in predicting the pathological stage of low-lying rectal cancer after preoperative chemoradiation therapy. Int J Radiat Oncol Biol Phys 1999;43:1043-1047.
21. Calvo FA, Cabezón L, González C, et al. (18)F-FDG PET bio-metabolic monitoring of neoadjuvant therapy effects in rectal cancer: focus on nodal disease characteristics. Radiother Oncol 2010;97:212-216.
22. Guillem JG, Chessin DB, Shia J, et al. Clinical examination following preoperative chemoradiation for rectal cancer is not a reliable surrogate end point. J Clin Oncol 2005;23:3475-3479.
23. Skibber JM, Hoff PM, Minsky BD. Cancer of the Rectum. In: DeVita VT, Hellman S, Rosenberg SA. eds. Cancer:

Principles and Practice of Oncology (ed 6). Philadelphia: Lippincott, Williams and Wilkens, 2001:1271-318.
24. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001;345:638-646.
25. van Gijn W, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol 2011;12:575-582.
26. Marijnen CA, Kapiteijn E, van de Velde CJ, et al. Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: report of a multicenter randomized trial. J Clin Oncol 2002;20:817-825.
27. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomised trial comparing short-term radiotherapy vs. conventionally fractionated radiochemotherapy. Radiother Oncol 2004;72:15-24.
28. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg 2006;93:1215-1223.
29. Ngan SY, Burmeister B, Fisher RJ, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. J Clin Oncol 2012;30:3827-3833.
30. Peeters KC, Marijnen CA, Nagtegaal ID, et al. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. Ann Surg 2007;246:693-701.
31. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol 2012;30:1926-1933.
32. Aschele C, Cionini L, Lonardi S, et al. Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. J Clin Oncol 2011;29:2773-2780.
33. Gérard JP, Azria D, Gourgou-Bourgade S, et al. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. J Clin Oncol 2010;28:1638-1644.
34. Gérard JP, Azria D, Gourgou-Bourgade S, et al. Clinical outcome of the ACCORD 12/0405 PRODIGE 2 randomized trial in rectal cancer. J Clin Oncol 2012;30:4558-4565.
35. Rödel C, Liersch T, Becker H, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. Lancet Oncol 2012;13:679-687.
36. Dewdney A, Cunningham D, Tabernero J, et al. Multicenter randomized phase II clinical trial comparing neoadjuvant oxaliplatin, capecitabine, and preoperative radiotherapy with or without cetuximab followed by total mesorectal excision in patients with high-risk rectal cancer (EXPERT-C). J Clin Oncol 2012;30:1620-1627.
37. Willett CG, Duda DG, di Tomaso E, et al. Efficacy, safety, and biomarkers of neoadjuvant bevacizumab, radiation therapy, and fluorouracil in rectal cancer: a multidisciplinary phase II study. J Clin Oncol 2009;27:3020-3026.
38. van Cutsem E, Lang I, D'haens G, et al. KRAS status and efficacy in the first-line treatment of patients with metastatic colorectal cancer (mCRC) treated with FOLFIRI with or without cetuximab: The CRYSTAL experience. J Clin Oncol 2008;26: abstr 2.
39. Dipetrillo T, Pricolo V, Lagares-Garcia J, et al. Neoadjuvant bevacizumab, oxaliplatin, 5-fluorouracil, and radiation for rectal cancer. Int J Radiat Oncol Biol Phys 2012;82:124-129.
40. Resch G, De Vries A, Öfner D, et al. Preoperative treatment with capecitabine, bevacizumab and radiotherapy for primary locally advanced rectal cancer--a two stage phase II clinical trial. Radiother Oncol 2012;102:10-13.
41. Nissan A, Stojadinovic A, Shia J, et al. Predictors of recurrence in patients with T2 and early T3, N0 adenocarcinoma of the rectum treated by surgery alone. J Clin Oncol 2006;24:4078-4084.
42. Greene FL, Stewart AK, Norton HJ. New tumor-node-metastasis staging strategy for node-positive (stage III) rectal cancer: an analysis. J Clin Oncol 2004;22:1778-1784.
43. Kim JH, Beets GL, Kim MJ, et al. High-resolution MR imaging for nodal staging in rectal cancer: are there any criteria in addition to the size? Eur J Radiol 2004;52:78-83.
44. Guillem JG, Díaz-González JA, Minsky BD, et al. cT3N0

rectal cancer: potential overtreatment with preoperative chemoradiotherapy is warranted. J Clin Oncol 2008;26:368-373.
45. Mendenhall WM, Bland KI, Rout WR, et al. Clinically resectable adenocarcinoma of the rectum treated with preoperative irradiation and surgery. Dis Colon Rectum 1988;31:287-290.
46. Cercek A, Weiser MR, Goodman KA, et al. Complete pathologic response in the primary of rectal or colon cancer treated with FOLFOX without radiation. J Clin Oncol 2010;28:abstr 3649.
47. Sauer R, Roedel C. The author's reply. New Engl J Med 2005;352:510-511.
48. Nash GM, Weiss A, Dasgupta R, et al. Close distal margin and rectal cancer recurrence after sphincter-preserving rectal resection. Dis Colon Rectum 2010;53:1365-1373.
49. Borschitz T, Wachtlin D, Möhler M, et al. Neoadjuvant chemoradiation and local excision for T2-3 rectal cancer. Ann Surg Oncol 2008;15:712-720.
50. Kundel Y, Brenner R, Purim O, et al. Is local excision after complete pathological response to neoadjuvant chemoradiation for rectal cancer an acceptable treatment option? Dis Colon Rectum 2010;53:1624-1631.
51. Garcia-Aguilar J, Shi Q, Thomas CR, et al. Pathologic complete response (pCR) to neoadjuvant chemoradiation (CRT) of uT2uN0 rectal cancer (RC) treated by local excision (LE): Results of the ACOSOG Z6041 trial. J Clin Oncol 2012;28:abstr 3510.
52. Brierley JD, Cummings BJ, Wong CS, et al. Adenocarcinoma of the rectum treated by radical external radiation therapy. Int J Radiat Oncol Biol Phys 1995;31:255-259.
53. Gerard JP, Chapet O, Ramaioli A, et al. Long-term control of T2-T3 rectal adenocarcinoma with radiotherapy alone. Int J Radiat Oncol Biol Phys 2002;54:142-149.
54. Lim L, Chao M, Shapiro J, et al. Long-term outcomes of patients with localized rectal cancer treated with chemoradiation or radiotherapy alone because of medical inoperability or patient refusal. Dis Colon Rectum 2007;50:2032-2039.
55. Habr-Gama A, Perez RO, Proscurshim I, et al. Patterns of failure and survival for nonoperative treatment of stage c0 distal rectal cancer following neoadjuvant chemoradiation therapy. J Gastrointest Surg 2006;10:1319-1328; discussion 1328-1329.
56. Campbell PT, Newton CC, Dehal AN, et al. Impact of body mass index on survival after colorectal cancer diagnosis: the Cancer Prevention Study-II Nutrition Cohort. J Clin Oncol 2012;30:42-52.
57. Dalton RS, Velineni R, Osborne ME, et al. A single-centre experience of chemoradiotherapy for rectal cancer: is there potential for nonoperative management? Colorectal Dis 2012;14:567-571.
58. Smith JD, Ruby JA, Goodman KA, et al. Nonoperative management of rectal cancer with complete clinical response after neoadjuvant therapy. Ann Surg 2012;256:965-972.
59. Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg 2004;240:711-717; discussion 717-718.
60. Maas M, Beets-Tan RG, Lambregts DM, et al. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. J Clin Oncol 2011;29:4633-4640.
61. Maas M, Nelemans PJ, Valentini V, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol 2010;11:835-844.
62. Glynne-Jones R, Wallace M, Livingstone JI, et al. Complete clinical response after preoperative chemoradiation in rectal cancer: is a "wait and see" policy justified? Dis Colon Rectum 2008;51:10-19; discussion 19-20.
63. Wong SJ, Winter K, Meropol NJ, et al. Radiation Therapy Oncology Group 0247: a randomized Phase II study of neoadjuvant capecitabine and irinotecan or capecitabine and oxaliplatin with concurrent radiotherapy for patients with locally advanced rectal cancer. Int J Radiat Oncol Biol Phys 2012;82:1367-1375.
64. Das P, Lin EH, Bhatia S, et al. Preoperative chemoradiotherapy with capecitabine versus protracted infusion 5-fluorouracil for rectal cancer: a matched-pair analysis. Int J Radiat Oncol Biol Phys 2006;66:1378-1383.
65. Chung KY, Minsky B, Schrag D, et al. Phase I trial of preoperative cetuximab with concurrent continuous infusion 5-fluorouracil and pelvic radiation in patients with local-regionally advanced rectal cancer. J Clin Oncol 2006;24:abstr 3560.
66. Rödel C, Arnold D, Hipp M, et al. Phase I-II trial of cetuximab, capecitabine, oxaliplatin, and radiotherapy as preoperative treatment in rectal cancer. Int J Radiat Oncol Biol Phys 2008;70:1081-1086.
67. Fernández-Martos C, Pericay C, Aparicio J, et al. Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX

followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo cancer de recto 3 study. J Clin Oncol 2010;28:859-865.
68. Guillem JG, Chessin DB, Cohen AM, et al. Long-term oncologic outcome following preoperative combined modality therapy and total mesorectal excision of locally advanced rectal cancer. Ann Surg 2005;241:829-836; discussion 836-838.
69. Capirci C, Valentini V, Cionini L, et al. Prognostic value of pathologic complete response after neoadjuvant therapy in locally advanced rectal cancer: long-term analysis of 566 ypCR patients. Int J Radiat Oncol Biol Phys 2008;72:99-107.
70. Yeo SG, Kim DY, Kim TH, et al. Pathologic complete response of primary tumor following preoperative chemoradiotherapy for locally advanced rectal cancer: long-term outcomes and prognostic significance of pathologic nodal status (KROG 09-01). Ann Surg 2010;252:998-1004.
71. Shia J, McManus M, Guillem JG, et al. Significance of acellular mucin pools in rectal carcinoma after neoadjuvant chemoradiotherapy. Am J Surg Pathol 2011;35:127-134.
72. Haddock MG, Miller RC, Nelson H, et al. Combined modality therapy including intraoperative electron irradiation for locally recurrent colorectal cancer. Int J Radiat Oncol Biol Phys 2011;79:143-150.
73. Wilson PM, Labonte MJ, Lenz HJ. Molecular markers in the treatment of metastatic colorectal cancer. Cancer J 2010;16:262-272.
74. Bertolini F, Bengala C, Losi L, et al. Prognostic and predictive value of baseline and posttreatment molecular marker expression in locally advanced rectal cancer treated with neoadjuvant chemoradiotherapy. Int J Radiat Oncol Biol Phys 2007;68:1455-1461.
75. Unsal Kilic D, Uner A, Akyurek N, et al. Matrix metalloproteinase-9 expression correlated with tumor response in patients with locally advanced rectal cancer undergoing preoperative chemoradiotherapy. Int J Radiat Oncol Biol Phys 2007;67:196-203.
76. Johnston PG. Prognostic markers of local relapse in rectal cancer: are we any further forward? J Clin Oncol 2006;24:4049-4050.
77. Kuremsky JG, Tepper JE, McLeod HL. Biomarkers for response to neoadjuvant chemoradiation for rectal cancer. Int J Radiat Oncol Biol Phys 2009;74:673-688.
78. Konski A, Li T, Sigurdson E, et al. Use of molecular imaging to predict clinical outcome in patients with rectal cancer after preoperative chemotherapy and radiation. Int J Radiat Oncol Biol Phys 2009;74:55-59.
79. Meyer J, Czito B, Yin FF, et al. Advanced radiation therapy technologies in the treatment of rectal and anal cancer: intensity-modulated photon therapy and proton therapy. Clin Colorectal Cancer 2007;6:348-356.
80. Aristu JJ, Arbea L, Rodriguez J, et al. Phase I-II trial of concurrent capecitabine and oxaliplatin with preoperative intensity-modulated radiotherapy in patients with locally advanced rectal cancer. Int J Radiat Oncol Biol Phys 2008;71:748-755.
81. Tatsuzaki H, Urie MM, Willett CG. 3-D comparative study of proton vs. x-ray radiation therapy for rectal cancer. Int J Radiat Oncol Biol Phys 1992;22:369-374.
82. Callister MD, Ezzell GA, Gunderson LL. IMRT reduces the dose to small bowel and other pelvic organs in the preoperative treatment of rectal cancer. Int J Radiat Oncol Biol Phys 2006;66: abstr s290.
83. Roels S, Duthoy W, Haustermans K, et al. Definition and delineation of the clinical target volume for rectal cancer. Int J Radiat Oncol Biol Phys 2006;65:1129-1142.
84. Myerson RJ, Garofalo MC, El Naqa I, et al. Elective clinical target volumes for conformal therapy in anorectal cancer: a radiation therapy oncology group consensus panel contouring atlas. Int J Radiat Oncol Biol Phys 2009;74:824-830.
85. Mohiuddin M, Winter K, Mitchell E, et al. Randomized phase II study of neoadjuvant combined-modality chemoradiation for distal rectal cancer: Radiation Therapy Oncology Group Trial 0012. J Clin Oncol 2006;24:650-655.

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Rectal cancer: a truly multidisciplinary challenge

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Over 40,000 people will be diagnosed with rectal cancer in the United States in 2014, and colorectal cancer remains the second leading cause of cancer death nationally despite renewed focus on diagnosis and management (1). That being said, the incidence of colorectal cancer has dropped significantly over the last several decades largely attributable to more successful screening programs (2). In addition, cancer-related mortality among those diagnosed with colorectal cancer has also dropped in recent years, which is likely a function of earlier intervention and improved treatment modalities (3).

The management of rectal cancer has evolved significantly over the last several decades and through this evolution, patients are now managed with a comprehensive multidisciplinary approach. From routine age-appropriate screening and history-taking through diagnostic work-up, cancer treatment, and survivorship, care of patients with rectal cancer requires a tremendous amount of resources and the expertise of an array of specialties working together to maximize patients' quality and quantity of life. In this focus issue, our contributors delve into the different aspects of rectal cancer prevention, treatment, and aftercare that are largely responsible for the reduced incidence and mortality associated with this disease.

After years of analysis, we now believe that as many as one in five patients diagnosed with colorectal cancer are genetically predisposed to developing invasive disease (4). Recognizing this at-risk population before they develop cancer, educating them, and enrolling them in proper screening protocols should help both in terms of disease prevention and earlier detection of invasive disease. In this issue, cancer genetics pioneer Dr. Lynch and fellow collaborators, Drs. Schlussel, Gagliano, Seto-Donlon, Eggerding, Donlon, and Berenberg have provided two manuscripts which together provide a definitive look at the evolution of colorectal cancer genetics. Part 1 details the background and history of colorectal cancer genetics and how that information has been incorporated into clinical practice (5). In part 2, Dr. Schlussel *et al.* review the hereditary cancer syndromes and the clinical implications and impact that providers need to be aware of when formulating a management strategy for patients and their families (6).

For those patients that are diagnosed with rectal cancer, definitive treatment carries significant morbidity and mortality risks and techniques are continually being refined to reduce these treatment-related risks (7). As knowledge and understanding of rectal cancer continues to grow, identifying and screening at-risk populations in a timely fashion is leading to earlier detection and treatment. With earlier detection come more favorable outcomes and the potential to obviate the need for more traditional radical therapies. Drs. Heafner and Glasgow present a detailed review of the role of local excision in the treatment of early rectal cancers (8). In this review, the authors outline the rationale behind less invasive surgery in rectal cancer, the different techniques utilized, the risks and benefits associated with local excision, and the population that should be considered for this less invasive approach.

Despite improvements in screening, prevention, and early detection, a large portion of patients with rectal cancer present with more advanced stages of disease. For patients with locally advanced disease, treatment has long featured combined modality therapy given the propensity of rectal cancer to recur both locally and distantly. Internationally, numerous trials have sought to determine the optimal sequence, duration, and intensity of therapy in an attempt to maximize outcomes while limiting treatment-related

toxicities. In the United States, the standard of care in patients with locally advanced disease (at least T3 or node positive) is preoperative 5-flurouracil-based chemotherapy concurrent with external beam irradiation to a dose of approximately 5,000 cGy followed by transabdominal resection 5-12 weeks after completion of neoadjuvant therapy followed by postoperative chemotherapy. This recommended course of therapy is based on the results of the German Rectal Cancer Study which showed improved local control rates and a more favorable morbidity profile with neoadjuvant chemoradiation when compared to adjuvant chemoradiation (9). Building on this and many other trials, there are several studies ongoing, and internationally, there continues to be much debate over the ideal sequencing of treatment. Dr. Fung-Kee-Fung explores the concept of combined modality therapy for locally advanced rectal cancer from a historical perspective, showing how we have arrived at the current standards and postulating on where we are heading in the future (10).

Local control following treatment is a major priority in rectal cancer both because of the historically high prevalence of local failure and due to the impact and morbidity associated with recurrent disease in the pelvis. Thus, many clinical trials for rectal cancer have focused on local control as a primary or secondary endpoint and based on the success of these studies, current treatment regimens yield long-term local control rates in excess of 90% (11). While local control rates in rectal cancer are now excellent, studies are finding that distant failure remains a persistent issue. There are a number of reasons to explain why, one being that after aggressive neoadjuvant chemoradiation and surgery, many patients never get their full course of adjuvant systemic therapy. In this issue, Drs. Boland and Fakih present the emerging role of neoadjuvant chemotherapy and how this change in therapy sequencing may further improve outcomes, particularly in terms of reducing rates of distant metastatic disease (12).

With improving systemic therapy approaches, refined surgical techniques, and emerging radiation technologies, patients with all stages of rectal cancer are experiencing better treatment outcomes than they had historically, even those with advanced stages of disease (3). Advances in systemic therapy have made long-term disease control a reality for patients with a small metastatic burden, opening the door for aggressive local therapy for the treatment of limited metastatic disease. The majority of studies investigating local treatment of metastatic colorectal cancer have focused on disease metastatic to the liver. The liver is the most common site for colorectal metastases and spread to the liver is responsible for the majority of colorectal cancer-related deaths (13,14). In their manuscript, Drs. Clark and Smith lead a comprehensive discussion on liver-directed therapies in metastatic colorectal cancer (15). They take a step-wise approach to this complex treatment algorithm, focusing on the when, why and how of each treatment strategy along with the potential alternatives depending on the specific scenario.

Rectal cancer is a challenging disease, and as outlined above and throughout this issue, the treatments themselves can be quite complex. Over the course of treatment, there is a significant physical and emotional toll on patients and their loved ones. And with improving outcomes, more and more patients are becoming long term survivors of this disease. And while these improving outcomes are cause for excitement, there is often disease- and treatment-related morbidity which complicates their recovery and impacts on their post-treatment quality of life. From the perceived stigma of dealing with a permanent ostomy to chronic sexual dysfunction, patients face an array of life-altering morbidity in the post-treatment setting and these issues many times go undetected by providers and thus are left untreated. In this focus issue, Drs. Averyt and Nishimoto have developed two unique manuscripts designed to help providers understand what patients are going through after treatment and to provide them with tools to help break down the barriers that are often faced in colorectal cancer survivorship. The first manuscript focuses specifically on addressing the sexual dysfunction that patients face following diagnosis and treatment (16). This topic is often largely ignored by providers and patients are many times reluctant to address this subject on their own in their routine follow-up. The authors present very effective tools to aid clinicians in opening a dialogue with patients early on in their treatment course and throughout their therapy and the end result is getting these patients the help and therapy that they need and ultimately improving their quality of life. The second manuscript takes the reader into the mind of the patient, giving insight into the top 10 questions that patients may be thinking but not asking (17). This manuscript serves as a valuable reference for providers to utilize, helping them build a strong and trusting relationship with their patients.

As outlined, rectal cancer represents a comprehensive multidisciplinary challenge for many different providers who must work in concert to maximize the patient care experience. The goals of this focus issue of the *Journal of*

Gastrointestinal Oncology are to educate our readership about many of the issues that are faced when treating rectal cancer and to provide the necessary tools needed to enhance their care of these unique patients.

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Footnote

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References

1. Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9-29.
2. Cheng L, Eng C, Nieman LZ, et al. Trends in colorectal cancer incidence by anatomic site and disease stage in the United States from 1976 to 2005. Am J Clin Oncol 2011;34:573-580.
3. Siegel R, Ward E, Brawley O, et al. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 2011;61:212-236.
4. Patel SG, Ahnen DJ. Familial colon cancer syndromes: an update of a rapidly evolving field. Curr Gastroenterol Rep 2012;14:428-438.
5. Schlussel AT, Gagliano RA, Seto-Donlon S, et al. The evolution of colorectal cancer genetics: unraveling the mystery—Part 1: from discovery to practice. J Gastrointest Oncol 2014;5:326-335.
6. Schlussel AT, Gagliano RA, Seto-Donlon S, et al. The evolution of colorectal cancer genetics: unraveling the mystery—Part 2: clinical implications and applications. J Gastrointest Oncol 2014;5:336-344.
7. Endreseth BH, Myrvold HE, Romundstad P, et al. Transanal excision vs. major surgery for T1 rectal cancer. Dis Colon Rectum 2005;48:1380-1388.
8. Heafner TA, Glasgow SC. A critical review of the role of local excision in the treatment of early (T1 and T2) rectal tumors. J Gastrointest Oncol 2014;5:345-352.
9. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731-1740.
10. Fung-Kee-Fung SD. Therapeutic approaches in the management of locally advanced rectal cancer. J Gastrointest Oncol 2014;5:353-361.
11. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol 2012;30:1926-1933.
12. Boland PM, Fakih M. The emerging role of neoadjuvant chemotherapy for rectal cancer. J Gastrointest Oncol 2014;5:362-373.
13. Donadon M, Ribero D, Morris-Stiff G, et al. New paradigm in the management of liver-only metastases from colorectal cancer. Gastrointest Cancer Res 2007;1:20-27.
14. Abdalla EK, Adam R, Bilchik AJ, et al. Improving resectability of hepatic colorectal metastases: expert consensus statement. Ann Surg Oncol 2006;13:1271-1280.
15. Clark ME, Smith RR. Liver directed therapies in metastatic colorectal cancer. J Gastrointest Oncol 2014;5:374-387.
16. Averyt JC, Nishimoto PW. Addressing sexual dysfunction in colorectal cancer survivorship care. J Gastrointest Oncol 2014;5:388-394.
17. Averyt JC, Nishimoto PW. Psychosocial issues in colorectal cancer survivorship: The top ten questions patients may not be asking. J Gastrointest Oncol 2014;5:395-400.

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Therapeutic approaches in the management of locally advanced rectal cancer

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Abstract: Combined-modality therapy, using radiotherapy and chemotherapy with surgery, has been the traditional therapeutic algorithm for locally advanced rectal cancer. Standard of care in the United States has evolved to include neoadjuvant concurrent chemotherapy and radiotherapy followed by surgical excision and adjuvant chemotherapy. This approach has led to a significant improvement in local recurrences (LR), to the point where distant sites are the more common site of failure. Further improvements in local control have failed to improve overall survival. This article reviews historical trials that shifted the treatment paradigm to the current standard of care, as well as recent research trials, which have sought to incorporate new treatment methodologies, and treatment agents to improve outcomes. Finally this article describes ongoing studies and their potential impact on the future of therapeutic management of locally-advanced rectal cancer.

Keywords: Rectal cancer; neoadjuvant therapy; combined modality therapy; radiation therapy

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Combined-modality therapy

Surgical resection has been the mainstay of definitive therapy for rectal cancer. Historically, recurrence rates with surgery alone were upwards of 50% (1-3). Adjuvant therapy in the form of combined post-operative radiotherapy and 5-fluorouracil (5-FU)—based chemotherapy was shown to improve local control and provide an overall survival benefit over surgery alone or surgery plus irradiation (4,5). As such, postoperative chemoradiotherapy (CRT) was recommended as the standard of care in patients with stage II (T3-T4) or stage III (node positive) rectal cancer by a National Institute of Health consensus conference in 1990 (6).

Total mesorectal excision (TME)

In addition to the incorporation of CRT, the now-widespread use of TME as pioneered by Heald *et al.* (7) significantly improved local recurrence (LR) rates when compared to rates using standard surgical technique. LR rates at 5 years in surgery-only arms of large randomized trials that did not mandate TME use were typically in excess of 25% (8,9), compared to 11% for surgery-only arms in trials that mandated TME use (10). When radiotherapy was added to surgical resection with standard technique, local control was improved by over 50% (local relapse rate of 11% with RT, 27% with surgery alone), and it also improved overall survival (9). Once TME was incorporated, radiotherapy had the same relative improvement in local relapse rates, but with less absolute benefit (5% with RT, 11% with TME alone) (11). Radiotherapy, when combined with TME, had a lesser absolute local control benefit, and thus failed to further increase overall survival.

Neoadjuvant chemoradiation

The current standard of care in the United States for stage II and stage III rectal cancer is neoadjuvant chemoradiation followed by surgical resection using a TME technique. The paradigm shift from postoperative to neoadjuvant therapy was largely a result of the German Rectal Cancer Study. The study randomized 823 patients with clinical

stage T3-4 or node positive rectal cancer to surgery with TME followed by postoperative CRT or preoperative CRT followed by TME 6 weeks later. The preoperative regimen consisted of 50.4 Gy delivered using either a 3- or 4-field box technique with continuous-infusion 5-FU (1,000 mg/m^2) on days 1-5 of weeks 1 and 5. The postoperative regimen was identical, except for a 5.4 Gy boost (55.8 Gy total) to the postoperative tumor bed. In both arms, an additional 4 cycles of bolus 5-FU (500 mg/m^2 every 4 weeks) was given, starting either 4 weeks after surgery (in the preoperative group), or 4 weeks after chemoradiation (in the postoperative group).

At 5 years, there was a statistically significant lower number of LRs in the preoperative CRT arm (6% *vs.* 13%, P=0.006). However, there were no significant differences in the rates of distant metastases, disease-free survival, or overall survival. After preoperative CRT, there was evidence of tumor downstaging, with 8% of patients demonstrating histopathological complete response (pCR). Twenty five percent of patients receiving preoperative CRT had positive lymph nodes (compared to 40% who had surgery first in the postoperative CRT arm). Prior to randomization, every patient was evaluated by a surgeon for the need to perform an abdominoperineal resection (APR), resulting in permanent colostomy. In the group of patients deemed to require APR, preoperative CRT resulted in a higher rate of sphincter-preserving surgeries (39% *vs.* 19%, P=0.004) actually performed. There were fewer grade 3 or 4 acute (27% *vs.* 40%, P=0.001) and late toxicities (14% *vs.* 24%, P=0.001) in the preoperative CRT group (12). After 11 years of follow up, the significant LR benefit persisted (10-year cumulative incidence of 7.1% *vs.* 10.1%, P=0.048). There were also no significant differences in the 10-year cumulative incidence of distant metastases, disease-free survival and overall survival (13).

The findings of the German rectal trial were further supported by that of the National Surgical Adjuvant Breast and Bowel Project (NSABP) R-03 trial, which also compared preoperative and postoperative CRT. The radiation (45 Gy plus a 5.4 Gy boost) and chemotherapy (5-FU plus leucovorin) were identical in both arms. Surgery (TME was not mandated) followed CRT after 8 weeks in the preoperative group. The trial closed early secondary to poor accrual. Despite enrolling only 267 of a planned 900 patients, the trial demonstrated a 5-year disease-free survival improvement (64.7% *vs.* 53.4%) favoring preoperatively-treated patients. A pCR was achieved in 15% of the preoperative patients (14).

Shortly after publication of the landmark German study, the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for locally advanced resectable rectal cancer included neoadjuvant RT with concurrent 5-FU infusion, followed by TME and an adjuvant course of consolidative chemotherapy. This approach has been widely adopted across the United States (15).

Neoadjuvant short-course radiotherapy

In some European countries, instead of preoperative CRT, a short-course of preoperative radiotherapy alone (SC-RT) is used. The Swedish Rectal Cancer Trial randomized 1,168 patients to receive 25 Gy in 5 fractions followed by surgery within 1 week, or surgery alone. TME was not mandated in this trial. At 5 years, radiotherapy reduced LRs (11% *vs.* 27%, P<0.001), and improved overall survival (58% *vs.* 48%, P<0.004) compared to surgery alone (9). After 13 years, these benefits persisted (8). The Dutch TME trial randomized 1,805 patients to be treated with or without SC-RT followed by TME. At 5 years, a LR benefit was seen (5.6% *vs.* 10.9%, P<0.001); however no improvement in overall survival was demonstrated. Additionally, the LR benefit was limited to those patients with negative circumferential resection margins (CRM) (10). After 12 years of follow up, the effect of SC-RT on LR persisted. In an unplanned subgroup analysis, in patients with a negative CRM, SC-RT was found to improve cancer-specific survival (50% *vs.* 40%, P=0.03) (11).

The Medical Research Council (MRC) in the United Kingdom and the National Cancer Institute of Canada (NCIC) randomized 1,350 patients in four countries to preoperative radiotherapy (25 Gy) or to surgery with selective postoperative CRT (45 Gy in 25 fractions with concurrent infusion 5-FU). CRT was given only to patients with positive CRM (57 of 606 patients). TME was not mandated but was performed in 92% of patients. With a median follow up of 4 years, LR was 4.4% in the preoperative SC-RT group, versus 10.6% in the selective postoperative CRT group (P<0.0001). Also noted was an improvement in disease-free survival (77.5% *vs.* 71.5%, P=0.013) without an overall survival benefit (16).

Neoadjuvant short-course radiotherapy versus long-course CRT

Both approaches to neoadjuvant therapy described above have shown benefits over no additional therapy and adjuvant

chemoradiation. However, due to differences in eligibility criteria, efficacy comparisons between trials using different approaches are problematic. Trials that used SC-RT enrolled patients with 'resectable' rectal cancer (cT1-3Nx), where the CRT trials allowed only Stage II (T3-4) or Stage III (node positive) disease.

Bujko *et al.* were the first to conduct a randomized trial between the two neoadjuvant therapies. A total of 316 patients with clinically staged T3 or T4 rectal cancers were randomized between neoadjuvant short-course radiotherapy (25 Gy in 5 fractions) followed by TME within 7 days or "long-course" CRT (LC-CRT, 50.4 Gy in 28 fractions with concurrent 5-FU and leucovorin) with TME to follow at 4-6 weeks. Postoperative chemotherapy was allowed as indicated. This trial was powered to show a difference of 15% or greater in sphincter preservation (17,18).

After 4 years of follow up, the authors reported no significant difference in sphincter-sparing, LR (9% *vs.* 14% in short course and long course, respectively), or survival. Acute toxicity was higher in the CRT group (18%, compared to 3% in the radiotherapy-alone group, P<0.001). However, there was no difference in late toxicity or severe late toxicities (17).

More recently, Ngan *et al.* reported the outcomes of the Trans-Tasmanian Radiation Oncology Group (TROG) trial 01.04. A total of 326 patients with ultrasound or MRI-staged T3N0-2 rectal cancers were randomized between short-course preoperative radiotherapy (25 Gy in 5 fractions) followed by surgery within 1 week or long-course preoperative CRT (50.4 Gy in 28 fractions with concurrent 5-FU) followed by surgery within 4-6 weeks. Both groups received adjuvant chemotherapy (six cycles for the short-course group, four cycles for the long-course group). The trial was powered to show a 10% absolute difference in LR (15% short course, 5% long course).

After 3 years of follow up, they reported no significant difference in local relapse (7.5% for short-course, compared to 4.4% for long course, P=0.24). Additionally, no difference was seen in 5-year distant recurrences, relapse-free survival, or overall survival. There was no difference noted in sphincter-sparing. Grade 3 or 4 late toxicity, as reported at 3 years, was not different between the two groups (19).

A third randomized trial of neoadjuvant regimens is the Stockholm III trial, and is only published as an interim analysis. This study randomized 303 patients amongst 3 treatment arms. Two treatment arms used short course RT (25 Gy in 5 fractions) followed by either immediate surgery within 1 week (n=118), or delayed surgery in 4-8 weeks (n=120). Patients in the third treatment arm received long course radiotherapy (50 Gy in 25 fractions) alone, followed by surgery in 4-8 weeks. The significant finding reported in the interim analysis was the rate of postoperative complications in patients randomized to short-course radiotherapy and surgery within a week. Postoperative complications differed according to the timing of surgery relative to the start date of radiotherapy. Significantly more complications were seen in 24 of 37 (65%) patients who underwent surgery 11-17 days after the start of RT, than in 29 of 75 (39%) patients who underwent surgery less than 11 days after the start of RT (P=0.04) (20).

Without any data to-date to suggest significant differences in survival, local control, or sphincter-sparing between neoadjuvant approaches, careful study of the long-term consequence of these treatments is paramount. Quality of life (QoL) data from the Polish study is reported at 1 year after surgery, with patient-reported QoL quantified using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire. Anorectal and sexual function were reported using a separate questionnaire. At a median time from surgery of approximately 1 year, there were no significant differences in global function in symptoms scales for QoL between patients who received SC-RT or LC-CRT prior to surgery. There were also no differences between patient groups in answers to questions regarding anorectal or sexual function (21).

QoL data from TROG 01.04 is reported in abstract form only. Unlike that from the Polish study, 5-year data is reported. The QLQ-C30 questionnaire was used to assess global health status, and the EORTC QLQ-CR38 module was used to measure pelvic function. At 5 years, global health status was not statistically different between arms. There was no clear difference in pelvic functioning or symptoms between the SC-RT and LC-CRT arms. This data has not yet been peer-reviewed (22). Finally, a German cross-sectional study was performed in 225 patients who either underwent SC-RT (29 Gy in 10 fractions) or LC-CRT prior to surgery and were still disease-free. With a median follow-up time of 67 months, QoL analysis was performed using the EORTC QLQ-C30 and QLQ-CR29 questionnaires. Despite a modified SC-RT fractionation, there was no difference in QoL observed between patients who received SC-RT and LC-CRT, except for improved physical functioning in the LC-CRT group (23).

The debate between SC-RT and LC-CRT as the optimal preoperative regimen prior to TME is ongoing. None of

Table 1 Outcomes of four recent trials incorporating oxaliplatin into neoadjuvant chemoradiation prior to surgical resection

Parameters	STAR-01	ACCORD 12	CARO/ARO/AIO-04	NSABP R-04
Number of patients	747	598	1,236	1,608
Preoperative RT (Gy)	50.4	50	50.4	50.4
5-FU based chemotherapy	CI-5-FU 225 mg/m^2 daily	Oral CAPE 1,600 mg/m^2 daily	CI-5-FU 250 mg/m^2 daily (+ OX) *vs.* Bolus 5-FU 1,000 mg/m^2 (week 1 and 5) alone	CI-5-FU 225 mg/m^2 daily OR CAPE 1,600 mg/m^2 daily
OX with *vs.* without	OX 60 mg/m^2 weekly	OX 50 mg/m^2 weekly	OX 50 mg/m^2 weekly	OX 50 mg/m^2 weekly
pCR rate (%)	16 *vs.* 16	19 *vs.* 14	17 *vs.* 13*	21 *vs.* 19
Sphincter-preservation (%)	81 *vs.* 79	78 *vs.* 75	76 *vs.* 75	60 *vs.* 64
Grade 3-4 toxicity (%)	24 *vs.* 8	25 *vs.* 11	23 *vs.* 20	15 *vs.* 7**

*, statistically significant; **, grade 3 and 4 diarrhea only; OX, oxaliplatin.

the data above shows significant differences either in long-term oncologic outcomes or patient-reported QoL.

Concurrent chemotherapy with preoperative radiotherapy

Fluorouracil-based chemotherapy has long been part of adjuvant therapy for rectal cancer. The route of administration (as a continuous or bolus infusion) has been examined in several studies when CRT was given in the adjuvant setting. One intergroup study compared continuous infusion (CI) 5-FU (225 mg/m^2 daily) and bolus 5-FU (500 mg/m^2 daily on days 1-3 and 36-39) during adjuvant radiotherapy. CI 5-FU was associated with reduced distant metastases and improved overall survival (24). In contrast, intergroup study INT-0144 showed that CI 5-FU and bolus 5-FU during adjuvant radiation for rectal cancer resulted in no difference in three-year disease-free survival or overall survival (25).

Capecitabine is an orally-administered prodrug that is enzymatically converted to 5-FU, and was designed to mimic CI 5-FU. In a German phase III trial, 392 patients with stage II/III rectal cancer were randomized to receive either CI 5-FU or capecitabine concurrently with radiotherapy (50.4 Gy) either in the adjuvant (213 patients) or neoadjuvant (161 patients) setting. There was no difference in local relapse or overall survival. However, patients receiving capecitabine had increased rates of tumor downstaging (55% *vs.* 39%) and pathological node-negative rates (71% *vs.* 56%) compared to those receiving CI 5-FU. Patients receiving capecitabine also had significantly more hand-foot skin reactions (31% *vs.* 2%), but less neutropenia (35% *vs.* 25%) overall (26). Results of NSABP R-04 have been reported twice in abstract form so far (27,28). In this phase III trial, patients were randomized between CI 5-FU and oral capecitabine, with or without the addition of oxaliplatin (4 arm study). In both abstract reports, there were no statistical differences between pCR rate, sphincter-preservation, or surgical-downstaging. Taken together, the results of these two trials support oral capecitabine as a substitute for CI 5-FU when given concurrently with preoperative radiotherapy for rectal cancer.

Oxaliplatin, in combination with 5-FU and leucovorin (folinic acid), as part of the FOLFOX chemotherapy regimen, plays an important role in the treatment of colorectal cancer (29). As such, several trials have investigated the addition of oxaliplatin to preoperative 5-FU-based chemoradiation. The results of these trials are shown in *Table 1*. In summary, the addition of oxaliplatin to concurrent preoperative CRT has shown no improvement in tumor response (based on pCR rates), or surgical outcomes (based on sphincter-preservation rates). Its addition does significantly increase the toxicity during preoperative treatment. Thus, its addition cannot be justified based on these results.

Adjuvant chemotherapy

Following neoadjuvant CRT and surgical resection for stage II/III rectal cancer, the NCCN Guidelines recommend adjuvant chemotherapy regardless of the surgical pathology results. Despite limited data demonstrating the efficacy of this approach, adherence to this recommendation is fairly high. A recent study of adjuvant chemotherapy use

at several NCCN institutions between 2005 and 2010 showed that of 1,193 patients who received neoadjuvant therapy, 990 (83%) were also prescribed and initiated further adjuvant chemotherapy (30). Of the remaining patients, the most frequent reason for not recommending chemotherapy was comorbid illness (25 of 50 patients). The most frequent reason that chemotherapy was recommended but not received by the patient was patient refusal (54 of 74 patients).

Most of the evidence for the role adjuvant chemotherapy is from older studies using postoperative therapy alone. EORTC trial 22921 was a four-armed study comparing preoperative radiotherapy (45 Gy in 25 fractions) with or without concurrent chemotherapy (5-FU and leucovorin) and adjuvant chemotherapy (4 or more cycles, every 3 weeks). A total of 1,011 patients were randomized; 787 patients who had an R0 surgical resection with no distant spread before or at surgery were eligible for analysis of outcome by adjuvant treatment. In the initial report, there was no effect of adjuvant chemotherapy on disease-free survival or overall survival for the group as a whole. Adherence to postoperative chemotherapy was poor (43% of patients received at least 95% of the planned fluorouracil without delay) (31). Later, an unplanned subgroup analysis was published, showing a statistically significant survival benefit in patients who underwent tumor downstaging (ypT0-2) from neoadjuvant therapy (32). Long-term results (median follow up of 10.4 years) showed no difference in disease-free survival or overall survival in patients with tumor pathological downstaging, those without, or the group as a whole (33).

Adjuvant chemotherapy, for now, remains as part of recommended therapy in the United States. At several NCCN institutions, the rate of adjuvant chemotherapy prescription and initiation is quite high. However, with increased toxicity, poor adherence to the full prescription course and limited evidence of its benefit, newer clinical trials appear to be shifting further chemotherapy upfront instead of the adjuvant setting.

Neoadjuvant chemotherapy and CRT (or radiotherapy)

The EORTC study above and others (34) have concluded that the addition of chemotherapy to 'long-course' preoperative radiotherapy significantly improved local control. Local control has improved to the point that distant relapses are the more common site of first recurrence. With poor adherence to adjuvant chemotherapy and little evidence of its value, the role of neoadjuvant chemotherapy prior to neoadjuvant CRT is being actively investigated. Potential advantages of upfront chemotherapy include improved compliance, and the early treatment of micrometastases.

One phase II trial (Expert) out of the United Kingdom enrolled patients with high risk disease (based on CRM margin risk, low-lying tumors, T4 and/or node positive tumors) to receive 12 weeks of neoadjuvant capecitabine and oxaliplatin (CAPOX) followed by single-agent (capecitabine) CRT (54 Gy), TME, and four cycles of postoperative adjuvant capecitabine. A total of 105 eligible patients were enrolled. A total of 95 patients underwent TME, of whom 21 had a pCR (20% of eligible patients). Three-year progression-free and overall survival were 68% (95% CI, 59-77) and 83% (95% CI, 76-91), respectively. The authors report acceptable safety despite nine cardiac or thromboembolic events (9%) of which four died, requiring amendment of the protocol for cardiovascular safety (35).

Another randomized, phase II Spanish trial (Grupo Cancer de Recto 3 Study) randomized 108 patients with locally advanced rectal cancer to receive either preoperative CRT (50.4 Gy with concurrent capecitabine and oxaliplatin) followed by TME and postoperative chemotherapy (capecitabine-oxaliplatin), or 'induction' chemotherapy (capecitabine-oxaliplatin) followed by the same CRT and TME (no postoperative chemotherapy). The group of patients that received induction chemotherapy had greater chemotherapy dose exposure than those patients that received adjuvant chemotherapy. However, there was no statistical difference between pCR rate (13.5% and 14.3%), downstaging, tumor regression, or R0 resection. Grade 3 and 4 toxicities were similar in both arms during CRT. Toxicity was compared between the adjuvant chemotherapy window in the first group and the induction chemotherapy window in the second group. Despite a greater chemotherapy exposure for patients who received induction chemotherapy, there was greater grade 3 and 4 toxicity during adjuvant chemotherapy (54% *vs.* 37%, respectively, P=0.0004) (36).

Another approach being investigated in phase III studies, is the use of short-course radiotherapy (25 Gy in 5 fractions), followed by neoadjuvant capecitabine-oxaliplatin chemotherapy and TME. This approach is the experimental arm in both the Rectal Cancer and Preoperative Induction Therapy Followed by Dedicated Operation (RAPIDO) trial, and a Polish Colorectal Cancer Study Group (5-FU,

leucovorin and oxaliplatin chemotherapy) trial. The standard arm in these trials is long-course CRT. It will be imperative for both trials to carefully detail not only differences in outcomes, but also toxicity (acute, late and post-surgical complications) and QoL to definitively differentiate the two approaches.

Neoadjuvant chemotherapy alone

In the TME era, with high-quality MRI and ultrasound staging, the option for omitting preoperative radiotherapy in carefully selected patients has been raised. Preliminary, pilot data out of Memorial Sloan-Kettering Cancer Center treated 32 patients with FOLFOX (5-FU, leucovorin and oxaliplatin) plus bevacizumab alone followed by TME. Pathologic complete response rate was 25% with a 4-year LR rate and disease-free survival of 0% and 84%, respectively (37).

These exciting results have prompted the preoperative radiation or selective preoperative radiation and evaluation before chemotherapy and TME (PROSPECT or N1048) trial. In this multi-institution, phase II/III study, only patients with 'low-risk' Stage II/III rectal cancer [candidates for sphincter-sparing surgeries, CRM not-threatened, non-T4 tumors, clinically node-positive disease must be N1 (1-3 nodes) only] are eligible. Patients are randomized to one of two treatment arms. Group 1 patients receive six cycles of FOLFOX alone followed by restaging. Patients with a greater than 20% tumor regression proceed to surgery with TME. Patients with a less than 20% tumor response undergo CRT followed by TME. Group 2 receives standard-of-care neoadjuvant CRT, followed by TME. Patients in both groups may receive adjuvant chemotherapy.

Targeted therapies

Bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor, has been studied in phase I and II trials incorporating it with conventional preoperative 5-FU based CRT. The data so far has shown encouraging pCR rates (16-32%) (38-41), but several studies report increased rates of postoperative wound complications (38-42).

Cetuximab and panitumumab are both humanized monoclonal antibodies against epidermal growth factor receptor approved for use in patients with metastatic colorectal cancer. Phase I/II trials with cetuximab use in preoperative CRT for rectal cancer, as a whole, have shown mixed efficacy with not-insignificant grade 3-4 gastrointestinal toxicity (43). One randomized phase II clinical trial (EXPERT-C) was conducted following a previous trial (EXPERT) looking at neoadjuvant chemotherapy, followed by chemoradiation then surgery. In the EXPERT-C trial, 165 patients received capecitabine-oxaliplatin chemotherapy, followed by capecitabine CRT with or without cetuximab, then TME. In tumors with wild-type k-ras, addition of cetuximab did not improve the primary endpoint of pCR or progression-free survival. Cetuximab did improve response rates and 3-year overall survival (HR 0.27, P=0.034) (44).

The effect of these targeted therapies on long-term outcomes and side-effects requires further study, although the mixed results thus far have been disappointing.

IMRT for rectal cancer

As seen in all of the studies described here, the ability of patients to adhere to treatment schedules and complete full courses of chemotherapy and CRT is a major issue. The most common radiation-induced toxicities are skin and gastrointestinal (diarrhea)-related. Intensity-modulated radiotherapy (IMRT) use in other disease sites within the pelvis, such as prostate, anus and GYN, has been shown to reduce treatment-related morbidities (45-47).

Thus far, evidence for IMRT use in rectal cancer has been building. One dosimetric study has shown that IMRT, when compared to 3D-conformal radiotherapy (3D), reduces the volume of small bowel receiving 15 Gy or higher (V15) (48), a factor shown to be associated with increased rates of Grade 3 diarrhea (49). Another dosimetric study showed that the small bowel V15 is improved, even if the patient is treated in the prone position with a belly board (a device often used to displace small bowel out of the radiation field (50). Clinical data, to-date, consists mostly retrospective series showing reduction in grade 2 or higher GI toxicity and diarrhea (51,52). A recently completed phase II study, RTOG 08-22, examined the role of preoperative radiotherapy using IMRT concurrently with capecitabine and oxaliplatin, and results are pending.

Conclusions

In the treatment of locally advanced rectal cancer, major paradigm shifts such as the TME surgical technique and the use of neoadjuvant therapy instead of adjuvant, have led to significant advances in the local control and overall survival of these patients. In the United States and several European

countries, the standard of care is neoadjuvant CRT followed by surgery with TME and adjuvant chemotherapy. In some countries, short-course radiotherapy, in lieu of CRT, is used. In that case, surgery follows immediately (within 1 week) as opposed to a 4-8 weeks after CRT. Two major phase III trials have compared these two approaches, neither of which found any differences in oncologic or QoL outcomes. A clear theme from several studies included in this review, is that adjuvant therapy adds to patient toxicity. The toxicity of adjuvant chemotherapy has resulted in low adherence to the protocols, and there does not appear to be a clear benefit to this approach. In the modern era of more accurate MRI and/or ultrasound staging, and newer chemotherapeutic drugs and targeted therapies, recent research has attempted to incorporate them into the neoadjuvant setting with mixed success. Current ongoing trials seek to use more aggressive chemotherapy up front, with or without radiotherapy or CRT prior to surgery. Going forward, it will be imperative to balance aggressive therapy to control local relapse and distant metastases with long-term toxicity and effects on patient QoL, as these patients live longer after surviving their disease. It is important to continue to investigate treatments to maximize therapeutic effect (neoadjuvant FOLFOX, targeted drugs), but also to minimize toxicity (IMRT use).

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Footnote

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References

1. Gunderson LL, Sosin H. Areas of failure found at reoperation (second or symptomatic look) following "curative surgery" for adenocarcinoma of the rectum. Clinicopathologic correlation and implications for adjuvant therapy. Cancer 1974;34:1278-1292.
2. Cass AW, Million RR, Pfaff WW. Patterns of recurrence following surgery alone for adenocarcinoma of the colon and rectum. Cancer 1976;37:2861-2865.
3. Gilbertsen VA, Nelms JM. The prevention of invasive cancer of the rectum. Cancer 1978;41:1137-1139.
4. Douglass HO Jr, Moertel CG, Mayer RJ, et al. Survival after postoperative combination treatment of rectal cancer. N Engl J Med 1986;315:1294-1295.
5. Krook JE, Moertel CG, Gunderson LL, et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. N Engl J Med 1991;324:709-715.
6. NIH consensus conference. Adjuvant therapy for patients with colon and rectal cancer. JAMA 1990;264:1444-1450.
7. Heald RJ. A new approach to rectal cancer. Br J Hosp Med 1979;22:277-281.
8. Folkesson J, Birgisson H, Pahlman L, et al. Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. J Clin Oncol 2005;23:5644-5650.
9. Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. N Engl J Med 1997;336:980-987.
10. Peeters KC, Marijnen CA, Nagtegaal ID, et al. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. Ann Surg 2007;246:693-701.
11. van Gijn W, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol 2011;12:575-582.
12. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731-1740.
13. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol 2012;30:1926-1933.
14. Roh MS, Colangelo LH, O'Connell MJ, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. J Clin Oncol 2009;27:5124-5130.
15. Reyngold M, Niland J, ter Veer A, et al. Neoadjuvant radiotherapy use in locally advanced rectal cancer at NCCN member institutions. J Natl Compr Canc Netw 2014;12:235-243.
16. Sebag-Montefiore D, Stephens RJ, Steele R, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet 2009;373:811-820.
17. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. Long-term results of a randomized trial comparing

preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg 2006;93:1215-1223.
18. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomised trial comparing short-term radiotherapy vs. conventionally fractionated radiochemotherapy. Radiother Oncol 2004;72:15-24.
19. Ngan SY, Burmeister B, Fisher RJ, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. J Clin Oncol 2012;30:3827-3833.
20. Pettersson D, Cedermark B, Holm T, et al. Interim analysis of the Stockholm III trial of preoperative radiotherapy regimens for rectal cancer. Br J Surg 2010;97:580-587.
21. Pietrzak L, Bujko K, Nowacki MP, et al. Quality of life, anorectal and sexual functions after preoperative radiotherapy for rectal cancer: report of a randomised trial. Radiother Oncol 2007;84:217-225.
22. Ngan S, Fisher R, Burmeister B, et al. Long-term Quality of Life in patients treated in TROG 01.04: a randomized trial comparing short course and long course preoperative radiation therapy for rectal cancer. Int J Radiat Oncol 2012;84:s143-s144.
23. Guckenberger M, Saur G, Wehner D, et al. Long-term quality-of-life after neoadjuvant short-course radiotherapy and long-course radiochemotherapy for locally advanced rectal cancer. Radiother Oncol 2013;108:326-330.
24. O'Connell MJ, Martenson JA, Wieand HS, et al. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. N Engl J Med 1994;331:502-507.
25. Smalley SR, Benedetti JK, Williamson SK, et al. Phase III trial of fluorouracil-based chemotherapy regimens plus radiotherapy in postoperative adjuvant rectal cancer: GI INT 0144. J Clin Oncol 2006;24:3542-3547.
26. Hofheinz RD, Wenz F, Post S, et al. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial. Lancet Oncol 2012;13:579-588.
27. Roh MS, Colangelo LH, O'Connell MJ, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. J Clin Oncol 2009;27:5124-5130.
28. Allegra CJ, Yothers G, O'Connell MJ, et al. Neoadjuvant therapy for rectal cancer: Mature results from NSABP protocol R-04. J Clin Oncol 2014;32:abstr 390.
29. Sanoff HK, Carpenter WR, Martin CF, et al. Comparative effectiveness of oxaliplatin vs non-oxaliplatin-containing adjuvant chemotherapy for stage III colon cancer. J Natl Cancer Inst 2012;104:211-227.
30. Khrizman P, Niland JC, ter Veer A, et al. Postoperative adjuvant chemotherapy use in patients with stage II/III rectal cancer treated with neoadjuvant therapy: a national comprehensive cancer network analysis. J Clin Oncol 2013;31:30-38.
31. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006;355:1114-1123.
32. Collette L, Bosset JF, den Dulk M, et al. Patients with curative resection of cT3-4 rectal cancer after preoperative radiotherapy or radiochemotherapy: does anybody benefit from adjuvant fluorouracil-based chemotherapy? A trial of the European Organisation for Research and Treatment of Cancer Radiation Oncology Group. J Clin Oncol 2007;25:4379-4386.
33. Bosset JF, Calais G, Mineur L, et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. Lancet Oncol 2014;15:184-190.
34. Gérard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. J Clin Oncol 2006;24:4620-4625.
35. Chua YJ, Barbachano Y, Cunningham D, et al. Neoadjuvant capecitabine and oxaliplatin before chemoradiotherapy and total mesorectal excision in MRI-defined poor-risk rectal cancer: a phase 2 trial. Lancet Oncol 2010;11:241-248.
36. Fernández-Martos C, Pericay C, Aparicio J, et al. Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo cancer de recto 3 study. J Clin Oncol 2010;28:859-865.
37. Schrag D, Weiser MR, Goodman KA, et al. Neoadjuvant chemotherapy without routine use of radiation therapy for patients with locally advanced rectal cancer: a pilot trial. J Clin Oncol 2014;32:513-518.
38. Willett CG, Duda DG, di Tomaso E, et al. Efficacy, safety, and biomarkers of neoadjuvant bevacizumab,

radiation therapy, and fluorouracil in rectal cancer: a multidisciplinary phase II study. J Clin Oncol 2009;27:3020-3026.
39. Resch G, De Vries A, Öfner D, et al. Preoperative treatment with capecitabine, bevacizumab and radiotherapy for primary locally advanced rectal cancer--a two stage phase II clinical trial. Radiother Oncol 2012;102:10-13.
40. Spigel DR, Bendell JC, McCleod M, et al. Phase II study of bevacizumab and chemoradiation in the preoperative or adjuvant treatment of patients with stage II/III rectal cancer. Clin Colorectal Cancer 2012;11:45-52.
41. Crane CH, Eng C, Feig BW, et al. Phase II trial of neoadjuvant bevacizumab, capecitabine, and radiotherapy for locally advanced rectal cancer. Int J Radiat Oncol Biol Phys 2010;76:824-830.
42. Uehara K, Hiramatsu K, Maeda A, et al. Neoadjuvant oxaliplatin and capecitabine and bevacizumab without radiotherapy for poor-risk rectal cancer: N-SOG 03 Phase II trial. Jpn J Clin Oncol 2013;43:964-971.
43. Glynne-Jones R, Mawdsley S, Harrison M. Cetuximab and chemoradiation for rectal cancer--is the water getting muddy? Acta Oncol 2010;49:278-286.
44. Dewdney A, Cunningham D, Tabernero J, et al. Multicenter randomized phase II clinical trial comparing neoadjuvant oxaliplatin, capecitabine, and preoperative radiotherapy with or without cetuximab followed by total mesorectal excision in patients with high-risk rectal cancer (EXPERT-C). J Clin Oncol 2012;30:1620-1627.
45. Kachnic LA, Winter K, Myerson RJ, et al. RTOG 0529: a phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. Int J Radiat Oncol Biol Phys 2013;86:27-33.
46. Zelefsky MJ, Fuks Z, Hunt M, et al. High-dose intensity modulated radiation therapy for prostate cancer: early toxicity and biochemical outcome in 772 patients. Int J Radiat Oncol Biol Phys 2002;53:1111-1116.
47. Mundt AJ, Lujan AE, Rotmensch J, et al. Intensity-modulated whole pelvic radiotherapy in women with gynecologic malignancies. Int J Radiat Oncol Biol Phys 2002;52:1330-1337.
48. Robertson JM, Lockman D, Yan D, et al. The dose-volume relationship of small bowel irradiation and acute grade 3 diarrhea during chemoradiotherapy for rectal cancer. Int J Radiat Oncol Biol Phys 2008;70:413-418.
49. Engels B, De Ridder M, Tournel K, et al. Preoperative helical tomotherapy and megavoltage computed tomography for rectal cancer: impact on the irradiated volume of small bowel. Int J Radiat Oncol Biol Phys 2009;74:1476-1480.
50. Kim JY, Kim DY, Kim TH, et al. Intensity-modulated radiotherapy with a belly board for rectal cancer. Int J Colorectal Dis 2007;22:373-379.
51. Parekh A, Truong MT, Pashtan I, et al. Acute gastrointestinal toxicity and tumor response with preoperative intensity modulated radiation therapy for rectal cancer. Gastrointest Cancer Res 2013;6:137-143.
52. Samuelian JM, Callister MD, Ashman JB, et al. Reduced acute bowel toxicity in patients treated with intensity-modulated radiotherapy for rectal cancer. Int J Radiat Oncol Biol Phys 2012;82:1981-1987.

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Considering value in rectal cancer surgery

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Provenance: This is a Guest Commentary commissioned by Editor-in-Chief Minhua Zheng (Department of General Surgery, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai Minimal Invasive Surgery, Shanghai, China).

Comment on: Silva-Velazco J, Dietz DW, Stocchi L, et al. Considering Value in Rectal Cancer Surgery: An Analysis of Costs and Outcomes Based on the Open, Laparoscopic, and Robotic Approach for Proctectomy. Ann Surg 2016. [Epub ahead of print].

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As new surgical technologies are introduced into the market, their cost and overall efficacy must be critically evaluated. One area of ongoing debate is the role of robotic surgery in rectal cancer resection. As it is clear that robotic surgery is becoming increasingly utilized for proctectomy in the US, a better understanding of the potential benefits and limitations is needed. Particularly three areas need to be addressed: (I) short-term oncologic outcomes: quality of TME resection, margin status, lymph node harvest; (II) cost; and (III) long-term oncologic outcomes. In the May 2016 issue of *Annals of Surgery* (Epub ahead of print), Silva-Velazco *et al*. have introduced an interesting and unique article titled "Considering value in rectal cancer surgery: an analysis of costs and outcomes based on the open, laparoscopic, and robotic approach for proctectomy" comparing value in open versus laparoscopic versus robotic rectal cancer surgery.

To compare the different approaches to rectal cancer surgery, the authors used a single center prospective database spanning from January 2010 to December 2014. An intent to treat analysis was used: if a minimally invasive surgery was converted to open, the patient remained in the original minimally invasive cohort. A total of 488 patients were included. Demographics between the three groups were similar with the exception of female sex (significantly higher in laparoscopic group) and body mass index (significantly lower in the laparoscopic group). Major comorbidities amongst the groups were similar. Tumor characteristics (pathological and clinical TNM staging, tumor grade, use of neoadjuvant chemoradiotherapy) were similar except for a significantly higher rate of positive lymph nodes on final pathology in the open surgery group. The endpoints evaluated were direct costs of hospitalization for the primary resection, 30-day readmissions, and ileostomy closure. Secondary endpoints were short-term oncologic results, postoperative outcomes, and 30-day perioperative morbidity. To compare cost data, total technical direct cost was collected for all hospitalizations. This cost data includes all costs accrued by the patient from admission to discharge: imaging, anesthesia, medications, OR time, consumable supplies, nursing, diagnostic procedures, laboratory tests, pathology assessment, and all other ancillary services needed during the admission. It does not included surgeon or other physician salaries. Of note, a portion of the total cost of the robot itself was applied evenly to all three patient groups, and no additional fees for robotic surgery were captured.

The first issue addressed when comparing the three groups is short-term oncologic outcomes. To characterize this variable, the authors used four criteria: (I) number of lymph nodes examined; (II) involvement of the distal margin; (III) involvement of the circumferential resection margin (CRM); (IV) mesorectal grading. If the distance between the tumor and the circumferential margin was less than or equal to 1 mm, the margin was considered involved. The authors defined a successful resection as one with a negative CRM, a negative distal margin, and completeness of the total mesorectal excision. When comparing the three groups, there were no significant differences between

any of the short-term oncologic outcome parameters. A successful resection was achieved in 83.9% to 89.5% of all cases. This data is compared to a recent national study examining the effects of surgical approach on short-term oncologic outcomes in rectal cancer. Utilizing the 2010 National Cancer Database, Midura *et al.* analyzed outcomes of 8,712 patients undergoing open, laparoscopic, and robotic resections (1). The short-term oncologic outcomes measured were resection margin status and lymph node harvest. Overall, 7% of cases had positive margins, and one-third of cases had an inadequate number of lymph nodes harvested (<12). After propensity score matching analysis, a minimally invasive approach was associated with an improved R0 resection rate, though despite matching, these patients were not randomized, and the distinct possibility of selection bias, where more difficult tumors received open surgery exists. The paper by Silva-Velazco *et al.* suggests overall higher success in regards to short term surgical outcomes than national data; however, a relatively small sample size and a single-center study can skew these results. Recent randomized clinical trials investigating laparoscopic approach versus open approach in rectal surgery have been published. ACOSOG Z-6051 failed to show non-inferiority of laparoscopic surgery when compared to open surgery regarding a composite oncologic outcome specified as a distal margin without tumor (greater than >1 mm), a circumferential radial margin greater than 1 mm, and the total mesorectal excision quality (complete: smooth surface of mesorectal fascia with all fat contained in the enveloping fascia to a level 5 cm below the tumor for upper rectal cancer or the entire mesorectal envelope for low rectal cancer; nearly complete: the mesorectal envelop was intact except for defects no more than 5 mm deep) (2). Additionally, in the COREAN trial, there was no statistically significant difference in short-term oncologic outcomes between laparoscopic and open surgical approaches following neoadjuvant therapy (3). While there are no large randomized controlled trials published evaluating laparoscopic versus robotic rectal surgery, the ROLARR trial currently underway aims to compare the two. Preliminary data shows no statistically significant difference in conversion to open surgery or completeness of the CRM, though long-term oncologic data have yet to be seen.

The second issue addressed in the paper by Silva-Velazco *et al.* is cost. The authors showed that the overall cost was 31% higher for patients undergoing robotic proctectomy when compared to open surgery. The cost of laparoscopic surgery was only 4% higher when compared to open surgery. This was despite shorter hospital stays and lower rates of complications. Recent literature supports this finding as well. Other studies demonstrate a 32% higher cost associated with robotic surgery when compared to laparoscopic surgery (4) and a 59% increase with robotic surgery compared to open surgery (5).

One issue not addressed in this study is long-term oncologic outcomes for rectal surgery. The COREAN study found that there was no significant difference in long term oncologic outcomes (3-year disease free survival) between laparoscopic and open rectal surgery following neoadjuvant therapy (3). Unfortunately, there is no data looking at long term oncologic outcomes following robotic rectal surgery.

Though robotic surgery is being utilized increasingly for rectal cancer, current data shows longer operative times, higher cost and unclear short-term oncologic benefit. The ultimate utility of this technology will be better understood when long-term oncologic outcomes are available.

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Footnote

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

References

1. Midura EF, Hanseman DJ, Hoehn RS, et al. The effect of surgical approach on short-term oncologic outcomes in rectal cancer surgery. Surgery 2015;158:453-459.
2. Fleshman J, Branda M, Sargent DJ, et al. Effect of Laparoscopic-Assisted Resection vs Open Resection of Stage II or III Rectal Cancer on Pathologic Outcomes: The ACOSOG Z6051 Randomized Clinical Trial. JAMA 2015;314:1346-1355.
3. Kang SB, Park JW, Jeong SY, et al. Open versus laparoscopic surgery for mid or low rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): short-term outcomes of an open-label randomised controlled trial. Lancet Oncol 2010;11:637-645.

4. Keller DS, Senagore AJ, Lawrence JK, et al. Comparative effectiveness of laparoscopic versus robot-assisted colorectal resection. Surg Endosc 2014;28:212-221.
5. Ramji KM, Cleghorn MC, Josse JM, et al. Comparison of clinical and economic outcomes between robotic, laparoscopic, and open rectal cancer surgery: early experience at a tertiary care center. Surg Endosc 2016;30:1337-1343.

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Defining the distal margin of rectal cancer for surgical planning

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Abstract: Accurate measurement of the distal rectal tumor margin is essential in selecting the appropriate surgical procedure. However, there is no standard measurement method. The National Cancer Institute consensus group recommends use of the anal verge (AV) as a landmark, and the European Society of Gastrointestinal and Abdominal Radiology recommends use of the anorectal ring (ARR). In addition, whether measurements should be made on double contrast barium enema (BE) radiographs or magnetic resonance (MR) images remains controversial. We measured the distal tumor margin on both BE and MR images obtained preoperatively from 52 patients who underwent sphincter-saving resection for rectal cancer. The distances from the distal end of the tumor to the AV and the ARR were measured on both types of images, and the variability was investigated by Bland-Altman analysis. The mean distance from the tumor to the AV was 8.9 cm on the BE radiographs and 7.7 cm on the MR images (P=0.013). The mean distances to the ARR were 6.8 and 5.6 cm, respectively (P=0.070). Significant proportional bias was shown as the measured distances increased, the difference between the BE- and magnetic resonance imaging (MRI)-based measurements increased. Use of one or the other landmark did not affect selection of the appropriate surgical procedure. We conclude that an approximate 1-cm underestimation should be taken into account when MRI-based measurement of the distal rectal tumor margin is used to choose between sphincter-saving resection and abdominoperineal resection.

Keywords: Double-contrast barium enema; magnetic resonance imaging (MRI); rectal cancer; sphincter-preserving surgery

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Introduction

Rectal cancer is a common but serious disease for which the mortality rate is high. Despite major advances in surgical, radiologic, and oncologic treatments, the management of rectal cancer remains difficult, with a high local recurrence rate of up to 33% (1). Local recurrence is related to the surgeon's skill and experience. Because of the risk of local recurrence and the associated poor prognosis, appropriate surgical resection is required. Patients' quality of life is another issue, and for this reason, sphincter-sparing surgery has become a desirable option; it results in fewer complications than those associated with abdominoperineal resection (2).

The tumor location and the distal tumor margin are important factors upon which the surgical plan for patients with rectal cancer is based. Accurate measurement of the distal tumor margin is essential in planning the surgical procedure, even sphincter-saving resection. However, in the major rectal cancer trials, there has been no standard definition of the distal tumor margin in terms of the anal landmark used for measurement (3).

The National Cancer Institute consensus group recommends use of the anal verge (AV) in measuring the distal tumor margin (4). The AV is the outer margin of the anal canal and has, for decades, been recognized as an important anatomical landmark, especially since double contrast barium enema (BE) came into widespread use as the standard examination for colorectal cancer. The European Society of Gastrointestinal and Abdominal

Radiology recommends use of the anorectal ring (ARR) as the landmark (5). The ARR is a muscular structure at the junction between the anal canal and the rectum and can be thought of as the top of the puborectalis muscle. It may be the best landmark because it is well defined by magnetic resonance imaging (MRI) and is not affected by the length of the anal canal.

In Asia, BE is still commonly used to evaluate both tumor volume and tumor location in patients with rectal cancer. However, in Western countries, preoperative assessment of rectal cancer has shifted toward MRI because it serves as an essential tool for investigating the relations between the tumor, the sphincter, and the levator ani muscle (6). Traditionally, rectal cancers located less than 5 cm from the AV or less than 2 cm from the ARR have been treated by abdominoperineal resection (7). Because a few centimeters can amount to a large difference for patients who desire a sphincter-saving procedure, determining the exact level of the tumor in the rectum is crucial in deciding upon the appropriate surgical procedure. An additional factor that influences measurement of the distal tumor margin and the distance between the tumor and the anal landmark is the imaging modality used. Neither the landmarks nor the imaging modality applied have been investigated in sufficient detail.

We conducted a retrospective study to evaluate whether a difference exists between BE and MRI in depiction of the level of the tumor in patients with rectal cancer. Included in our evaluation was an assessment of whether image-based measurement of the distal tumor margin should be to the AV or to the ARR.

Methods

Study patients

Included in the study were 52 patients (34 men, 18 women) with primary rectal cancer who underwent sphincter-saving resection between April 2014 and March 2015 and for whom both BE and MRI had been performed preoperatively. Median age of these patients was 67 (range, 45–90) years, and median body mass index was 21.5 (15.1–28.7). All patients provided written informed consent for the surgical procedure.

BE, MRI, and measurements for surgical planning

BE was performed as a standard double contrast study under fluoroscopic guidance, by which we monitored progression of the barium column, colon distension, and mucosal coating. The following spot and overhead radiographs were obtained: anteroposterior, posteroanterior, and lateral views of the rectum. MRI was performed with a 1.5-tesla magnet (GE Healthcare Japan, Tokyo, Japan) and axial T1-, T2-, and diffusion-weighted images were obtained through the pelvis as well as sagittal 3D Cube T2-weighted sequences at the level of the tumor in the rectum. All T1- and T2-weighted sequences were turbo spin echo sequences. The distance from the distal end of the tumor at the rectal wall to the AV and then to the ARR was measured on both BE and magnetic resonance (MR) images. All measurements were recorded in centimeters.

Statistical analysis

Distances from the distal margin of the cancer to the AV and the ARR were measured for all patients individually, and mean (SD) and median (range) values were calculated for the total patients. Wilcoxon matched-pairs analysis was applied to differences in measured distances between imaging modalities. A P value of ≤ 0.05 was considered statistically significant. Bland-Altman plots were constructed to show the difference between the BE- and MRI-based measurements against the mean of the two measurements for each patient. Pearson correlation coefficients were calculated, and proportional bias between the two methods was estimated with a test of non-correlation.

Results

As shown on *Table 1*, mean distance from the distal end of the tumor to the AV was 8.9 (3.0) cm (median, 8.0 cm; range, 4.8–17.2 cm) on BE radiographs and 7.7 (2.6) cm (median, 7.0 cm; range, 4.3–15.5 cm) on MR images. The maximum difference between the BE-based and MRI-based distances to the AV was 4.7 cm, with a mean distance of 1.2 cm, and this difference was significant (P=0.013). Differences between the BE- and MRI-based measurements varied, as shown on the Bland-Altman plot in *Figure 1*. The plot also shows significant proportional bias: as the distance to the AV increased, the difference between the BE- and MRI-based measurements increased.

As shown on *Table 2*, mean distance to the ARR was 6.8 (2.8) cm (median, 5.8 cm; range, 2.8–15.0) cm on BE radiographs and 5.6 (2.6) cm (median, 5.0 cm; range, 2.0–12.5 cm) on MR images. This difference was not significant

Table 1 The distance from the distal end of the tumor to the AV

Variable	Barium enema (cm)	MRI (cm)
Mean (SD)	8.9 (3.0)	7.7 (2.6)
Minimum	4.8	4.3
25th percentile	6.8	5.9
Median	8.0	7.0
75th percentile	11.2	9.4
Maximum	17.2	15.5

AV, anal verge; MRI, magnetic resonance imaging.

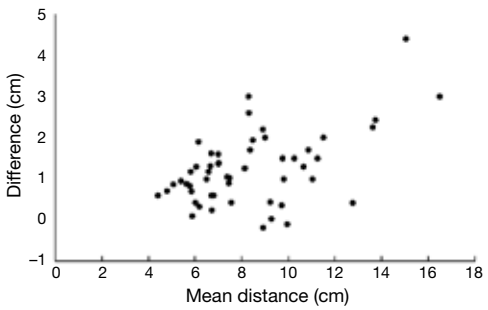

Figure 1 Bland-Altman plot of differences in barium enema- and magnetic resonance imaging-based measurements of the distance from the distal end of the tumor at the rectal wall to the anal verge.

Table 2 The distance from the distal end of the tumor to the ARR

Variable	Barium enema (cm)	MRI (cm)
Mean (SD)	6.8 (2.8)	5.6 (2.6)
Minimum	2.8	2.0
25th percentile	4.6	4.0
Median	5.8	5.0
75th percentile	8.4	7.0
Maximum	15.0	12.5

ARR, anorectal ring; MRI, magnetic resonance imaging.

(P=0.070). Differences between these BE- and MRI-based measurements varied, as shown on the Bland-Altman plot in *Figure 2*, and a proportional bias was again evident: as the distance to the ARR increased, the difference between the BE- and MRI-based measurements increased. The mean difference from the distal tumor margin to the ARR was, like that to the AV, 1.2 (median 1.1; range, −0.8–4.4) cm,

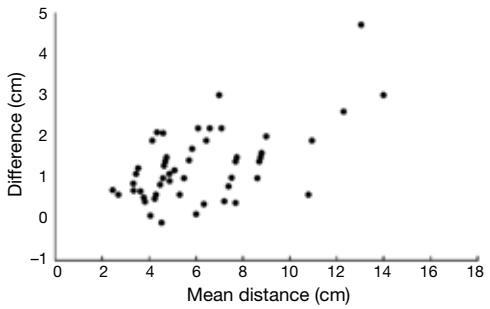

Figure 2 Bland-Altman plot of differences in barium enema- and magnetic resonance imaging-based measurements of the distance from the distal end of the tumor at the rectal wall to the anorectal ring.

and the difference in measurements, whether to the AV or to the ARR, was not significant (P=0.74).

Discussion

Studies conducted in Japan have documented 98–100% correspondence between the location of the tumor as detected on BE radiographs and the location of the tumor determined at the time of surgery. The reported correspondence when MRI is used is 75–83%. However, the precise difference between measurements determined by means of the two modalities was not described (8). We found an average difference of 1.2 cm in our total patient group. When the distance met the standard criteria for choosing a sphincter-preserving procedure, i.e., less than 5 cm to the AV or less than 2 cm to the ARR, the mean differences were 0.78 and 0.87 cm, respectively. The depth of extramural tumor spread and involvement of the mesorectal fat and mesorectal fascia are important factors when it comes to treatment planning. MRI is an excellent tool for depicting the tumor and the mesorectal fat by showing the contrast between them and also showing relations between the tumor, the sphincter, and the levator ani muscle. Reported agreement between MRI and pathologic T staging has ranged from 66% to 94% (9,10). MRI is often preferred because it contributes to both tumor detection and preoperative staging of the rectal cancer without radiation exposure, which poses a slight carcinogenic risk. BE remains an important complementary modality for evaluating the colon when intestinal stenosis prevents colonoscopy, and, over the past 40 years, BE has been widely used in Asia, including Japan, as the most cost-effective screening tool. BE is believed to be safer than

colonoscopy, and it shows the shape of the colon more precisely than does MRI (6). In cases of rectal cancer, a distal resection margin greater than 2 cm is considered optimal for avoiding local recurrence. The anal canal is approximately 3–4 cm in length; thus, rectal cancers located less than 5 cm from the AV are not generally considered for sphincter-saving resection (11). Therefore, the distance from the distal end of the tumor to the AV is an important factor in determining whether sphincter-sparing surgery can be performed. If the distance is inadequate, patients must undergo standard abdominoperineal resection, i.e., removal of the rectum with the anal sphincter complex, before creation of an abdominal colostomy. Complete tumor resection that spares the anal sphincters serves to preserve patients' quality of life.

Accurate measurement of the distal tumor margin is essential in planning the surgical procedure, but there is no standard definition that accounts for the imaging modality used. Ferri *et al.* (12) described measuring the distance from the distal tumor margin to the ARR on MR images to assess whether sphincter-sparing resection with an adequate tumor margin is feasible in their patients. They reported that invasion of the anal sphincter was correctly identified by means of MRI in 87% of their patients.

In our study, we evaluated and compared two imaging modalities for measurements upon which to base a decision to perform sphincter-preserving resection. We believe that when BE is performed, air pumped into the colon to achieve a double contrast effect is responsible for the difference we found between BE- and MRI-based measurements. We documented an average difference of 1.2 cm, which hitherto had not been reported. Whether the AV or ARR was used as the landmark, the results were the same.

We also found that the difference between MRI- and BE-based measurements increased as the distance from the AV increased. The maximum difference was 4.7 cm to the AV and 4.4 cm to the ARR, and these values are enough to warrant a change in the surgical plan from abdominoperineal resection to sphincter-saving resection. In fact, the tumor in 8 (15.3%) of our patients was less than 5 cm from the AV upon MRI-based measurement. On BE radiographs, however, the tumor was more than 5 cm from the AV in five of these eight patients. All eight patients were treated by sphincter-saving resection, some of whom might have undergone abdominoperineal resection if we had not relied on the MRI-based measurements.

Our study results appear to be of clinical importance. The difference between modalities in the resulting measurements is a critical factor upon which surgical decisions should be made. Rectal cancers initially determined on BE radiographs to be less than 5 cm from the AV might actually be indicated for sphincter-preserving resection.

MRI is being used increasingly for preoperative evaluation of rectal cancer. However, the distance from the distal tumor margin to the chosen anal landmark, which is a key factor in the feasibility of sphincter-sparing surgery, may be underestimated by MRI-based measurement. Clinicians should bear in mind that BE can more precisely locate the tumor within the rectum.

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None.

Footnote

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References

1. Moriya Y. Treatment strategy for locally recurrent rectal cancer. Jpn J Clin Oncol 2006;36:127-131.
2. Ghieda U, Hassanen O, Eltomey MA. MRI of rectal carcinoma: Preoperative staging and planning of sphincter-sparing surgery. Egypt J Radiol Nucl Med 2014;45:1-5.
3. Keller DS, Paspulati R, Kjellmo A, et al. MRI-defined height of rectal tumours. Br J Surg 2014;101:127-132.
4. National Institutes of Health. National Cancer Institute. Rectal Cancer Treatment (PDQ®)–Health Professional Version. Available online: http://www.cancer.gov/types/colorectal/hp/rectal-treatment-pdq
5. Beets-Tan RG, Lambregts DM, Maas M, et al. Magnetic resonance imaging for the clinical management of rectal cancer patients: recommendations from the 2012 European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus meeting. Eur Radiol 2013;23:2522-2531.
6. Murono K, Kawai K, Tsuno NH, et al. Barium enema and CT volumetry for predicting pathologic response to preoperative chemoradiotherapy in rectal cancer patients. Dis Colon Rectum 2014;57:715-724.
7. Lichliter WE. Techniques in total mesorectal excision surgery. Clin Colon Rectal Surg 2015;28:21-27.
8. Koshiduka S, Yamanoha K. Usefulness of the double contrast barium enema in the anorectal region. J Jap Soc

Gastrointest Image 2015;10:55-58.
9. Brown G, Radcliffe AG, Newcombe RG, et al. Preoperative assessment of prognostic factors in rectal cancer using high-resolution magnetic resonance imaging. Br J Surg 2003;90:355-364.
10. Videhult P, Smedh K, Lundin P, et al. Magnetic resonance imaging for preoperative staging of rectal cancer in clinical practice: high accuracy in predicting circumferential margin with clinical benefit. Colorectal Dis 2007;9:412-419.
11. Ota DM, Jacobs L, Kuvshinoff B. Rectal cancer: the sphincter-sparing approach. Surg Clin North Am 2002;82:983-993.
12. Ferri M, Laghi A, Mingazzini P, et al. Pre-operative assessment of extramural invasion and sphincteral involvement in rectal cancer by magnetic resonance imaging with phased-array coil. Colorectal Dis 2005;7:387-393.

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A review on robotic surgery in rectal cancer

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Abstract: Robotic surgery has the upper hand when compared to the laparoscopic approach in terms of superior visualisation, flexibility in movement, steadiness and accessibility to confined anatomical spaces. Nevertheless, limitations still exist with regards to cost, reduced tactile sensation, time-consuming setup and a significant learning curve to achieve. Although studies have shown better or at least comparable outcomes between the robotic and laparoscopic approach, the limitations mentioned result in poor penetrance among centres and surgeons. Advancements in robotic surgery technology and attaining the acquired skillset will translate into better clinical outcomes for patients.

Keywords: Robotic surgery; robotic-assisted surgery; rectal dissection; total mesorectal excision (TME); minimally invasive surgery (MIS)

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Introduction

Robotic surgery in the field of colorectal has been around since 2001. The first published experience was reported in 2002, where two colonic resections were performed on benign cases. With the rapid advancement in the field of medical science, there is definite potential for robotic surgery to overcome some of the limitations of conventional laparoscopic surgery.

Rectal dissection has always been a challenge due to its confined location and various dimensions of the rectum and mesorectum. Since it was described in 1982, total mesorectal excision (TME) has been the gold standard of rectal cancer surgery (1). In order to obtain good quality TME, a precise sharp dissection must be performed along the avascular plane while encompassing the entire mesorectum, which bears potential malignant lymph nodes (2).

Worldwide, laparoscopic surgery has been acknowledged as a safe and effective modality of rectal cancer surgery (3). However, a randomised controlled multicentre trial has recently suggested that the use of laparoscopic surgery in T3/T4 tumours may result in incomplete resection, affecting the oncological outcome in this group of patients (3).

The challenges of an incomplete TME in laparoscopic surgery are often encountered when faced with anatomical difficulties i.e., a narrowed male pelvis; bulky tumours and obese patients. Robotic rectal surgery, with superior visualisation and agility of its EndoWrist® (Intuitive Surgical Inc., Sunnyvale, CA, USA), might be the answer to this predicament.

This review will shed light on the potential benefits, clinical outcomes and pitfalls of robotic rectal surgery.

Surgical techniques

The da Vinci® robotic system (Intuitive Surgical Inc., Sunnyvale, CA, USA) is widely used in robotic rectal surgery. Robotic rectal surgery can generally be performed in two ways—the hybrid technique or the totally robotic technique (4).

The hybrid technique comprises of standard laparoscopic isolation and ligation of the inferior mesenteric vessels, mobilisation of the left colon and splenic flexure take down. The robotic system is then brought in to complete the pelvic dissection for TME. Distal rectal dissection can be performed laparoscopically or via robotics.

The totally robotic technique is typically a two-stage or three-stage procedure depending on the number of times the robotic cart is repositioned. A desirable single-stage totally robotic technique in which the robotic cart remains stationary throughout the surgery, has been described (5). Only the robotic arms were repositioned from the colonic phase to the pelvic and TME phase.

Potential benefits

Superior visualization

Minimally invasive surgery (MIS) would not have been successful if not for the technology that permits indirect viewing of the operating field either on a monitor or console. The quality and steadiness of the images produced are paramount to excellent surgical dissection.

Laparoscopic surgery gives a conventional 2-dimensional (2D) view, whilst robotic surgery produces a 3-dimensional (3D) image. This confers the added advantage to the surgeon by allowing better judgement in terms of depth and spatial relationships (6). The relative anatomy between important structures will be more apparent, thus allowing meticulous dissection.

With the advent of 3D vision systems in conventional laparoscopic surgery, some parties question the necessity for a robotic system. Furthermore, the usage of conventional laparoscopy with 3D images was comparable to robotic surgery in terms of short-term operative outcomes (7). We believe, however, that a mounted 3D camera system eliminates unavoidable assistant drawbacks such as fatigue or inexperience, thus producing impeccable steady images throughout surgery.

Enhanced motion

A limited range of movement as a result of the rigid design of conventional laparoscopic instruments beckons for the need of a more versatile appliance. The answer to this was the development of the EndoWrist®, an intuitive robotic instrument which mimics the human wrist. The motion is totally regulated by the surgeon's hand and finger movement (8). The system provides improved dexterity, seven degrees of freedom and motion scaling, while eliminating physiological tremor (9). This avoids iatrogenic injuries and improves peri-operative outcomes (10).

Ergonomics

Laparoscopic surgery has been related to an increased musculoskeletal discomfort for the surgeon, with studies reporting a rate of 73–87% (11). Ergonomic stress was believed to be a compounding factor. In laparoscopic surgery, the substantial use of muscles of the upper torso is associated with more fatigue (11). In robotic surgery, the surgeon is seated within the console, with an armrest in place. This ergonomic design reduces musculoskeletal discomfort.

Achievable learning curve

In general a learning curve can be ascertained from two methods; observation of a consecutive case series and cumulative sum (CUSUM) analysis.

In the first method, a consecutive case series is split into smaller segments i.e., quartiles. A univariate analysis will be performed to compare the means of these quartiles. Most publications look into decreased operative times, complications and estimated blood loss as indicators of improvement (12-14).

In the CUSUM analysis, the learning curve is divided into three phases (15,16). Bokhari *et al*. (16) and Yamaguchi *et al*. (17) described the initial phase (phase I) as a phase comprising of 15 and 25 cases respectively. As the surgeon becomes more experienced, they reach a plateau in the learning curve (phase II). Subsequent cases will be represented in phase III of the curve.

Interestingly, a study has reported that novice rectal surgeons—with limited experience of less than five cases in open/laparoscopic low rectal cancer resection—were able to achieve a similar learning curve in robotic-assisted low rectal resection (18). This faster learning curve may be compensated by their experience in other forms of minimally invasive colonic resection.

It should be reiterated that robotic surgery is technically demanding. We therefore propose a formal form of training in rectal dissection before undertaking robotic rectal surgery. This is best achieved through the proctorship of cases within a robotic rectal cancer surgery setting.

Clinical outcomes

The use of robotics for the treatment of rectal cancer has recently shown to be feasible, and numerous studies have looked into the short- and long-term clinical outcomes of robotic rectal surgery. The short-term outcomes that have been studied include the conversion rate, estimated blood loss, length of hospital stay, functional outcomes and post-operative complications. In the long-term, the oncological outcomes in robotic rectal surgery are discussed.

Conversion rate

Conversion to open surgery is an important predictor of the feasibility of minimally invasive approaches (19). Most studies report rates of conversion of 10–20% in laparoscopic low anterior resection (19). In robotic rectal surgery however, data with regards to conversion rate remains inconsistent.

A recent nationwide analysis showed a significant reduction of conversion for robotic versus laparoscopic rectal resections (5.38% *vs*. 13.38%). Similar findings were presented in other studies, where robotic surgery was shown to have lower or even a zero conversion rate (20-22). Despite this, other studies found no difference in conversion rates between robotic and laparoscopic surgery (23-26).

The on-going ROLARR (Robotic versus Laparoscopic Resection for Rectal Cancer) trial, that has now completed the phase of patient recruitment, aims to compare multiple outcomes between robotic and laparoscopic surgery. Conversion rate to open surgery is the primary endpoint of this study. Early reports have criticised the study design of this trial with regards to this primary endpoint, as a high assumption of 25% was hypothesised in the laparoscopic group. Due to this postulation, this study has failed to detect a clinically relevant difference in terms of conversion rate between robotic and laparoscopic surgery (robotic 8.1% *vs*. laparoscopic 12.2%; odds ratio 0.61, 95% CI: 0.31–1.21, P=0.158) (27).

Causes of conversion are multifactorial, but can be simply classified into patient factors and tumour characteristics. The most common cause for conversion was the inability to perform pelvic dissection satisfactorily; attributed to obesity or a narrow pelvis (28). Other reasons for conversion included presence of adhesions, excessive bleeding and bowel dilatation.

Estimated blood loss

A systemic review of 21 studies showed the amount of blood loss was only ranging from 16 to 400 mL for colorectal robotic surgery (29). A recent case-controlled analysis comparing TME between robotic and laparoscopic methods did not show any significant difference in the amount of blood loss (30). A separate meta-analysis review reaffirmed these findings (31).

Length of stay (LOS)

The LOS for robotic surgery was either similar (7) or shorter compared to laparoscopic surgery. The mean LOS differed between studies, with some reporting a mean LOS of approximately 5–7 days, while others quoting a post-operative LOS of 9–12 days (22,32,33). These findings are not unexpected, as both modalities are minimally invasive.

Postoperative complications

With regards to postoperative complications, again, many studies have shown similar or lower rates compared with laparoscopic surgery. Among the complications reported were anastomotic leakage, surgical site infection and ileus. Anastomotic leakage is a common postoperative complication after MIS, at a rate of 5–11% (5,8,34-36). In a meta-analysis review, Trastulli *et al*. (26) showed a lower leak rate with robotic resection.

The advantages of robotic surgery that were discussed earlier, including superior visualisation systems and enhanced motion allow for more precise dissection, thus resulting in favourable postoperative outcomes.

Preservation of function

When performing rectal cancer surgery, preservation of sexual function and urinary continence are essential, particularly as indicators of postoperative quality of life. The main cause of genitourinary dysfunction is injury to the hypogastric and/or sacral splanchnic nerves during surgery. These essential nerves are preserved when there is good visualisation and precise dissection that to our knowledge can best be achieved by robotic TME.

Most studies use the International Index of Erectile Function (IIEF) and International Prostate Symptoms Score (IPSS) to determine sexual and urinary function respectively. An IIEF score of less than 10 is defined as having sexual dysfunction whereas an IPSS score of more than 8 as urinary dysfunction.

In a recent prospective study, it was concluded that there

was no difference in sexual dysfunction in open *vs*. robotic TME (37). In terms of urinary function, it was noted that patients who underwent open surgery suffered from urinary dysfunction in the first 3 months following surgery, but were able to regain their baseline function within a 3 to 12 months follow-up period (37). Another paper that discussed genitourinary outcomes in laparoscopic *vs*. robotic TME found that robotic TME for rectal cancer was associated with earlier recovery of normal voiding and sexual function compared to patients who underwent laparoscopic TME (38).

Survival rate

With regards to short-term oncologic outcomes, Baek *et al*. (39) reported that the 3-year overall survival (OS) rate after robotic surgery was 96.2% with a 3-year disease free survival (DFS) rate of 73.7%. This was found over a mean 20.2-month follow-up period. Pigazzi *et al*. (28) reported similar figures in his multicentric study, with a 3-year OS of 97% and a 3-year DFS of 77.6%. The mean follow-up rate in this study was 17.4 months. Both studies did not report any isolated loco-regional recurrence, but there were patients who developed distant metastasis, with or without local recurrence.

Long term OS rate was comparable between laparoscopic and robotic rectal surgery. At least two publications (25,33), have reported similar 5-year OS rates; 93.1% and 93.5% respectively in the laparoscopic arm, and 92.2% and 92.8% respectively in the robotic arm. A 5-year DFS rate was higher in the robotic group for both studies, at about 81%; 78% in the laparoscopic group. These values, however, did not translate into any significant difference between the OS and DFS rates between the two arms. Park *et al*. (33) showed a cumulative local recurrence of only 2.3% in the robotic group with no involvement of port and wound site.

It was initially hypothesised that robotic surgery, with its precise TME would improve survival rate. However, as evidenced by various studies looking into the short- and long-term OS and DFS rates, it appears that robotic surgery does not produce superior results compared to conventional laparoscopic technique.

Pitfalls

Technical limitations

Tissue handling is an important aspect in surgery. In laparoscopic surgery, there is presence of tactile feedback. In robotic surgery however, the surgeon has to rely more on visual cues to know how much force to exert in handling delicate tissue. As the tactile feedback is not apparent, sensation of pressure, vibration and sheer force are being masked. This leads to tissue injuries in inexperienced hands. In addition, robotic arm collisions can occur as a result of unplanned placement of working ports and the inability of the surgeon to visualise the movements of robotic arms during surgery.

Cost

Cost is a major issue and becomes a hindrance for new technology to flourish. In robotic surgery the cost comprises the robotic appliance, annual maintenance and changing of ancillary equipment.

The robotic systems typically costs anywhere between $1–$2.3 million. As a result of the steep price of equipment, patients who opt for MIS have to pay more when robotic surgery is performed. The charges range from $7,150 to $10,700 for robotic surgery, a 7- to 10-fold increase compared to laparoscopic surgery ($1,240) (40). Inevitably, total hospital charges were noted to be 1.5 times higher in the robotic group ($14,647 *vs*. $9,978). Furthermore, authors also reported a significantly lowered hospital profit (40).

Whether the high cost associated with robotic surgery translates into better clinical outcomes is yet to be proven in a cost-effectiveness study. To date, there are limited publications on this issue. A recent study by Kim *et al*. concluded that there was no evidence of cost-effectiveness of robotic surgery compared with laparoscopic surgery in 30 days. However, the functional i.e., sexual and bladder functions, and long-term outcomes were not analysed to give a more comprehensive understanding on the economical worth of robotic surgery (41).

With the increased awareness of the advantages that robotic colorectal surgery has to offer, coupled with competitive industry players, we are optimistic that there will be reductions in cost in the new future, making this modality more appealing for the masses.

What the future holds

Advancement in robotic systems will be apparent in years to come. Currently the fourth generation da Vinci® surgical system, the Xi® has revolutionised robotic surgery with its multiple enhancements and upgrades. Simpler docking, laser guided port placement and mounted robotic arms

on a rotated-boom are among the key features in this new system. This is claimed to ease a single-stage fully robotic rectal dissection i.e., splenic flexure and pelvic dissection.

In the reported early experience performing rectal dissection with the da Vinci Xi®, there were no apparent intraoperative and postoperative complications. In addition, no conversion to open surgery has been reported (42).

Already, there are several novel technologies that have been incorporated to complement the existing robotic system. One such example is the da Vinci EndoWrist® Stapler 45 with its SmartClamp® feedback. This application allows for full range of motion while providing adequate tissue compression based on tissue thickness during stapling. Whether this advancement translates into better clinical outcomes, particularly in terms of anastomotic leak, is yet to be studied (43).

Another fascinating addition is the FireFly® Fluorescence Imaging application. The integration of this equipment, which utilises near-infrared technology, provides real-time, image-guided identification of key anatomical landmarks. This assists in better oncological resection, i.e., identification and preservation of anatomical structures, lymph node dissection, differentiating malignancy from normal tissue, and assessing organ and tissue perfusion (44,45).

Numerous research and technology groups are working towards transforming the robotic system that we use today. Concurrent with the growth in the fields of artificial intelligence, nanotechnology and communication systems, it is promising that our current robotic surgical systems will undergo revolutionary changes over the next few decades (46-48).

Conclusions

Patient safety is central to modern surgical treatment. With MIS making headway, it is promising that robotic surgery will provide the next major breakthrough in the treatment of rectal cancer. As of today, robotic systems have already revolutionised the surgical field, proving its advantage over laparoscopic techniques in terms of superior visualisation, enhanced motion, ergonomics and comparable clinical outcomes.

Before robotic rectal surgery is widely adopted however, the long-term prospects need to be better established. At present, the Robotic versus Laparoscopic Resection for Rectal cancer (ROLARR) trial is underway. Believed to be a robust study comprising of about 20 centres and involving eight countries, this study that is estimated to be completed by mid-2018 will address not just the short- and long-term clinical outcomes, but also the economical feasibility of robotic rectal surgery. It will be interesting to see if this trial changes the standard of care for rectal cancer surgery in the future. As an old saying goes—little do we know what the future holds.

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Footnote

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

References

1. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery--the clue to pelvic recurrence? Br J Surg 1982;69:613-616.
2. Lichliter WE. Techniques in total mesorectal excision surgery. Clin Colon Rectal Surg 2015;28:21-27.
3. Bonjer HJ, Deijen CL, Abis GA, et al. A randomized trial of laparoscopic versus open surgery for rectal cancer. N Engl J Med 2015;372:1324-1332.
4. Aly EH. Robotic colorectal surgery: summary of the current evidence. Int J Colorectal Dis 2014;29:1-8.
5. Choi DJ, Kim SH, Lee PJ, et al. Single-stage totally robotic dissection for rectal cancer surgery: technique and short-term outcome in 50 consecutive patients. Dis Colon Rectum 2009;52:1824-1830.
6. Chmarra MK, Kolkman W, Jansen FW, et al. The influence of experience and camera holding on laparoscopic instrument movements measured with the TrEndo tracking system. Surg Endosc 2007;21:2069-2075.
7. Guerrieri M, Campagnacci R, Sperti P, et al. Totally robotic vs 3D laparoscopic colectomy: A single centers preliminary experience. World J Gastroenterol 2015;21:13152-13159.
8. Baik SH, Kwon HY, Kim JS, et al. Robotic versus laparoscopic low anterior resection of rectal cancer: short-term outcome of a prospective comparative study. Ann Surg Oncol 2009;16:1480-1487.
9. Moorthy K, Munz Y, Dosis A, et al. Dexterity enhancement with robotic surgery. Surg Endosc 2004;18:790-795.
10. Park S, Kim NK. The Role of Robotic Surgery for

Rectal Cancer: Overcoming Technical Challenges in Laparoscopic Surgery by Advanced Techniques. J Korean Med Sci 2015;30:837-846.
11. Zihni AM, Ohu I, Cavallo JA, et al. Ergonomic analysis of robot-assisted and traditional laparoscopic procedures. Surg Endosc 2014;28:3379-3384.
12. Tsao AK, Smaldone MD, Averch TD, et al. Robot-assisted laparoscopic prostatectomy: the first 100 patients-improving patient safety and outcomes. J Endourol 2009;23:481-484.
13. Kim YW, Lee HM, Kim NK, et al. The learning curve for robot-assisted total mesorectal excision for rectal cancer. Surg Laparosc Endosc Percutan Tech 2012;22:400-405.
14. Akmal Y, Baek JH, McKenzie S, et al. Robot-assisted total mesorectal excision: is there a learning curve? Surg Endosc 2012;26:2471-2476.
15. Sng KK, Hara M, Shin JW, et al. The multiphasic learning curve for robot-assisted rectal surgery. Surg Endosc 2013;27:3297-3307.
16. Bokhari MB, Patel CB, Ramos-Valadez DI, et al. Learning curve for robotic-assisted laparoscopic colorectal surgery. Surg Endosc 2011;25:855-860.
17. Yamaguchi T, Kinugasa Y, Shiomi A, et al. Learning curve for robotic-assisted surgery for rectal cancer: use of the cumulative sum method. Surg Endosc 2015;29:1679-1685.
18. Foo CC, Law WL. The Learning Curve of Robotic-Assisted Low Rectal Resection of a Novice Rectal Surgeon. World J Surg 2016;40:456-462.
19. Collinson FJ, Jayne DG, Pigazzi A, et al. An international, multicentre, prospective, randomised, controlled, unblinded, parallel-group trial of robotic-assisted versus standard laparoscopic surgery for the curative treatment of rectal cancer. Int J Colorectal Dis 2012;27:233-241.
20. Liao G, Zhao Z, Lin S, et al. Robotic-assisted versus laparoscopic colorectal surgery: a meta-analysis of four randomized controlled trials. World J Surg Oncol 2014;12:122.
21. Lin S, Jiang HG, Chen ZH, et al. Meta-analysis of robotic and laparoscopic surgery for treatment of rectal cancer. World J Gastroenterol 2011;17:5214-5220.
22. Sawada H, Egi H, Hattori M, et al. Initial experiences of robotic versus conventional laparoscopic surgery for colorectal cancer, focusing on short-term outcomes: a matched case-control study. World J Surg Oncol 2015;13:103.
23. Bianchi PP, Ceriani C, Locatelli A, et al. Robotic versus laparoscopic total mesorectal excision for rectal cancer: a comparative analysis of oncological safety and short-term outcomes. Surg Endosc 2010;24:2888-2894.
24. Park JS, Choi GS, Lim KH, et al. Robotic-assisted versus laparoscopic surgery for low rectal cancer: case-matched analysis of short-term outcomes. Ann Surg Oncol 2010;17:3195-3202.
25. Cho MS, Baek SJ, Hur H, et al. Short and long-term outcomes of robotic versus laparoscopic total mesorectal excision for rectal cancer: a case-matched retrospective study. Medicine (Baltimore) 2015;94:e522.
26. Trastulli S, Farinella E, Cirocchi R, et al. Robotic resection compared with laparoscopic rectal resection for cancer: systematic review and meta-analysis of short-term outcome. Colorectal Dis 2012;14:e134-e156.
27. Jayne DG. On behalf of the ROLARR trial. Astract presented at the 23rd International Congress of the European Association for Endoscopis Surgery (EAES), Bucharest, Romania. June 3-6, 2015.
28. Pigazzi A, Luca F, Patriti A, et al. Multicentric study on robotic tumor-specific mesorectal excision for the treatment of rectal cancer. Ann Surg Oncol 2010;17:1614-1620.
29. AlAsari S, Min BS. Robotic Colorectal Surgery: A Systemic Review. ISRN Surg 2012;2012:293894.
30. Allemann P, Duvoisin C, Di Mare L, et al. Robotic-Assisted Surgery Improves the Quality of Total Mesorectal Excision for Rectal Cancer Compared to Laparoscopy: Results of a Case-Controlled Analysis. World J Surg 2016;40:1010-1016.
31. Lee SH, Lim S, Kim JH, et al. Robotic versus conventional laparoscopic surgery for rectal cancer: systematic review and meta-analysis. Ann Surg Treat Res 2015;89:190-201.
32. Colombo PE, Bertrand MM, Alline M, et al. Robotic Versus Laparoscopic Total Mesorectal Excision (TME) for Sphincter-Saving Surgery: Is There Any Difference in the Transanal TME Rectal Approach?: A Single-Center Series of 120 Consecutive Patients. Ann Surg Oncol 2015. [Epub ahead of print].
33. Park EJ, Cho MS, Baek SJ, et al. Long-term oncologic outcomes of robotic low anterior resection for rectal cancer: a comparative study with laparoscopic surgery. Ann Surg 2015;261:129-137.
34. Hellan M, Anderson C, Ellenhorn JD, et al. Short-term outcomes after robotic-assisted total mesorectal excision for rectal cancer. Ann Surg Oncol 2007;14:3168-3173.
35. Ng KH, Lim YK, Ho KS, et al. Robotic-assisted surgery for low rectal dissection: from better views to better outcome. Singapore Med J 2009;50:763-767.
36. Zimmern A, Prasad L, Desouza A, et al. Robotic colon

and rectal surgery: a series of 131 cases. World J Surg 2010;34:1954-1958.
37. Ozeki S, Maeda K, Hanai T, et al. Effects of robotic rectal surgery on sexual and urinary function. Surg Today 2016;46:491-500.
38. Kim JY, Kim NK, Lee KY, et al. A comparative study of voiding and sexual function after total mesorectal excision with autonomic nerve preservation for rectal cancer: laparoscopic versus robotic surgery. Ann Surg Oncol 2012;19:2485-2493.
39. Baek JH, McKenzie S, Garcia-Aguilar J, et al. Oncologic outcomes of robotic-assisted total mesorectal excision for the treatment of rectal cancer. Ann Surg 2010;251:882-886.
40. Baek SJ, Kim SH, Cho JS, et al. Robotic versus conventional laparoscopic surgery for rectal cancer: a cost analysis from a single institute in Korea. World J Surg 2012;36:2722-2729.
41. Kim CW, Baik SH, Roh YH, et al. Cost-effectiveness of robotic surgery for rectal cancer focusing on short-term outcomes: a propensity score-matching analysis. Medicine (Baltimore) 2015;94:e823.
42. Morelli L, Guadagni S, Di Franco G, et al. Use of the new Da Vinci Xi during robotic rectal resection for cancer: technical considerations and early experience. Int J Colorectal Dis 2015;30:1281-1283.
43. Intuitive surgical brings stapler instrumentation to da Vinci robotic-assisted surgical systems in the U.S., Europe & Asia. Available online: (accessed 30 January 2016).https://globenewswire.com/news-release/2015/07/14/751891/10141572/en/Intuitive-Surgical-Brings-Stapler-Instrumentation-to-da-Vinci-Robotic-Assisted-Surgical-Systems-in-the-U-S-Europe-Asia.html
44. Daskalaki D, Aguilera F, Patton K, et al. Fluorescence in robotic surgery. J Surg Oncol 2015;112:250-256.
45. Bae SU, Min BS, Kim NK. Robotic Low Ligation of the Inferior Mesenteric Artery for Rectal Cancer Using the Firefly Technique. Yonsei Med J 2015;56:1028-1035.
46. Camarillo DB, Krummel TM, Salisbury JK Jr. Robotic technology in surgery: past, present, and future. Am J Surg 2004;188:2S-15S.
47. Tiwari MM, Reynoso JF, Lehman AC, et al. In vivo miniature robots for natural orifice surgery: State of the art and future perspectives. World J Gastrointest Surg 2010;2:217-223.
48. Rentschler ME, Dumpert J, Platt SR, et al. Natural orifice surgery with an endoluminal mobile robot. Surg Endosc 2007;21:1212-1215.

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Have we improved in laparoscopic resection of rectal cancer: critical reflection on the early outcomes of COLOR II study

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Jacob *et al.* reported the first series of a combination of laparoscopic colonic & rectal resections in 1991 (1). It took just over a decade of debate and several trials to prove that laparoscopic colonic surgery (LCS) unequivocally results in better short-term outcomes when compared to open colonic surgery (OCS) (2). Several randomised controlled trials (RCTs) (3-5) have demonstrated that LCS offers reduced intra-operative blood loss, length of incision, post-operative analgesia requirements as well as shorter hospital stay. In malignant resections, LCS also offers comparable clearance margins and lymph node harvest. Therefore, LCS is now a well-accepted alternative to open surgery (2). However, the debate involving the role of laparoscopic approach in rectal cancer resection continues and is far from over (6).

The CLASSIC (Conventional *vs.* Laparoscopic- Assisted Surgery in Colorectal Cancer) trial was the first RCT to include patients with rectal cancer (4). The CLASSIC trial was very successful in increasing the awareness of the morbidity associated with laparoscopic rectal cancer surgery as the laparoscopic group in the study had increased rates of positive circumferential resection margin, even though this did not reach statistical significance and it did not result in increased incidence of local recurrence on long-term follow up (7). The short-term outcomes of laparoscopic rectal surgery were probably marginally better; however, there was a clear trend towards a less favorable outcome of patients who had conversion (4). Long-term follow up demonstrated no difference between open and laparoscopic groups in the 3-year overall survival, disease-free survival or local recurrence (7). There was no difference in the quality of life. The CLASSIC trial as well as other studies demonstrated that laparoscopic rectal resection is associated with increased risk of sexual and urinary dysfunction as 41% of men in the laparoscopic rectal surgery group had sexual dysfunction after laparoscopic anterior resection in comparison with 23% in the open group as well as increased anastomotic leak (2,4,6).

However, the outcomes of the MRC CLASICC trial should be interpreted with caution as the study design had set the surgeons' learning curve at 20 laparoscopic resections which was based on the best available data at that time (8) and clearly this was an underestimation of the learning curve for laparoscopic rectal surgery (LRS) (9). The reduction in the conversion rates for every year of the study is an indication that the learning curve was functional during the trial (4). Therefore, there has been a strong need for another RCT that compares the postoperative outcomes of open and laparoscopic rectal cancer surgery beyond the initial learning curve in LRS. COLOR II study (10) was specifically designed to answer this question.

COLOR II was designed as a non-inferiority open-label randomised trial that was carried out across 30 centers and hospitals in eight countries (Belgium, Canada, Denmark, Germany, the Netherlands, Spain, Republic of Korea, and Sweden). Inclusion criteria were patients who have a single rectal cancer within 15 cm without evidence of distant metastases. Exclusion criteria were T4 tumours, or T3 rectal cancers within 2 mm of the endopelvic fascia, as seen on pre-operative CT or MRI and T1 tumours treated with local transanal excision.

Patients were randomised in a 2:1 ratio to laparoscopic surgery or open surgery. Peri-operative care as well as the use of preoperative radiotherapy and chemo- therapy were left to the local protocols. However, COLOR II study was strict in allowing surgical teams to participate in the study as each team had to submit unedited recordings of five consecutive laparoscopic TMEs with their pathology

reports for assessment or were directly observed by one of the five governors of the study. It should be noted that quality approval within the COLOR II trial was only done at entry into the trial and unfortunately the same assessment was not done for the quality of open resections. The authors in their report acknowledged these limitations. Processing and assessment of the pathology specimens were done locally according to a pre-agreed detailed description in the study protocol. The primary outcome in the COLOR II trial is the proportion of patients with local recurrence at 3 years after index surgery; these data are not yet mature and will be reported at a later date. The current report only outlines the short-term secondary endpoints, which are the early post-operative outcomes (10).

Previous publications (2,6) have clearly demonstrated that LRS is associated with better post-operative outcomes when compared to open rectal surgery (ORS) in terms of decreased intraoperative blood loss, reduced opiates requirements, earlier return of gut function and shorter hospital stay and these findings were confirmed by COLOR II study. However, it was hoped that with the increasing expertise in laparoscopic rectal surgery other less favorable short-term outcomes in the earlier studies would improve. These include longer operating time, post-operative morbidity and mortality, increased resection margin positivity, higher rate of anastomotic leak and a trend for postoperative urinary and sexual dysfunction.

COLOR II study confirms that LRS was associated with less blood loss, reduced use of epidural analgesia, earlier restoration of bowel function, and shorter hospital stay when compared to open rectal surgery (ORS). These findings are similar to those in other trials (2,6). Despite the extensive laparoscopic experience of the surgical teams involved in the study laparoscopic procedures took longer than open [LRS: 240 mins (184-300 mins) *vs.* ORS: 188 mins (150-240 mins); P<0.0001].

There were similar oncological outcomes in terms of the resected surgical specimens. Macroscopically, completeness of the resection was not different between laparoscopic & open groups (LRS: 88% *vs.* ORS: 92% respectively; P=0.250). Positive circumferential resection margin (<2 mm) was noted in 10% of LRS as well as 10% OSR (P=0.850). Median tumour distance to distal resection margin did not differ significantly between the groups [LSR: 3.0 cm (2.0-4.8 cm) *vs.* OSR: 3.0 cm (1.8-5.0 cm); P=0.676]. However, the proportion of patients with low rectal cancers with positive CRM was significantly lower in the laparoscopic surgery group than in the open surgery group (P=0.014), which could be attributed to the better visibility offered by the laparoscopic approach. The median number of lymph nodes harvested after surgery was not significantly different in the two groups.

Compared to the CLASSIC trial, there has been a definite improvement in conversion rate from 29% in the CLASSIC trial to 17% in COLOR II study. This probably does not only reflect the increasing experience with LRS, but it could also be related to the availability of improved equipment such as better optics with high definition video, better quality energy devices and more reliable instruments. However, conversion rate for standard LRS reported in COLOR II study remains higher than that reported for robotic rectal surgery (RRS), which is 1-7% (11). As the surgical teams in COLOR II study have extensive experience in LRS, this conversion rate should be attributed to other factors such as the limitation of the current generation of laparoscopic instruments, which is in part addressed by the increased dexterity available with the robotic system.

The proportion of patients who needed re-intervention within 28 days after surgery was similar in the two groups. However, LRS continues to be associated with increased anastomotic leak rate, which was 13% in the laparoscopic group and 10% in the open surgery group (P=0.462). The authors acknowledge that this anastomotic leak rates have not improved in comparison those reported in the CLASSIC trail (LRS: 7% and ORS: 10%) (4). Morbidity was similar in both groups, (LSR: 40% *vs.* OSR: 37%, respectively; P=0.424). Also, mortality within 28 days after surgery was similar (LSR: 1% *vs.* OSR: 2%; P=0.409).

Urinary continence and sexual function were not reported in the current publication. These adverse events were recorded in the COLOR II trial 1 year after the index surgery and will be reported later with the long-term outcomes (10).

The authors indicate that '*the short-term outcomes of the COLOR II trial show that the radicality of laparoscopic resection (as assessed by pathology report) in patients with rectal cancer is no different to that of open surgery, and that laparoscopic surgery was associated with similar rates of intra-operative complications, morbidity, and mortality*' (10). This in part implies that LRS is not superior to the open approach and there is no clear reduction in morbidity or mortality for patients with rectal cancer subjected to surgical resection when the laparoscopic approach is used.

The currently published report on COLOR II study (10) did not address 2 major points, namely the outcomes in the converted group of patients and the cost-effectiveness of LRS. One of the main concerns from the CLASSIC trial was the clear trend towards a less favorable outcome in patients who

had conversion. In the published COLOR II report, there was no separate sub-analysis of the outcomes of the converted group to ascertain if, with increasing experience, timely conversion would not result in poorer outcomes.

The second issue that was not addressed is cost-effectiveness analysis of LRS *vs.* ORS. Currently most, if not all, health care systems across the world are under undue financial pressure and therefore cost-effectiveness analysis comparing the costs of LRS *vs.* OSR per each country would have been useful. Previous analysis of the cost of laparoscopic colorectal surgery over time, projected that the results of future economic evaluations will unequivocally show that laparoscopic colorectal surgery would be cheaper than open surgery when practiced in Western health care systems where postoperative care cost is high (12). The reduction in hospital stay following laparoscopic colorectal surgery reduces the overall cost of the procedure. However, in Asian health care systems, operative costs overshadow the cost savings gained by reduced hospital stay. However, this previous analysis included both colonic and rectal resections. Providing detailed cost-effectiveness analysis for LRS *vs.* ORS were going to be an invaluable addition to the current literature. As the main savings associated with LRS comes from reduced post-operative stay, the reported reduction in COLOR II study in the LRS group by 1 day is unlikely to result in cost-effective savings.

The findings in the COLOR II study answered an important question that was raised after the CLASSIC trial: can increased experience in LRS address the limitations of the laparoscopic approach seen in the CLASSIC trial. COLOR II study indicates that LRS could offer better short-term outcomes but with no reduction in morbidity or morality. Given that ORS is well known to be associated with inherent morbidity and mortality it was assumed that the reduction in the trauma of access could help to provide better outcomes. However, it is difficult to support this hypothesis from the current evidence.

This is in an agreement with the findings in two systematic reviews on the outcomes of minimally invasive approach in rectal cancer recently published by our group. A systematic review that included all the published studies on laparoscopic rectal cancer surgery over the last 20 tears failed to show clear evidence of improvement in the early post-operative outcomes over time. The fact that despite 20 years of practice of LRS there has been no clear trend of improvement in the rate of postoperative complications indicate that other factors, apart from the learning curve, could be involved such as limitations of the current laparoscopic instrumentation, possibly exceptionally long learning curve or it could be that rectal resection is associated with inherent morbidity regardless of the approach used (13). Also a systematic review on the studies reporting the use of the robotic approach to resection of rectal cancer failed to show clear significant reduction in early post-operative complications when compared with standard laparoscopic surgery with only potentially better short-term outcomes when applied in selected patients such as obesity, male sex, preoperative radiotherapy, and tumors in the lower two-thirds of the rectum (11).

The findings in the currently available literature indicate the need for a different approach in resection of rectal cancer, as it is unlikely that further experience in laparoscopic rectal surgery will result in improved short-term outcomes. The challenges in LRS could be possibly addressed by development of specifically designed laparoscopic instruments to tackle the limitation of the current instruments which is usually manifested by difficulty in obtaining adequate retraction and tissue tension to help precise dissection in the confines of the pelvis. This is in part has been addressed by robotic surgery. However, there are still several well-known limitations with the currently available laparoscopic staplers especially when used low down in the male pelvis (14).

It is more likely that we need to adopt a novel approach to surgical resection of rectal cancer as the available evidence suggests that it is unlikely that further experience with the currently available minimally invasive approaches would result in better outcomes compared to ORS. There is an increasing interest in rectum-preservation strategies for patients with early rectal cancer. Currently, two CRTs are examining rectum-preserving strategies in early rectal cancer. The CARTS study [chemoradiation therapy for rectal cancer in the distal rectum followed by organ-sparing transanal endoscopic microsurgery (TEMS)] has been designed to assess the adequacy of TEMS following pre-operative radiotherapy. Patients with a clinical T1-3 N0 M0 rectal adenocarcinoma below 10 cm from the anal verge will receive neoadjuvant chemoradiation therapy followed by TEMS 8-10 weeks later. The UK-TREC trial (TEM and Radiotherapy in Early Rectal Cancer) is offered for patients with early rectal cancer (T1-2N0) where patients are randomised between radical TME surgery and short-course preoperative radiotherapy with delayed local excision at 8-10 weeks. If local recurrence rate in these studies were found to be acceptable or comparable to standard TME surgery then TEMS might become the standard treatment of rectal cancer in the future.

There is also some growing interest in these rectum-preserving techniques even for some locally advanced rectal

cancer given the encouraging long-term results of patients with complete pathological response after chemoradiotherapy. These patients could be offered 'close follow up' if they were found to be stage 0 rectal cancer following neoadjuvant chemoradiation (15). Alternatively, tumours that either do not disappear or "regrow" during the first 12-month follow up period are referred to surgery, either TEMS or TME (16).

There are also several emerging reports on 'bottom to top' approach for resection of rectal cancer in an attempt to address the difficulties faced during LRS in terms of tumour localization, achieving adequate distal resection margin and to deal with the difficulty in firing the stapler distal to the tumour (17).

In conclusion, it is evident that the quest for the optimal approach for surgical resection of rectal cancer is far from over. COLOR II study, as well as other studies, indicates that further experience in LRS is doubtful to offer significantly better short-term outcomes when compared with ORS. Therefore, it is very likely that we will see increasing reports on various novel approaches for resection of rectal cancer.

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Footnote

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References

1. Jacobs M, Verdeja JC, Goldstein HS. Minimally invasive colon resection (laparoscopic colectomy). Surg Laparosc Endosc 1991;1:144-150.
2. Aly EH. Laparoscopic colorectal surgery: summary of the current evidence. Ann R Coll Surg Engl 2009;91:541-544.
3. Lacy AM, García-Valdecasas JC, Delgado S, et al. Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. Lancet 2002;359:2224-2229.
4. Guillou PJ, Quirke P, Thorpe H, et al. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. Lancet 2005;365:1718-1726.
5. Veldkamp R, Kuhry E, Hop WC, et al. Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. Lancet Oncol 2005;6:477-484.
6. Aly EH. Laparoscopic Surgery for Rectal Cancer: Approaches, Challenges and Outcome. Contemporary Issues in Colorectal Surgical Practice, 2012. doi: 10.5772/33501.
7. Jayne DG, Guillou PJ, Thorpe H, et al. Randomized trial of laparoscopic-assisted resection of colorectal carcinoma: 3-year results of the UK MRC CLASICC Trial Group. J Clin Oncol 2007;25:3061-3068.
8. Simons AJ, Anthone GJ, Ortega AE, et al. Laparoscopic-assisted colectomy learning curve. Dis Colon Rectum 1995;38:600-603.
9. Good DW, O'Riordan JM, Moran D, et al. Laparoscopic surgery for rectal cancer: a single-centre experience of 120 cases. Int J Colorectal Dis 2011;26:1309-1315.
10. van der Pas MH, Haglind E, Cuesta MA, et al. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. Lancet Oncol 2013;14:210-218.
11. Scarpinata R, Aly EH. Does robotic rectal cancer surgery offer improved early postoperative outcomes? Dis Colon Rectum 2013;56:253-262.
12. Aly OE, Quayyum Z. Has laparoscopic colorectal surgery become more cost-effective over time? Int J Colorectal Dis 2012;27:855-860.
13. Shearer R, Gale M, Aly OE, et al. Have early post-operative complications from laparoscopic rectal cancer surgery reduced over the past 20 years? Colorectal Dis 2013;15:1211-1226.
14. Cecil TD, Taffinder N, Gudgeon AM. A personal view on laparoscopic rectal cancer surgery. Colorectal Dis 2006;8 Suppl 3:30-32.
15. Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg 2004;240:711-717; discussion 717-718.
16. Perez RO, Habr-Gama A, Lynn PB, et al. Transanal endoscopic microsurgery for residual rectal cancer (ypT0-2) following neoadjuvant chemoradiation therapy: another word of caution. Dis Colon Rectum 2013;56:6-13.
17. Lacy AM, Adelsdorfer C, Delgado S, et al. Minilaparoscopy-assisted transrectal low anterior resection (LAR): a preliminary study. Surg Endosc 2013;27:339-346.

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Laparoscopic resection for rectal cancer: the new standard of care?

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The highly anticipated long-term oncologic outcomes of the landmark "Colorectal Cancer Laparoscopic or Open Resection (COLOR) II trial" were finally released in the April 2015 edition of the *New England Journal of Medicine* (1). The authors are to be congratulated for their success in designing and conducting a rigorous, large-scale trial, requiring a substantial investment in time and effort to answer a pertinent clinical question regarding the care of colorectal cancer patients worldwide.

Laparoscopic colorectal resection was first introduced in the early 1990s (2). Since then, there has been widespread enthusiasm towards utilizing laparoscopic approaches to treat patients that require a colorectal resection. The advantages of laparoscopy such as decreased postoperative pain, faster return of bowel function, shorter hospital stay and improved cosmesis were attractive to surgeons and patients alike. Laparoscopic colorectal resection however, requires advanced laparoscopic skills, which has hampered its adoption. The considerable learning curve raised skepticism with regards to whether laparoscopic colorectal resection would compromise the quality and completeness of colorectal oncologic resection. This meant that initial adoption of the laparoscopic technique was largely limited to patients with benign disease only. In the early 2000s, mounting evidence started to suggest that laparoscopic colon resection was oncologically equivalent to open resection for patients with colon cancer. The COST and COLOR I trial results confirmed these findings (3,4).

Despite over a decade of additional experience since those studies were published, the question remained as to whether these same techniques were appropriate for the treatment of rectal cancer. It has been widely established that total mesorectal excision (TME) is the golden standard technique of curative rectal cancer resection (5). This technique is predicated on resection of a complete mesorectal envelope, clear circumferential resection margins, with en-bloc resection of regional lymph node basins. The COLOR II trial by Bonjer *et al*. was designed to establish the equivalency of laparoscopic colorectal resection compared to open resection for patients with rectal malignancy. The COLOR II trial is a non-inferiority, open label and multicenter trial that was conducted at 30 centers in eight countries. The study was sponsored by Ethicon Endo-Surgery Europe but the sponsor had no role in study design, data gathering or analysis. The study enrolled a total of 1,044 patients that were randomized in a 2:1 fashion resulting in 699 laparoscopic resections and 345 open resections for rectal cancer. The two groups were found to be similar in terms of patient characteristics, comorbidities and tumor location.

The short term outcomes of this trial were reported 2 years ago, showing that patients treated with laparoscopic resection had improved short-term surgical outcomes. These included, specifically, faster return of bowel function and shorter hospital stay. There was also no difference in the incidence of perioperative complications (6). The highly awaited long term oncologic outcomes were finally reported in April 2015. Minimal required follow-up included annual clinical examinations for 5 years after resection. Three years after the index surgery, CT or MRI of the pelvis combined with imaging of the liver and the chest were performed. Recurrent disease was defined as the presence of locoregional recurrence, the presence of distant metastases, or death from rectal cancer. The trial found no statically significant differences in locoregional recurrence, disease free survival

and overall survival between the two treatment groups.

The trial did elicit some thought-provoking findings between the two groups. Interestingly, when used for distal lesions, laparoscopic resection was found to have a lower rate of circumferential resection margin involvement (9% *vs.* 22% respectively) and lower rate of locoregional recurrence (4.4% *vs.* 11.7%) compared to open. Furthermore, although the trial did not find any differences in overall survival or disease free survival amongst stage I and stage II disease, there was a trend towards improvement in disease free survival (64.9% in laparoscopic group *vs.* 52% in open group) in patients with more advanced disease (stage III). Whether this survival advantage is due to the less taxing and invasive nature of laparoscopy remains to be seen (7,8).

The COLOR II trial by Bonjer *et al.* clearly demonstrates that laparoscopic colorectal resection for rectal cancer is a non-inferior modality of performing proctectomy with curative intent. Laparoscopic resection does not compromise oncologic outcomes and has some palpable advantages in terms of postoperative recovery, and may even provide some oncologic benefit in patients with more advanced disease. This trial establishes laparoscopic rectal resection as the new standard of care in rectal cancer surgical treatment. The frontier now shifts towards ensuring that this advantageous technique is available to patients that need it. Laparoscopic colorectal resection remains technically challenging. The estimated learning curve has been estimated to be anywhere between 50 to 150 cases and remains the biggest hurdle for patients and care providers to overcome (9,10). Colorectal surgery training practices must evolve to ensure that the surgeons preforming these procedures are technically proficient to ensure that patients receive the true benefit of laparoscopy, as the expert surgeons in the COLOR II trial were able to demonstrate.

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Footnote

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References

1. Bonjer HJ, Deijen CL, Abis GA, et al. A randomized trial of laparoscopic versus open surgery for rectal cancer. N Engl J Med 2015;372:1324-1332.
2. Jacobs M, Verdeja JC, Goldstein HS. Minimally invasive colon resection (laparoscopic colectomy). Surg Laparosc Endosc 1991;1:144-150.
3. Clinical Outcomes of Surgical Therapy Study Group. A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med 2004;350:2050-2059.
4. Veldkamp R, Kuhry E, Hop WC, et al. Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. Lancet Oncol 2005;6:477-484.
5. MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. Lancet 1993;341:457-460.
6. van der Pas MH, Haglind E, Cuesta MA, et al. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. Lancet Oncol 2013;14:210-218.
7. Bouvy ND, Marquet RL, Jeekel J, et al. Laparoscopic surgery is associated with less tumour growth stimulation than conventional surgery: an experimental study. Br J Surg 1997;84:358-361.
8. Lacy AM, García-Valdecasas JC, Delgado S, et al. Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. Lancet 2002;359:2224-2229.
9. Miskovic D, Ni M, Wyles SM, et al. Learning curve and case selection in laparoscopic colorectal surgery: systematic review and international multicenter analysis of 4852 cases. Dis Colon Rectum 2012;55:1300-1310.
10. Kim CH, Kim HJ, Huh JW, et al. Learning curve of laparoscopic low anterior resection in terms of local recurrence. J Surg Oncol 2014;110:989-996.

Local excision for early rectal cancer: transanal endoscopic microsurgery and beyond

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Abstract: The goal of treatment for early stage rectal cancer is to optimize oncologic control while minimizing the long-term impact of treatment on quality of life. The standard of care treatment for most stage I and II rectal cancers is radical surgery alone, specifically total mesorectal excision (TME). For early rectal cancers, this procedure is usually curative but can have a substantial impact on quality of life, including the possibility of permanent colostomy and the potential for short and long-term bowel, bladder, and sexual dysfunction. Given the morbidity associated with radical surgery, alternative approaches to management of early rectal cancer have been explored, including local excision (LE) via transanal excision (TAE) or transanal endoscopic microsurgery (TEM) and transanal minimally invasive surgery (TAMIS). Compared to the gold standard of radical surgery, local procedures for strictly selected early rectal cancers should lead to identical oncological results and even better outcomes regarding morbidity, mortality, and quality of life.

Keywords: Rectal cancer; local excision (LE); transanal excision (TAE); transanal endoscopic microsurgery (TEM); transanal minimally invasive surgery (TAMIS)

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Introduction

Colorectal cancer (CRC) is the third most common cancer diagnosis and the third leading cause of cancer death in the United States (US). With the increase in population screening, the overall incidence of CRC in the US has decreased (1). Furthermore, there has been an increase in the detection of early stage CRC. In 2013, the American Cancer Society reported data from the National Cancer Institute indicating that approximately 40% of all CRC are early stage cancers (1). Early stage cancer is associated with higher (~90%) 5-year survival. Early stage CRC is defined as lesions limited to the bowel wall with no disease extension beyond the submucosa (T1) or the muscularis mucosa (T2). Furthermore, there is no evidence of lymph node spread (N0).

The management of early stage CRC, in particular rectal cancer, can be challenging. Traditionally, treatment has involved major radical abdominal surgery known as the total mesorectal excision (TME) with the potential for a temporary or permanent stoma. The aim of this procedure is to achieve adequate tumor clearance through the removal of the primary tumor including the mesorectum with the associated regional lymph nodes (2-4). TME or radical surgery is the primary surgery that offers excellent rates of local control and therefore, excellent long-term survival. Patients who undergo radical surgery for stage I and II rectal cancer can expect excellent long-term results which approach 4.5% 5-year local recurrence rates and 90% 5-year disease free survival (DFS) rates (5). However, the morbidity is high (30-68%) with a mortality that approaches 7% (2,5-7). Radical surgery is often followed by significant complications including anastomotic leakage, sepsis, permanent or temporary stoma, perineal wound complications, and urinary, sexual and bowel dysfunction that may diminish quality of life (2,3,5-9).

Given these significant complications, there has been increased interest in the locoregional treatment of early

Table 1 Suggested criteria for LE

Physical examination
Tumor <3 cm
Tumor <30% of bowel circumference
Tumor within 15 cm of dentate line
Tumor freely mobile
Imaging (ERUS/MRI)
Tumor limited to submucosa (T1)
No lymph node involvement (N0)
Histology
Well to moderately differentiated
Absence of LVI or PNI
No mucinous or signet cell component

LE, local excision; ERUS, endorectal ultrasound; MRI, magnetic resonance imaging; LVI, lymphovascular invasion; PNI, perineural invasion.

rectal cancer, as some patients may be cured by avoidance of radical surgery and its concomitant disadvantages (10,11). Local excision (LE) of early rectal cancer is an attractive alternative to radical surgery for several reasons. First, the surgery is less invasive and associated with less postoperative pain and a shorter length of stay. The surgery preserves normal bowel function without the use of a stoma. There is less associated perioperative morbidity. Furthermore, newer methods known as transanal endoscopic microsurgery (TEM) or transanal minimally invasive surgery (TAMIS) have been introduced that provide better visualization of tumors in the mid and upper rectum. The aim of this review is to guide the reader in the understanding of the current debates in the management of early stage rectal cancer. This review will include a discussion of patient selection, surgical techniques, and expected oncological outcomes following treatment.

Patient selection

Strict patient selection for LE, together with full-thickness and margin-free excision is crucial for patient outcomes (12). In carefully selected patients local recurrence rates have been reported to be <4% and LE can be curative, with similar oncological outcomes to radical surgery (10). There are several variables that must be evaluated when considering a patient for LE. The key variables include the following characteristics of the tumor: differentiation, the presence of lymphovascular invasion (LVI), the location in the rectum, the size, and the clinical stage. Other key variables that are important to consider prior to performing surgery for rectal cancer are the characteristics of the patient that may put him or her at a higher surgical risk.

To properly select the patients that will benefit from LE, first, digital rectal exam is performed which may determine the mobility of the tumor, the distance from anal verge, and the strength of the anal sphincter. Further, proctoscopy will help in examining more proximal tumors for size and distance from the anal verge. In general, LE can be technically performed for tumors that occupy no more than 30% of the bowel circumference, are no larger than 3 cm in size, and are mobile.

The best method for clinical staging of rectal cancer remains a controversial topic among health care providers. Preoperative identification of tumor depth of invasion (T stage) in the rectal wall and lymph nodes (N stage) can be a challenge. Both modern imaging modalities of endorectal ultrasound (ERUS) and magnetic resonance imaging (MRI) have been used to detect depth of tumor invasion and lymph nodes metastases in rectal cancer (3,10). The reported sensitivity and specificity of ERUS for depth of tumor invasion, perirectal tissue invasion and lymph node involvement is 94%, 90% and 67%, and 86%, 75% and 78%, respectively (13). The major disadvantage of ERUS is the variability in the interpretation of the study due to its dependence on one individual to perform and read the study accurately. MRI has a sensitivity and specificity for T staging ranging from 85% to 100% and from 91% to 98%, respectively (14,15). MRI is also superior at mesorectal lymph node staging with similar sensitivity and specificity as T staging (16). Both imaging modalities will not determine the absence of occult nodal metastases with complete certainty, and some authors suggest that both modalities can be used in combination to increase the likelihood of accurate local staging (3,17).

Histological evaluation of the initial endoscopic biopsy of a rectal tumor may aid in determining tumors at a higher risk of lymphatic spread. Important histopathological indicators of aggressive tumor behavior include: histological grade, mucinous tumors, signet cell tumors, and the presence of LVI or perineural invasion (PNI) (*Table 1*) (18,19). Though controversial, tumor histologic grade is considered a stage-independent prognostic indicator and poorly differentiated colorectal adenocarcinoma is associated with worse patient survival (20-22). Mucinous adenocarcinoma is defined by the findings of >50% of the tumor volume composed of extracellular mucin.

Table 2 Comparison of techniques for LE

Variables	TAE	TEM	TAMIS
Tumor distance in the rectum (from dentate line)	Up to 8 cm	>4 cm-up to 15 cm	Up to 15 cm
Bowel preparation	Required	Required	Required
Patients position	Tumor dependent	Tumor dependent	Lithotomy
Anesthesia	Spinal or general	General	General
Instrument	Rigid	Rigid	Flexible
Cost	Low cost	Expensive	Low cost
Learning curve	Moderate learning curve	Steep learning curve	Shallow learning curve
View	~180 degree view	220 degree view	360 degree view

LE, local excision; TAE, transanal excision; TEM, transanal endoscopic microsurgery; TAMIS, transanal minimally invasive surgery.

These tumors are frequently associated with hereditary non-polyposis CRC (HNPCC) and have the potential to behave more aggressively especially if the tumor is found to be microsatellite stable (23,24). Signet ring adenocarcinoma occurs in less than 1% of patients with colorectal adenocarcinoma. By definition this tumor is poorly differentiated and carries a worse outcome than conventional adenocarcinoma (24-26). Several authors have identified both PNI and LVI as being poor predictors for survival both in those patients treated with multimodality therapy and those treated with surgery alone. Cienfuegos *et al*. demonstrated a nearly 4-fold risk of recurrence in patient following neoadjuvant therapy for rectal cancer with PNI or LVI. Furthermore PNI and LVI have been shown to be independent predictive variables for poor survival (27). For this reason, many support more radical surgery in this cohort of patients.

Traditionally, only rectal cancer below 10 cm was considered a candidate for LE. This was due to the limitation of the surgeons' ability to reach higher and the lack of proper visualization of the rectal tumor. With advances in technology and instrumentation, tumors that are higher up can be reached with good visualization. Newer methods including TEM and TAMIS may allow access up to 15 cm in the rectum. It is important that the patient is aware that these procedures will most likely result in a perforation of the bowel above the retroperitoneum and into the peritoneal cavity which will require repair. The details of these procedures are discussed further in this review.

Extended indications for LE have been reported. Currently, patients with a clinical stage ≥T2 rectal adenocarcinoma should undergo radical surgery. Patients with a diagnosis of more advanced rectal cancer who are not candidates for radical surgery due to high operative risk or those who refuse to undergo radical surgery may be considered for neoadjuvant therapy followed by LE of residual disease (28). Furthermore, the use of LE in patients with early rectal cancer treated with neoadjuvant therapy has been studied in clinical trials with mixed results (29-31). Currently, there is limited data supporting LE or close observation in those patients with a complete clinical response following neoadjuvant therapy as an alternative to radical surgery (5,7,10).

Surgical methods of local excision (LE)

Transanal excision (TAE)

Tumors that are less than 10 cm from the anal verge can be resected with a TAE. In preparation for surgery, a full bowel prep is prescribed, systemic antibiotics are administered, and all anticoagulant use is discontinued. Positioning in the operating room is dependent on the location of the tumor. The patient is placed in lithotomy position for posterior tumors and in prone jackknife for anterior and lateral tumors. Regional or general anesthesia can be utilized to remove the tumor (*Table 2*). To aid in visualization, the anus is gently dilated and retracted with a Lone Star® (32). The goal of TAE is a full thickness excision of the tumor down to the mesorectal fat with at least 1 cm radial/circumferential margin. In anterior tumors that abut the posterior vaginal wall, this may not be possible and a partial excision is then carried out. Good hemostasis is obtained and the defect in the bowel wall is closed in a transverse manner to avoid narrowing the lumen using interrupted absorbable sutures. The specimen should be oriented by the surgeon for pathological assessment of the margins. Postoperatively, patients experience minimal pain but fever

is not uncommon. Patients can resume regular diet and activity within 24 hours (33). Postoperative complications are infrequent and include rectal bleeding which is the most common (6%), rectal stenosis (5.5%), urinary retention (1.5%), fecal incontinence (0.5%), and rectovaginal fistula (<1%) (34,35). If patients receive radiation prior to resection, rectal pain is the most common complication (8%) (36).

The major disadvantage for TAE is the poorer surgical outcomes. Moore and others have demonstrated that newer procedures such as TEM yields clear margins more frequently than with the traditional TAE (90% *vs.* 71%) and significant less chance of tumor fragmentation, 94% *vs.* 65% respectively (37). Intraoperative suboptimal visualization has been hypothesized as the cause for the increase risk of positive margins and tumor fragmentation following TAE (34).

Transanal endoscopic microsurgery (TEM)

TEM was first introduced in 1980's by Beuss as an alternative to radical surgery for the removal of rectal polyps. The TEM system consists of a dedicated beveled rectoscope with a 4.5 cm diameter and a maximum distance of 200 mm. This scope is placed in the anus forming an airtight seal to allow for insufflation of the rectum and greatly aiding in visualization (11,38,39). The view is magnified and approximately 220 degrees of the rectum can be seen at once. In preparation for surgery, a full bowel prep is prescribed, systemic antibiotics are administered, and all anticoagulant use is discontinued. Anesthesia is provided with either spinal or general and the patient is positioned on the operating room table so the tumor is in the dependent position (*Table 2*) (32,40). The resectoscope allows access to more proximal rectal lesions up to 15 cm. Because the distal rectum will form the seal with the resectoscope, very low tumors (<5 cm from the anal verge) are not visualized adequately with the TEM procedure. The rectum is insufflated with a standard laparoscopic CO_2 insufflator, and then a full thickness excision is performed using laparoscopic instruments to achieve a 1 cm circumferential margin (32,33). The bowel wall defect is closed transversely, and the specimen oriented for pathological review. If the tumor is above the peritoneal reflection, the abdominal cavity may be perforated and this may require a laparotomy to repair (33). Postoperatively, patients are expected to have an overnight hospital stay and quick recovery with early resumption of normal diet and activities (32,33).

The conversion rate from TEM to radical surgery from an abdominal approach has been reported to be 4.3% in one large series of 693 patients (41). The most common complications reported are hemorrhage (27%), urinary tract infection (21%), and suture line dehiscence (14%) (41). Bleeding and perforation can become life threatening especially in multimorbid or elderly patients. They frequently require reoperations and extend hospital stays (42-44). The reported incidence of fecal incontinence developing after insertion of the resectoscope is 1% and this is generally temporary (41).

The major disadvantage to the TEM procedure which has resulted in a slow adoption in the US is the expense of the resectoscope. Although it clearly demonstrates better visualization, it has a very limited clinical role to smaller tumors in the rectum located from 5 to 15 cm. Another disadvantage of TEM is the steep learning curve that is associated with its use. Barendse *et al.* demonstrated by observing four different providers resect 693 lesions with TEM that a significant learning curve was associated with lowering conversion rates, peritoneal entrance, and procedure time (41). This same study also demonstrated that in patients undergoing TEM after the surgeon had performed at least 35 procedures, the risk of recurrence for malignant lesions declined by 10% as compared to those individuals undergoing surgery in the first 1-35 procedures (41).

Transanal minimally invasive surgery (TAMIS)

TAMIS was first described in 2009 as an alternative to the more expensive system for TEM. The "Tamis platform" uses any of the several available single incision laparoscopy surgery (SILS) ports. By using this port, conventional laparoscopic instrumentation including the camera can be used to perform the procedure. In preparation for surgery, a full bowel prep is prescribed, systemic antibiotics are administered, and all anticoagulant use is discontinued. Anesthesia is provided with either spinal or general and the patient is placed in the dorsal lithotomy position (*Table 2*). A SILS port is first lubricated and introduced into the anal canal and pneumorectum is established with a standard laparoscopic CO_2 insufflator (45,46). Laparoscopic camera lens (preferably using a 5-mm 30 degree or 45 degree lens) and instruments such as graspers, thermal energy devices, and needle drives are introduced through the SILS port to assist the operator in performing a full-thickness resection of the neoplasm with 1 cm margins. The remaining rectal defect is closed in the transverse direction and the specimen oriented for pathological review (46). If the tumor is above the peritoneal reflection, the abdominal

cavity may be perforated and this may require laparotomy to repair (33). Postoperatively, patients are expected to have an overnight hospital stay and quick recovery with early resumption of normal diet and activities. Several investigators are designing the TAMIS platform so that the procedure can be performed with the assistance of the Da Vinci® robot.

Complications following the TAMIS procedure are infrequent with an overall rate of 7.4% (45). The conversion rate in 390 cases performed for both benign and malignant lesions was 2.3% (45). Inadvertent peritoneal entry during TAMIS was reported in 1% of cases and in some cases, the closure of the rectum was successful transanally (45). In malignant polyps, the rate of positive margins was 4.4% and the rate of tumor fragmentation was 4.1% (45).

Oncological outcomes from LE

The advances in the management of rectal cancer have risen from a desire by those who take care of these patients to improve oncological outcomes while maintaining good quality of life. This desire has been the leading force for the development of newer surgical methods which are less invasive. Colorectal surgery is one of the leading specialties in minimally invasive and robotic surgery techniques and the desire to expand the role of LE follows naturally. Early results from studies examining LE for rectal cancer have been mixed (*Table 3*). For this reason, TAE became a procedure reserved for benign lesions. Presently, only clinically staged T1 rectal tumors with favorable histopathology are considered eligible for LE alone without multimodality therapy (54-58).

Interest in developing newer procedures for LE of rectal tumors was driven by the findings of high recurrence rates seen after transanal resection of benign and malignant lesions. Pigot *et al.* demonstrated that in large rectal tumor up to 6 cm, the risk or recurrence of benign polyps was 10% (34). If a malignancy was identified, the risk of recurrence was 20%. Others have reported local recurrence rates up to 39% (59-63). Pigot further speculated that the results from TAE can be explained by inadequate intraoperative exposure and suggested that the newer and improved techniques of LE may improve outcomes (34).

Several single series have been published demonstrating superiority of new procedures such as TEM or TAMIS over TAE with regards to margin of resection and tumor fragmentation. Baatrup *et al.* examined his series of 143 consecutive TEM resections for rectal cancer. Of the patients that were pathological stage T1 tumors, the local recurrence rate was 12% (64). He also found that the significant predictors for survival in his group of patients were tumor size and patient age. He strongly urged that tumors greater than 3 cm should not be removed by LE. In a similar study by Lezoche *et al.*, 135 patients were followed who underwent TEM (65). There were no local recurrences noted in patients with pathological stage T1 tumors and the overall survival rate was 86% at 193 months. Moore *et al.* in 2007 reported a retrospective comparison of TEM to TAE for rectal cancer (37). In this study, 171 patients (82 with TEM) were analyzed. This study included equal number of patients in each group with T2 and T3 tumors. Patients undergoing TEM had an overall lower recurrence rate (8%) when compared to patients undergoing TAE (24%) but this did not reach statistical significance.

When comparing the results of LE to radical surgery, local recurrence rates tend to be higher for both T1 (8.2-23%) and T2 adenocarcinomas (13-30%) undergoing LE when compared to radical surgery for T1-T2 disease (3-7.2%) (36,49,53,66). However, in the studies evaluating LE there has not been a significant difference in DFS when compared to radical surgery. In patients undergoing LE for T1-T2 disease the DFS at 5 years following LE was 55-93% (36,53). This was comparable to patients undergoing radical surgery whose DFS at 5 years was 77-97% (48,49). The inability to demonstrate improved survival following radial surgery may be due to the retrospective analysis that occurred in many of these studies and the lack of adequate follow up. Only recently has there been an emphasis on appropriate follow up following LE. In addition, Nash *et al.* emphasizes from his review of this topic that when he analyzed the patients he followed after LE, there was a survival difference seen between LE and radical surgery and this difference was the result of longer follow up (50). He noted a significantly increased rate of cancer-related death at 4-8 years following LE when compared to radical surgery. He recommend that all patients undergoing LE be committed to long term follow-up.

Whether LE compromises the oncological outcome with the risk of recurrence and local failure remains unknown. Lymph node metastasis occurs in 0-12% in T1 and 10-22% in T2 rectal cancer, however, as local lymph nodes are not sampled using TEM, it is reliant on preoperative staging and histopathological features of the tumor to direct further adjuvant treatment (3,67,68). Comparing different LE techniques; the negative margin is most likely achieved with TEM compared to TAE (64,65). Furthermore, the local

Table 3 Summary of the studies comparing LE *vs.* radical surgery for early rectal cancer

Study	T stage	Patients (n)	Excision technique	FU (mos)	5-year local recurrence (%)	5-year distant recurrence (%)	5-year disease-free survival (%)	5-year overall survival (%)	Negative margin (%)	Intact specimen (%)	Post op complications (%)
TAE *vs*. TME											
Nascimbeni	T1	70	TAE	54	6.6	14.2	66.6	72.4	–	–	–
et al. (47), 2004		74	TME	–	2.8	6.9	83.6	90.4	–	–	–
Endreseth	T1	35	TAE	60	12.0	0	64.0	70.0	46	–	–
et al. (48), 2005		256	TME	60	6.0	7.0	77.0	80.0	100	–	–
Bentrem	T1	151	TAE	48	15.0	12.0	93.0	89.0	–	–	–
et al. (49), 2005		168	TME	58	3.0	3.0	97.0	93.0	–	–	–
Nash	T1	137	TAE	59	13.0	–	83.0	–	–	–	–
et al. (50), 2009		145	TME	77	2.7	–	96.0	–	–	–	–
TEM *vs*. TME											
De Graaf	T1	80	TEM	42	24.0	0	90.0	75.0	–	–	5.8
et al. (51), 2009		75	TME	84	0	8.0	87.0	77.0	–	–	64
Palma	–	34	TEM	86.5	5.9	5.9	82.4	88.2	–	–	2.9
et al. (11), 2009		17	TME	93	0	0	82.4	82.4	–	–	23.5
TAE *vs*. TEM *vs*. TME											
Ptok	T1	85	TAE	44	6.0 (combined LE)	4.0 (combined LE)	91.4 (combined LE)	83.6	–	–	9.4
et al. (52), 2007		35	TEM	–	–	–	–	–	–	–	2.9
		359	TME	–	2.0	4.0	92.3	91.5	–	–	25.1
LE *vs*. TME											
You	T1	601	LE	60	8.2	3.6	93.2	77.4	–	–	LE (T1 + T2)
et al. (53), 2007		493	TME	–	4.3	2.6	97.2	81.7	–	–	5.6
	T2	164	LE	–	12.6	5.0	90.2	67.6	–	–	TME (T1 + T2)
		866	TME	–	7.2	7.7	91.7	76.6	–	–	14.6
TAE *vs*. TEM											
Moore	T1, T2 T3	89	TAE	53	24.0	4.0	–	–	71	65	17
et al. (37), 2008		82	TEM	20	4.0	1.0	–	–	90	94	15

LE, local excision; TAE, transanal excision; TME, total mesorectal excision; TEM, transanal endoscopic microsurgery.

recurrence rate is lower with TEM compared to TAE (37). This is likely the direct result of improved visibility that is achieved with TEM (69) Whether or not these differences ultimately affect DFS is yet to be determined.

Radical resection immediately after LE

Due to the variability in the sensitivity and specificity of the preoperative staging modalities, it is not uncommon for a preoperatively staged T1N0 rectal cancer to have a final pathological stage of T2 or T3. Moreover; a positive margin following LE carries a high risk of recurrence (68). One method of managing unfavorable pathology is to offer the patient immediate radical surgery. Hahnloser *et al.* reported his experience at Mayo clinic with immediate radical resection after LE of rectal cancer (70). In this series, 52 patients underwent radical surgery within 30 days after LE were matched with 90 patients with a T2-3N0-1 primary as a radical surgery control group. The indications for radical re-resection were: cancerous polyp, positive margins, LVI, advanced stage, nodal disease and residual cancer. The five-year overall survival for the study cases *vs.* the control case was (79% *vs.* 91%), respectively and the ten-year survival was (65% *vs.* 78%), respectively with no statistical significant.

Several studies have reported that the oncologic outcomes in patients treated by immediate radical surgery after LE for unfavorable histologic findings are comparable to that of radical surgery performed as a primary treatment (2,10,33,70). However, there is no consensus on the timing of radical surgery or on the use of radiotherapy before radical surgery (9).

LE following neoadjuvant therapy

Excellent response to neoadjuvant therapy for rectal cancer has been observed with complete tumor regression even for advance clinical stages in 10 % to 30% of patients (10,71,72). These finding have translated into a significant reduction in local recurrence rates from 12% to 4% (73). In patients with pathological complete response (pCR), the risk of lymph node involvement is 1.8% compared to 24-52% in those who didn't have pCR (9). Furthermore, patients with a pCR tend to have favorable long-term outcomes, including better overall survival and lower recurrence rates (9,74,75). This had led some clinician to question the need for radical surgery with its associated morbidity in those who have a clinically complete response (cCR) confirmed by endoscopic exam.

Habr-Gama *et al.* compared the long term outcomes between patients who were found to have incomplete clinical response (iCR) and underwent radical surgery with patients who had cCR and underwent a "watch and wait" approach (30). In this series, a total of 265 patients with T2-4 rectal adenocarcinoma received neoadjuvant chemoradiotherapy (CRT). A total of 71 (26.8%) had cCR and underwent watch and wait approach and 194 (73.2%) had iCR and underwent radical resection. At resection, 22 (8.3%) were found to have pCR on the resection specimen. The five-year overall and DFS was 100% and 92% in the watch and wait group and 88% and 83% in the radical resection group respectively. In addition, Perez *et al.* reported on 15 patients with clinical stage T2N0 rectal cancer who underwent neoadjuvant therapy (31). Therapy was followed by "watch and wait" if a cCR occurred, TEM was performed for a partial response with minimal residual disease, and radical surgery was performed for non-responders. The findings from this study demonstrated that for T2N0 tumors, if a cCR to neoadjuvant therapy does not occur, this appears to be a poor prognostic indicator for unfavorable pathological features as nearly 70% of these patients had ypT2 or ypT3 features and those patients are not ideal candidates for LE.

Currently, the standard of care for T2 rectal adenocarcinoma is radical surgery to ensure accurate staging and decrease the risk of local recurrence but with the promising results of pCR; extended indications for LE have been considered as a middle ground between radical surgery and observation in good responders. The American College of Surgeons Oncology Group (ACOSOG) completed a prospective phase II trial that examined the efficacy and safety of neoadjuvant chemoradiotherapy and LE for T2N0 rectal cancer (76). A total of 77 patients who underwent neoadjuvant therapy and LE were included in the analysis. The pCR rate was 44% and tumor downstaging occurred in 64% of patients. The rate of margin positivity at the time of resection approached 0%. However, 39% of patients developed CRT-related grade ≥3 complications and the trial was closed early. Therefore, long-term survival data is not available, presently. Belluco *et al.* compared patients with T3N0-1M0 mid and distal rectal adenocarcinoma who underwent TME or LE and were found to have a pCR (74). A total of 139 patients were included and 110 (93%) underwent TME and 29 (17%) underwent LE, 42 (30.2%) were found to have a pCR. In follow up of 55.4 months, there was no difference in the local recurrence between

radical surgery *vs.* LE. Currently, although neoadjuvant therapy may benefit some patients with early stage rectal cancer, indiscriminate use is not recommended in this population owing to the overtreatment of the majority (36).

Adjuvant therapy following LE

In an attempts to improve the oncological outcome and decrease recurrence; adjuvant therapy has been given following LE. To examine the efficacy of this approach, the Cancer and Leukemia Group B (CALGB) has performed a prospective, multi-institutional study on patients with T1 and T2 distal rectal cancer treated with LE with and without adjuvant therapy (77). In this study, 59 patients with T1 tumor were treated with LE alone and 51 patients with T2 tumor were treated with LE followed by adjuvant CRT. The median follow up was 7 years. The ten-year overall survival and DFS were 84% and 75% for T1, and 66% and 64% for T2 respectively. The local recurrence and distant failure rates for T1 tumors were 8% and 5%, while T2 tumors were 18% and 12% respectively. This results show that T2 tumors had a higher rate of recurrence and shorter overall and DFS even with the administration of adjuvant CRT when compared to T1 or historic radical resection. Therefore, adjuvant CRT following LE maybe reserved for patients with high risk pathology who are unfit to undergo radical resection.

Surveillance following LE

Surveillance guidelines published by the National Comprehensive Cancer Network (NCCN) following LE for T1 rectal cancer include the following: (I) a complete history and physical exam every 3-6 months for 2 years, then every 6 months for a total of 5 years; (II) CEA every 3-6 months for 2 years; (III) chest, abdomen, and pelvic computerized tomogram annually for 3 years; (IV) colonoscopy at one year and thereafter depending on findings; (V) proctoscopy every 6 months for 5 years (78). However, as stated early, others have demonstrated a benefit in follow up for up to 9 years following LE (67).

Conclusions

Historically, oncological outcomes from the use of LE for the treatment of early rectal cancer have been disappointing. However, in carefully selected patients with early (T1) rectal cancer, LE by means of the newer methods of TEM and TAMIS is a promising alternative to radical surgery with minimal morbidity and acceptable oncological outcomes. Currently, there are minimal studies evaluating combined use of neoadjuvant therapy and LE for ≥ T2 lesions which limits its generalizability. Furthermore, several authors are supporting no surgery with a "watch and wait" approach for patients with a cCR because the oncological outcomes are no different than radical surgery. Further prospective clinical trials are needed to determine the most promising roles for LE in the management of rectal cancer.

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Footnote

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References

1. Colorectal Cancer Facts & Figures 2014-2016. Atlanta, GA: American Cancer Society, 2014.
2. Elmessiry MM, Van Koughnett JA, Maya A, et al. Local excision of T1 and T2 rectal cancer: proceed with caution. Colorectal Dis 2014;16:703-709.
3. Ung L, Chua TC, Engel AF. A systematic review of local excision combined with chemoradiotherapy for early rectal cancer. Colorectal Dis 2014;16:502-515.
4. Heald RJ, Moran BJ, Ryall RD, et al. Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978-1997. Arch Surg 1998;133:894-899.
5. Mellgren A, Sirivongs P, Rothenberger DA, et al. Is local excision adequate therapy for early rectal cancer? Dis Colon Rectum 2000;43:1064-1071; discussion 1071-1074.
6. Nelson H, Sargent DJ. Refining multimodal therapy for rectal cancer. N Engl J Med 2001;345:690-692.
7. Peeters KC, van de Velde CJ, Leer JW, et al. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients--a Dutch colorectal cancer group study. J Clin Oncol 2005;23:6199-6206.
8. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. Lancet 1986;1:1479-1482.
9. Nesbakken A, Nygaard K, Bull-Njaa T, et al. Bladder and sexual dysfunction after mesorectal excision for rectal

cancer. Br J Surg 2000;87:206-210.
10. Hompes R, Cunningham C. Extending the role of Transanal Endoscopic Microsurgery (TEM) in rectal cancer. Colorectal Dis 2011;13 Suppl 7:32-36.
11. Palma P, Horisberger K, Joos A, et al. Local excision of early rectal cancer: is transanal endoscopic microsurgery an alternative to radical surgery? Rev Esp Enferm Dig 2009;101:172-178.
12. Kwok H, Bissett IP, Hill GL. Preoperative staging of rectal cancer. Int J Colorectal Dis 2000;15:9-20.
13. Bipat S, Glas AS, Slors FJ, et al. Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MR imaging--a meta-analysis. Radiology 2004;232:773-783.
14. Brown G, Richards CJ, Bourne MW, et al. Morphologic predictors of lymph node status in rectal cancer with use of high-spatial-resolution MR imaging with histopathologic comparison. Radiology 2003;227:371-377.
15. Kim JH, Beets GL, Kim MJ, et al. High-resolution MR imaging for nodal staging in rectal cancer: are there any criteria in addition to the size? Eur J Radiol 2004;52:78-83.
16. Glasgow SC. Advancing Dr Wong's vision for evaluating rectal cancer. Dis Colon Rectum 2013;56:1325-1326.
17. Muthusamy VR, Chang KJ. Optimal methods for staging rectal cancer. Clin Cancer Res 2007;13:6877s-6884s.
18. Saraste D, Gunnarsson U, Janson M. Predicting lymph node metastases in early rectal cancer. Eur J Cancer 2013;49:1104-1108.
19. Stitzenberg KB, Sanoff HK, Penn DC, et al. Practice patterns and long-term survival for early-stage rectal cancer. J Clin Oncol 2013;31:4276-4282.
20. Blenkinsopp WK, Stewart-Brown S, Blesovsky L, et al. Histopathology reporting in large bowel cancer. J Clin Pathol 1981;34:509-513.
21. Jass JR, Atkin WS, Cuzick J, et al. The grading of rectal cancer: historical perspectives and a multivariate analysis of 447 cases. Histopathology 1986;10:437-459.
22. Compton CC. Pathology report in colon cancer: what is prognostically important? Dig Dis 1999;17:67-79.
23. Verhulst J, Ferdinande L, Demetter P, et al. Mucinous subtype as prognostic factor in colorectal cancer: a systematic review and meta-analysis. J Clin Pathol 2012;65:381-388.
24. Kang H, O'Connell JB, Maggard MA, et al. A 10-year outcomes evaluation of mucinous and signet-ring cell carcinoma of the colon and rectum. Dis Colon Rectum 2005;48:1161-1168.
25. Chen JS, Hsieh PS, Chiang JM, et al. Clinical outcome of signet ring cell carcinoma and mucinous adenocarcinoma of the colon. Chang Gung Med J 2010;33:51-57.
26. Makino T, Tsujinaka T, Mishima H, et al. Primary signet-ring cell carcinoma of the colon and rectum: report of eight cases and review of 154 Japanese cases. Hepatogastroenterology 2006;53:845-849.
27. Cienfuegos JA, Rotellar F, Baixauli J, et al. Impact of perineural and lymphovascular invasion on oncological outcomes in rectal cancer treated with neoadjuvant chemoradiotherapy and surgery. Ann Surg Oncol 2015;22:916-923.
28. Tsai BM, Finne CO, Nordenstam JF, et al. Transanal endoscopic microsurgery resection of rectal tumors: outcomes and recommendations. Dis Colon Rectum 2010;53:16-23.
29. Hughes R, Harrison M, Glynne-Jones R. Could a wait and see policy be justified in T3/4 rectal cancers after chemo-radiotherapy? Acta Oncol 2010;49:378-381.
30. Habr-Gama A, Gama-Rodrigues J, São Julião GP, et al. Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: impact of salvage therapy on local disease control. Int J Radiat Oncol Biol Phys 2014;88:822-828.
31. Perez RO, Habr-Gama A, São Julião GP, et al. Transanal local excision for distal rectal cancer and incomplete response to neoadjuvant chemoradiation - does baseline staging matter? Dis Colon Rectum 2014;57:1253-1259.
32. Papagrigoriadis S. Transanal endoscopic micro-surgery (TEMS) for the management of large or sessile rectal adenomas: a review of the technique and indications. Int Semin Surg Oncol 2006;3:13.
33. Heafner TA, Glasgow SC. A critical review of the role of local excision in the treatment of early (T1 and T2) rectal tumors. J Gastrointest Oncol 2014;5:345-352.
34. Pigot F, Bouchard D, Mortaji M, et al. Local excision of large rectal villous adenomas: long-term results. Dis Colon Rectum 2003;46:1345-1350.
35. Piccinini EE, Ugolini G, Rosati G, et al. Transanal local resection for benign and malignant rectal tumours. Int J Colorectal Dis 1995;10:112-116.
36. Garcia-Aguilar J, Mellgren A, Sirivongs P, et al. Local excision of rectal cancer without adjuvant therapy: a word of caution. Ann Surg 2000;231:345-351.
37. Moore JS, Cataldo PA, Osler T, et al. Transanal endoscopic microsurgery is more effective than traditional transanal excision for resection of rectal masses. Dis Colon Rectum 2008;51:1026-1030; discussion 1030-1031.
38. Buess G, Mentges B, Manncke K, et al. Technique and

results of transanal endoscopic microsurgery in early rectal cancer. Am J Surg 1992;163:63-69; discussion 69-70.
39. Zoller S, Joos A, Dinter D, et al. Retrorectal tumors: excision by transanal endoscopic microsurgery. Rev Esp Enferm Dig 2007;99:547-550.
40. Atallah SB, Albert MR. Transanal minimally invasive surgery (TAMIS) versus transanal endoscopic microsurgery (TEM): is one better than the other? Surg Endosc 2013;27:4750-4751.
41. Barendse RM, Dijkgraaf MG, Rolf UR, et al. Colorectal surgeons' learning curve of transanal endoscopic microsurgery. Surg Endosc 2013;27:3591-3602.
42. Kreissler-Haag D, Schuld J, Lindemann W, et al. Complications after transanal endoscopic microsurgical resection correlate with location of rectal neoplasms. Surg Endosc 2008;22:612-616.
43. Featherstone JM, Grabham JA, Fozard JB. Per-anal excision of large, rectal, villous adenomas. Dis Colon Rectum 2004;47:86-89.
44. Kosciñski T, Malinger S, Drews M. Local excision of rectal carcinoma not-exceeding the muscularis layer. Colorectal Dis 2003;5:159-163.
45. Martin-Perez B, Andrade-Ribeiro GD, Hunter L, et al. A systematic review of transanal minimally invasive surgery (TAMIS) from 2010 to 2013. Tech Coloproctol 2014;18:775-788.
46. Atallah S, Albert M, Larach S. Transanal minimally invasive surgery: a giant leap forward. Surg Endosc 2010;24:2200-2205.
47. Nascimbeni R, Nivatvongs S, Larson DR, et al. Long-term survival after local excision for T1 carcinoma of the rectum. Dis Colon Rectum 2004;47:1773-1779.
48. Endreseth BH, Wibe A, Svinsås M, et al. Postoperative morbidity and recurrence after local excision of rectal adenomas and rectal cancer by transanal endoscopic microsurgery. Colorectal Dis 2005;7:133-137.
49. Bentrem DJ, Okabe S, Wong WD, et al. T1 adenocarcinoma of the rectum: transanal excision or radical surgery? Ann Surg 2005;242:472-477; discussion 477-479.
50. Nash GM, Weiser MR, Guillem JG, et al. Long-term survival after transanal excision of T1 rectal cancer. Dis Colon Rectum 2009;52:577-582.
51. De Graaf EJ, Doornebosch PG, Tollenaar RA, et al. Transanal endoscopic microsurgery versus total mesorectal excision of T1 rectal adenocarcinomas with curative intention. Eur J Surg Oncol 2009;35:1280-1285.
52. Ptok H, Marusch F, Meyer F, et al. Oncological outcome of local vs radical resection of low-risk pT1 rectal cancer. Arch Surg 2007;142:649-655; discussion 656.
53. You YN, Baxter NN, Stewart A, et al. Is the increasing rate of local excision for stage I rectal cancer in the United States justified?: a nationwide cohort study from the National Cancer Database. Ann Surg 2007;245:726-733.
54. Heintz A, Mörschel M, Junginger T. Comparison of results after transanal endoscopic microsurgery and radical resection for T1 carcinoma of the rectum. Surg Endosc 1998;12:1145-1148.
55. Palma P, Freudenberg S, Samel S, et al. Transanal endoscopic microsurgery: indications and results after 100 cases. Colorectal Dis 2004;6:350-355.
56. Sengupta S, Tjandra JJ. Local excision of rectal cancer: what is the evidence? Dis Colon Rectum 2001;44:1345-1361.
57. Varma MG, Rogers SJ, Schrock TR, et al. Local excision of rectal carcinoma. Arch Surg 1999;134:863-867; discussion 867-868.
58. Winde G, Nottberg H, Keller R, et al. Surgical cure for early rectal carcinomas (T1). Transanal endoscopic microsurgery vs. anterior resection. Dis Colon Rectum 1996;39:969-976.
59. Chiu YS, Spencer RJ. Villous lesions of the colon. Dis Colon Rectum 1978;21:493-495.
60. Sakamoto GD, MacKeigan JM, Senagore AJ. Transanal excision of large, rectal villous adenomas. Dis Colon Rectum 1991;34:880-885.
61. Nivatvongs S, Nicholson JD, Rothenberger DA, et al. Villous adenomas of the rectum: the accuracy of clinical assessment. Surgery 1980;87:549-551.
62. Thomson JP. Treatment of sessile villous and tubulovillous adenomas of the rectum: experience of St. Mark's Hospital. 1963-1972. Dis Colon Rectum 1977;20:467-472.
63. Keck JO, Schoetz DJ Jr, Roberts PL, et al. Rectal mucosectomy in the treatment of giant rectal villous tumors. Dis Colon Rectum 1995;38:233-238.
64. Baatrup G, Breum B, Qvist N, et al. Transanal endoscopic microsurgery in 143 consecutive patients with rectal adenocarcinoma: results from a Danish multicenter study. Colorectal Dis 2009;11:270-275.
65. Lezoche G, Guerrieri M, Baldarelli M, et al. Transanal endoscopic microsurgery for 135 patients with small nonadvanced low rectal cancer (iT1-iT2, iN0): short- and long-term results. Surg Endosc 2011;25:1222-1229.
66. Madbouly KM, Remzi FH, Erkek BA, et al. Recurrence after transanal excision of T1 rectal cancer: should we be concerned? Dis Colon Rectum 2005;48:711-719;

discussion 719-721.
67. Zenni GC, Abraham K, Harford FJ, et al. Characteristics of rectal carcinomas that predict the presence of lymph node metastases: implications for patient selection for local therapy. J Surg Oncol 1998;67:99-103.
68. Paty PB, Nash GM, Baron P, et al. Long-term results of local excision for rectal cancer. Ann Surg 2002;236:522-529; discussion 529-530.
69. McLemore EC, Coker A, Jacobsen G, et al. eTAMIS: endoscopic visualization for transanal minimally invasive surgery. Surg Endosc 2013;27:1842-1845.
70. Hahnloser D, Wolff BG, Larson DW, et al. Immediate radical resection after local excision of rectal cancer: an oncologic compromise? Dis Colon Rectum 2005;48:429-437.
71. Habr-Gama A, de Souza PM, Ribeiro U Jr, et al. Low rectal cancer: impact of radiation and chemotherapy on surgical treatment. Dis Colon Rectum 1998;41:1087-1096.
72. Hiotis SP, Weber SM, Cohen AM, et al. Assessing the predictive value of clinical complete response to neoadjuvant therapy for rectal cancer: an analysis of 488 patients. J Am Coll Surg 2002;194:131-135; discussion 135-136.
73. Folkesson J, Birgisson H, Pahlman L, et al. Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. J Clin Oncol 2005;23:5644-5650.
74. Belluco C, De Paoli A, Canzonieri V, et al. Long-term outcome of patients with complete pathologic response after neoadjuvant chemoradiation for cT3 rectal cancer: implications for local excision surgical strategies. Ann Surg Oncol 2011;18:3686-3693.
75. Coco C, Manno A, Mattana C, et al. The role of local excision in rectal cancer after complete response to neoadjuvant treatment. Surg Oncol 2007;16 Suppl 1:S101-S104.
76. Garcia-Aguilar J, Shi Q, Thomas CR Jr, et al. A phase II trial of neoadjuvant chemoradiation and local excision for T2N0 rectal cancer: preliminary results of the ACOSOG Z6041 trial. Ann Surg Oncol 2012;19:384-391.
77. Greenberg JA, Shibata D, Herndon JE 2nd, et al. Local excision of distal rectal cancer: an update of cancer and leukemia group B 8984. Dis Colon Rectum 2008;51:1185-1191; discussion 1191-1194.
78. Engstrom PF, Arnoletti JP, Benson AB 3rd, et al. NCCN Clinical Practice Guidelines in Oncology: rectal cancer. J Natl Compr Canc Netw 2009;7:838-881.

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The influence of anastomotic leakage on patients' outcomes after rectal cancer surgery

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Rectal cancer surgery is still evolving and various resection techniques such as laparoscopy, robotics, or transanal minimally invasive surgery have been introduced (1). However, establishing intestinal continuity following tumor resection is an unchanged part of rectal cancer surgery (2). Colorectal anastomosis is performed by stapled or hand-sewn method between the proximal colon and rectal stump (3).

Anastomotic leakage is one of most devastating complication after rectal cancer resection. Anastomotic leakage compromises immediate postoperative outcomes and, although controversial, oncologic outcomes. Earlier studies have reported that anastomotic leakage increases local recurrence rate (4-6) or local and distant recurrence rates (7-9). In some studies, anastomotic leakage deteriorated overall (5,7,10) and disease-specific survivals (5,8,9). Recently, Hain *et al.* (11) investigated the impact of anastomotic leakage on oncological outcomes after rectal cancer surgery. Laparoscopic total mesorectal excision was performed in all patients (n=428) and anastomotic leakage was occurred in 120 patients (28%). Based on multivariate analyses, symptomatic anastomotic leakage was an independent risk factor for local recurrence-free survival (odds ratio =2.13). However, asymptomatic anastomotic leakage was not a meaningful risk factor for local recurrence-free survival. In their series, 28% of anastomotic leakage rate (symptomatic: n=70, 16% and asymptomatic: n=50, 12%) is somewhat high when compared to previous studies (12,13). This reason may be due to difference in definition of anastomotic leakage or study population.

Unfortunately, the mechanism for unfavorable survival rate has not been clearly elucidated. Potential mechanisms have been suggested that anastomotic leakage may cause implantation of occult tumor cells around the anastomosis site (14). Stress response following anastomotic leakage can suppress the function of cytotoxic T cells and natural killer cells and thereby promote cancer cell survival (15). Inflammatory reaction is related to cancer development and progression. Infectious condition by anastomotic leakage can induce systemic inflammatory response and thereby promote disease recurrence (16). In addition, anastomotic leakage may preclude appropriate adjuvant chemotherapy. Occurrence of postoperative complications such as anastomotic leakage is associated with the lack of chemotherapy or delayed commencement of chemotherapy (6). To understand the impact of anastomotic leakage on oncologic outcomes, underlying mechanism should be revealed. Future study should be directed to translational or prospective clinical studies.

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References

1. Kim NK, Kim YW, Cho MS. Total mesorectal excision for rectal cancer with emphasis on pelvic autonomic nerve preservation: Expert technical tips for robotic surgery. Surg Oncol 2015;24:172-180.
2. Kim IY, Kim BR, Kim YW. Applying reinforcing sutures to stapled colorectal anastomosis after low anterior resection for rectal cancer. Eur J Surg Oncol 2015;41:808-809.
3. Kim YW, Kim IY. The new stapler device is good, but needs more evaluation. Ann Coloproctol 2014;30:59.
4. Ptok H, Marusch F, Meyer F, et al. Impact of anastomotic leakage on oncological outcome after rectal cancer resection. Br J Surg 2007;94:1548-1554.
5. Branagan G, Finnis D. Wessex Colorectal Cancer Audit Working Group. Prognosis after anastomotic leakage in colorectal surgery. Dis Colon Rectum 2005;48:1021-1026.
6. Kim IY, Kim BR, Kim YW. The impact of anastomotic leakage on oncologic outcomes and the receipt and timing of adjuvant chemotherapy after colorectal cancer surgery. Int J Surg 2015;22:3-9.
7. Kube R, Mroczkowski P, Granowski D, et al. Anastomotic leakage after colon cancer surgery: a predictor of significant morbidity and hospital mortality, and diminished tumour-free survival. Eur J Surg Oncol 2010;36:120-124.
8. Eberhardt JM, Kiran RP, Lavery IC. The impact of anastomotic leak and intra-abdominal abscess on cancer-related outcomes after resection for colorectal cancer: a case control study. Dis Colon Rectum 2009;52:380-386.
9. Law WL, Choi HK, Lee YM, et al. Anastomotic leakage is associated with poor long-term outcome in patients after curative colorectal resection for malignancy. J Gastrointest Surg 2007;11:8-15.
10. Marra F, Steffen T, Kalak N, et al. Anastomotic leakage as a risk factor for the long-term outcome after curative resection of colon cancer. Eur J Surg Oncol 2009;35:1060-1064.
11. Hain E, Maggiori L, Manceau G, et al. Oncological impact of anastomotic leakage after laparoscopic mesorectal excision. Br J Surg 2017;104:288-295.
12. Paun BC, Cassie S, MacLean AR, et al. Postoperative complications following surgery for rectal cancer. Ann Surg 2010;251:807-818.
13. Kim NK, Kim YW, Min BS, et al. Operative safety and oncologic outcomes of anal sphincter-preserving surgery with mesorectal excision for rectal cancer: 931 consecutive patients treated at a single institution. Ann Surg Oncol 2009;16:900-909.
14. Walker KG, Bell SW, Rickard MJ, et al. Anastomotic leakage is predictive of diminished survival after potentially curative resection for colorectal cancer. Ann Surg 2004;240:255-259.
15. Hensler T, Hecker H, Heeg K, et al. Distinct mechanisms of immunosuppression as a consequence of major surgery. Infect Immun 1997;65:2283-2291.
16. McMillan DC, Canna K, McArdle CS. Systemic inflammatory response predicts survival following curative resection of colorectal cancer. Br J Surg 2003;90:215-219.

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Implication of the low anterior resection syndrome (LARS) score for bowel dysfunction after rectal cancer surgery with symptomatic anastomotic leakage

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Hain *et al.* investigated bowel dysfunction after laparoscopic sphincter-saving rectal resection. To assess the influence of anastomotic leakage (AL) they compared symptomatic AL with asymptomatic leakage and a matched control group without AL after low rectal surgery (1). Assessment of the low anterior resection syndrome (LARS) and postoperative quality of life was performed and scored by the LARS score and the disease-specific questionnaire of the European Organization for Research and Treatment of Quality of Life Questionnaire for Colorectal Cancer (EORTC QLQ-CR29). Data were received of a prospectively maintained database. Overall, out of 432 patients with laparoscopic low rectal cancer surgery 46 patients with a postoperative AL (symptomatic n=23, asymptomatic n=23) were identified between January 2005 and December 2014. Each patient with an AL was matched with all (one or more) similar patients without an AL. The following criteria were used: age (±2 years), sex, type of neoadjuvant treatment (no treatment or chemoradiotherapy), and type of anastomosis (colorectal stapler anastomosis or hand sewn coloanal anastomosis). All study groups were well balanced with respect to patients, tumor, and surgery characteristics. At least, to avoid any disturbing factors in the postoperative setting all patients had to have restoration of intestinal continuity (no temporary or permanent stoma) with a minimal follow-up of more than 1 year and no ongoing chemotherapy.

The study results demonstrated that patients with a symptomatic AL had impaired bowel function compared with the control group with somewhat greater, though of little consequence, LARS score {median: 30 [23–39] *vs.* 27 [15–34], P=0.02} and worse LARS categories (no LARS in 4% *vs.* 31%, minor LARS in 52% *vs.* 52%, and major LARS in 44% *vs.* 17%, P=0.004). In contrast to the patients with a symptomatic AL, the LARS score was not different between the asymptomatic AL group and the control group {median 24 [14–37] *vs.* 27 [15–34], P=0.70}. Multivariate analysis identified as independent risk factors for the onset of impaired bowel function after low rectal surgery the symptomatic AL, neoadjuvant radiotherapy, intersphincteric resection and a hand-sewn coloanal anastomosis. Furthermore, the results of the EORTC QLQ CR-29 questionnaires showed that patients with a postoperative symptomatic AL reported more blood and mucus in stool, frequent bowel movements per day, and frequent urination per day.

The presented results of this study by Hain *et al.* are of relevant clinical importance. With respect to the last two decades most studies about rectal cancer surgery were focused on oncologic results, namely the incidence of loco-regional recurrence rates and the frequency of AL. Postoperative bowel function and postoperative quality of life were secondary outcome parameters and were not accurately evaluated and reported. The presented study

used for the first time adequately assessment instruments for this topic. Hain *et al.* found that patients with symptomatic AL have impaired functional results and that every second patient with a symptomatic AL had major LARS. In contrast to this finding, quality of life and function of patients with an asymptomatic AL can be considered close to those of patients without AL. These results are in good accordance with the everyday clinical work experience. Additionally, the results of this study also showed that independently of the onset of AL nearly 2/3 of our patients are suffering from the underestimated LARS. Overall, the presented data gave good reasons to start postoperative early evaluation of the LARS and initiating early postoperative treatment. Future studies should be initiated to identify and establish treatment modalities to improve long-term results of bowel function and quality of life after rectal surgery. This would best serve the interests for our patients.

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References

1. Hain E, Manceau G, Maggiori L, et al. Bowel dysfunction after anastomotic leakage in laparoscopic sphincter-saving operative intervention for rectal cancer: A case-matched study in 46 patients using the Low Anterior Resection Score. Surgery 2017;161:1028-1039.

The best timing for administering systemic chemotherapy in patients with locally advanced rectal cancer

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Abstract: Over the past several decades, outcomes for patients with rectal cancer have improved considerably. However, several questions have emerged as survival times have lengthened and quality of life has improved for these patients. Currently patients with locally advanced rectal cancer (LARC) are often recommended multimodality therapy with fluoropyrimidine-based chemotherapy (CT) and radiation followed by total mesorectal excision (TME), with consideration given to FOLFOX before chemoradiotherapy (CRT). Recently, Garcia-Aguilar and colleagues reported in *Lancet Oncology* that the addition of mFOLFOX6 administered between CRT and surgery affected the number of patients achieving pathologic complete response (pathCR), which is of great interest from the standpoint of pursuit of optimal timing of systemic CT delivery. This was a multicenter phase II study consisting of 4 sequential treatment groups of patients with LARC, and they reported that patients given higher number CT cycles between CRT and surgery achieved higher rates of pathCR than those given standard treatment. There was no association between response improvement and tumor progression, increased technical difficulty, or surgical complications. Ongoing phase III clinical trial further assessing this strategy might result in a paradigm shift.

Keywords: Locally advanced rectal cancer (LARC); mFOLFOX6; neoadjuvant therapy

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Multimodality therapy consisting of concurrent fluoropyrimidine-based chemoradiotherapy (CRT), followed by surgery and systemic chemotherapy (CT), is the standard of care for patients with locally advanced rectal cancer (LARC); this is based on results of the German Rectal Cancer Study Group phase III trial (protocol CAO/ARO/AIO-94) (1). Although treatment outcomes and quality of life for patients with LARC have impressively improved over the past several decades, many controversies remain regarding the optimal treatment paradigm for this common disease—an estimated 39,610 new cases of rectal cancer occurred in the United States in 2014 (2).

Garcia-Aguilar and colleagues recently published a report (3) in which they assessed the impact of adding mFOLFOX6 between CRT and surgery on the proportion of patients achieving pathologic complete response (pathCR). This nonrandomized study consisted of 4 sequential study groups of patients with stage II-III LARC at centers in the United States and Canada; a total of 259 patients were analyzed (the 4 groups consisted of 60, 67, 67, and 65 patients). The primary endpoint was the proportion of patients who achieved pathCR in each study group, analyzed by intention to treat. Patients in group 1 were treated with CRT and underwent total mesorectal excision (TME) 6–8 weeks after CRT; the proportion achieving pathCR in this group was set as a baseline. Patients in groups 2–4 received 2, 4, or 6 cycles of mFOLFOX6 4–5 weeks after the completion of CRT and underwent TME 3–5 weeks after the last cycle of mFOLFOX6. CRT consisted of 225 mg/m^2 fluorouracil per day by continuous

infusion throughout radiotherapy, which consisted of 45.0 Gy in 25 fractions, 5 days per week for 5 weeks, followed by a minimum boost of 5.4 Gy and possible second boost of 3.6 Gy, within which the entire small bowel could be excluded from the final cone down (54 Gy total cumulative dose). Each cycle of mFOLFOX6 consisted of 200 or 400 mg/m^2 racemic leucovorin, according to the discretion of the treating investigator, as well as 85 mg/m^2 oxaliplatin in a 2-h infusion, bolus 400 mg/m^2 fluorouracil on day 1, and a 46-h infusion of 2,400 mg/m^2 fluorouracil. Disease response had been assessed using the Response Evaluation Criteria in Solid Tumors guidelines (4) during the neoadjuvant treatment course for patients in groups 2–4, so that they would not be at risk of disease progression due to the lengthened CRT-to-surgery interval.

They reported that an increased proportion of patients achieved pathCR with the addition of mFOLFOX6 between CRT and TME, and the lengthened CRT-to-surgery interval. The proportions of patients achieving pathCR were as follows: 11/60 in group 1 [18%; 95% confidence interval (CI), 10–30], 17/67 in group 2 (25%; 95% CI, 16–37), 20/67 in group 3 (30%; 95% CI, 19–42), and 25/65 in group 4 (38%; 95% CI, 27–51; P=0.0036). Patients in group 4 were significantly more likely to achieve pathCR than those in group 1 (odds ratio 3.49; 95% CI, 1.39–8.75; P=0.011). On the basis of these findings, the authors concluded that the additional mFOLFOX6 between CRT and surgery and prolongation of the CRT-to-surgery interval contributed to the increase in the proportion of patients achieving pathCR, which was among the highest proportions reported for LARC to date (5-9). The study also demonstrated that the treatment approach used in groups 2–4 did not increase the risk of tumor progression or surgical complications, which is favorable from both an oncologic and surgical standpoint.

However, this study has a number of limitations. First, because it was a nonrandomized phase II trial with a relatively small number of patients enrolled, unrecognized confounders and selection bias could have affected the results. Second, the primary endpoint was the proportion of patients achieving pathCR, which means limited follow-up, although pathCR is associated with high recurrence-free survival rates (5,10). Third, the trial was not originally powered to assess surgical and oncologic complications and the measurement of surgical complications was limited because only a few parameters were represented. Given these limitations, the findings of the study should be interpreted with caution and are still in need of confirmation in a randomized trial.

Current therapy for LARC, with a combination of CRT, TME, and systemic CT, has greatly improved patient outcomes, but many controversies remain even just within the neoadjuvant treatment setting. First, the optimal timing of the delivery of chemoradiation needs to be investigated further. The German Rectal Cancer Study Group compared preoperative CRT with postoperative CRT for LARC (1) and found that preoperative CRT resulted in improved local control and reduced toxicity, with similar overall survival outcomes to those observed with postoperative CRT. Including that study, several trials have been conducted to compare the administration of radiation preoperatively and postoperatively, but a clear answer has not yet been reached.

In terms of preoperative CRT, several options exist. Both preoperative short-course radiotherapy (5 Gy per day; total dose of 25 Gy) and preoperative CRT have been shown to improve local disease control in patients with LARC treated with surgery (11,12). Short-course radiotherapy followed by surgery within 7 days has the advantage of shorter treatment duration, more efficient use of medical resources, and fewer costs than CRT followed by surgery within 6–8 weeks. Unfortunately, two prospective randomized studies comparing short-course radiotherapy with CRT (13,14) did not provide a clear answer as to which is the most efficacious method.

In addition, several recent trials have shown that the oral capecitabine (converted to fluorouracil by intracellular thymidine phosphorylase) could be substituted for continuous venous infusion of fluorouracil, which would be easier for patients. In both a European trial (15) and the National Surgical Adjuvant Breast and Bowel Project R04 (16), capecitabine was not inferior to continuous venous infusion of fluorouracil, although long-term oncologic outcomes are still awaited.

Recent studies have also investigated whether oxaliplatin could be added to fluoropyrimidine as a radiosensitizer to improve treatment outcomes. Most of these trials failed to show improved clinical outcomes with oxaliplatin, and it was shown to result in more toxic effects and worse therapeutic ratios (7,8,16). Although the CAO/ARO/AIO-04 trial (9) showed an increased proportion of pathCR with similar toxic effects in patients treated with oxaliplatin and fluoropyrimidine compared with fluoropyrimidine alone, this finding must be interpreted with caution because the fluorouracil dosage and schedule were not same between the two arms. In summary, so far it is not recommended to add oxaliplatin to fluorouracil as a radiosensitizer during

CRT for patients with LARC.

Targeted therapy with anti-vascular endothelial growth factor and anti-endothelial growth factor receptor agents is expected to enhance treatment strategies for LARC, and plenty of targeted agents play a crucial role in the treatment of unresectable or metastatic colorectal cancer. The AVACROSS study assessed the efficacy and toxicity of bevacizumab added to induction CT followed by preoperative bevacizumab-based CRT in patients with LARC (17). Although that study demonstrated an impressive proportion of patients achieving pathCR with the addition of bevacizumab (36%, which is similar to the 38% achieving pathCR in group 4 of the study by Garcia-Aguilar and colleagues), with manageable toxic effects, 24% of patients experienced serious surgical complications that required additional surgical intervention. Several other phase II trials that assessed the effectiveness and feasibility of adding bevacizumab to the combined-modality treatment failed to reach the primary endpoint or demonstrated increased toxic effects or surgical complications, and thus did not proceed to phase III trials (18,19).

Other targeted therapies have also been studied. The randomized phase II EXPERT-C trial assessed neoadjuvant oxaliplatin, capecitabine, and preoperative radiotherapy with or without cetuximab followed by TME, and results of that study showed that the secondary endpoints of radiologic response and overall survival significantly improved in patients with wild-type KRAS/BRAF rectal cancer whose treatment included cetuximab. However, the primary endpoint of improved pathCR was not met (20). The SAKK41/07 trial, a randomized, multicenter, phase II trial, assessed the impact of adding panitumumab to neoadjuvant CRT in patients with wild-type KRAS LARC. In that study, the primary endpoint was pathologic near-complete response plus complete tumor response, which was achieved in 53% of patients in the panitumumab arm compared with 32% in the control arm. However, patients receiving panitumumab also experienced increased rates of grade 3 or higher toxic effects (21). On the basis of these findings, unfortunately, targeted therapies have so far failed to play a role in neoadjuvant treatment of patients with potentially resectable LARC outside of clinical trials.

Controversies surrounding the optimal LARC treatment strategy also extend to the multimodality treatment paradigm itself, although it is clear that coordination of preoperative treatment, surgery, and adjuvant therapy is important. The strategy of induction CT preceding CRT and surgery was added to the 2015 version of the National Comprehensive Cancer Network (NCCN) clinical practice guidelines as an acceptable option for the treatment of LARC, indicating that the strategy of shifting systemic therapy to earlier in the treatment is receiving a lot of attention. This may be in part because the advances in modern treatment for LARC, consisting of preoperative CRT and improved surgical techniques, have considerably decreased local disease recurrence rates, which are currently below distant recurrence rates. However, although preoperative CRT and TME have improved local disease control, overall survival and the incidence of distant metastasis with LARC remain problematic.

Despite the NCCN guideline recommendation for adjuvant systemic CT, up to 27% of eligible patients with LARC never start adjuvant CT and less than 50% (22) receive the full prescribed course without interruptions or delays, owing to postoperative complications, delayed recovery, or interference caused by the need for a temporary ostomy closure (23). Systemic CT has advanced as oxaliplatin was added to 5-fluorouracil and FOLFOX was later administrated, which has led to relatively high routine response rates of up to 50% for patients with metastatic colorectal cancer (24). The next key step to advance the treatment of LARC is to determine the optimal timing for delivery of systemic CT.

Several potential advantages of systemic CT given in earlier setting of multimodality treatment are early prevention or eradication of micrometastases, increased rates of pathCR, minimized time needed for a diverting ostomy, avoidance of the challenges of undergoing CT in the presence of an ostomy, and improved tolerance and completion rates of CT. Several studies have investigated the efficacy and feasibility of systemic CT in the neoadjuvant setting. Cercek and colleagues assessed the safety and efficacy of initial FOLFOX followed by CRT and TME in 61 patients with LARC (25). In that study, a relatively high proportion of patients (36%) achieved pathCR or clinical complete response without any serious adverse events causing treatment delay during administration of FOLFOX or CRT. The AVACROSS study, which we mentioned earlier, then assessed the impact of induction CT as well (17). Although patients in that study experienced serious surgical complications, which might have been caused mainly by the addition of bevacizumab, the high proportion of patients achieving pathCR (36%) is still impressive in terms of the efficacy of neoadjuvant CT.

The positive attention given to the strategy of administering systemic CT ahead of CRT and surgery

leads to another question: why not administer systemic CT between CRT and surgery? Several studies have demonstrated an association between increased intervals from completion of CRT to surgery and an increase in pathCR rates (26,27), which also suggests that this question is worth pursuing. The study by Garcia-Aguilar and colleagues (3) might serve as a first step to answer this question, but further research is needed to determine whether the results of the study will ultimately change clinical practice. The results of ongoing phase III trials assessing this strategy are awaited, although the question remains which factor, the length of the interval from CRT to surgery or the administration of mFOLFOX6, had the most effect on achieving increased the pathCR rates. Approaching the answers of those questions with further studies and improving the pathCR rate can also contribute to advance the discussion about wait-and-see nonoperative strategy, i.e., deferral of surgery and close follow-up in LARC patients with clinical complete response after CT and CRT, which is still part of clinical trial (28). For now, many controversies remain in terms of how to manage patients with LARC, but further studies of rigorous protocol-based treatment will help the management of rectal cancer become truly individualized. In addition, molecular assessment will need to be incorporated in personalizing care.

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Footnote

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References

1. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731-1740.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015;65:5-29.
3. Garcia-Aguilar J, Chow OS, Smith DD, et al. Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial. Lancet Oncol 2015;16:957-966.
4. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205-216.
5. Maas M, Nelemans PJ, Valentini V, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol 2010;11:835-844.
6. Belluco C, De Paoli A, Canzonieri V, et al. Long-term outcome of patients with complete pathologic response after neoadjuvant chemoradiation for cT3 rectal cancer: implications for local excision surgical strategies. Ann Surg Oncol 2011;18:3686-3693.
7. Aschele C, Cionini L, Lonardi S, et al. Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. J Clin Oncol 2011;29:2773-2780.
8. Gérard JP, Azria D, Gourgou-Bourgade S, et al. Clinical outcome of the ACCORD 12/0405 PRODIGE 2 randomized trial in rectal cancer. J Clin Oncol 2012;30:4558-4565.
9. Rödel C, Liersch T, Becker H, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. Lancet Oncol 2012;13:679-687.
10. de Campos-Lobato LF, Stocchi L, da Luz Moreira A, et al. Pathologic complete response after neoadjuvant treatment for rectal cancer decreases distant recurrence and could eradicate local recurrence. Ann Surg Oncol 2011;18:1590-1598.
11. Cedermark B, Johansson H, Rutqvist LE, et al. The Stockholm I trial of preoperative short term radiotherapy in operable rectal carcinoma. A prospective randomized trial. Stockholm Colorectal Cancer Study Group. Cancer 1995;75:2269-2275.
12. Peeters KC, van de Velde CJ, Leer JW, et al. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients--a Dutch colorectal cancer group study. J Clin Oncol 2005;23:6199-6206.
13. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative

conventionally fractionated chemoradiation for rectal cancer. Br J Surg 2006;93:1215-1223.
14. Ngan SY, Burmeister B, Fisher RJ, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. J Clin Oncol 2012;30:3827-3833.
15. Hofheinz RD, Wenz F, Post S, et al. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial. Lancet Oncol 2012;13:579-588.
16. O'Connell MJ, Colangelo LH, Beart RW, et al. Capecitabine and oxaliplatin in the preoperative multimodality treatment of rectal cancer: surgical end points from National Surgical Adjuvant Breast and Bowel Project trial R-04. J Clin Oncol 2014;32:1927-1934.
17. Nogué M, Salud A, Vicente P, et al. Addition of bevacizumab to XELOX induction therapy plus concomitant capecitabine-based chemoradiotherapy in magnetic resonance imaging-defined poor-prognosis locally advanced rectal cancer: the AVACROSS study. Oncologist 2011;16:614-620.
18. Dipetrillo T, Pricolo V, Lagares-Garcia J, et al. Neoadjuvant bevacizumab, oxaliplatin, 5-fluorouracil, and radiation for rectal cancer. Int J Radiat Oncol Biol Phys 2012;82:124-129.
19. Landry JC, Feng Y, Prabhu RS, et al. Phase II Trial of Preoperative Radiation With Concurrent Capecitabine, Oxaliplatin, and Bevacizumab Followed by Surgery and Postoperative 5-Fluorouracil, Leucovorin, Oxaliplatin (FOLFOX), and Bevacizumab in Patients With Locally Advanced Rectal Cancer: 5-Year Clinical Outcomes ECOG-ACRIN Cancer Research Group E3204. Oncologist 2015;20:615-616.
20. Dewdney A, Cunningham D, Tabernero J, et al. Multicenter randomized phase II clinical trial comparing neoadjuvant oxaliplatin, capecitabine, and preoperative radiotherapy with or without cetuximab followed by total mesorectal excision in patients with high-risk rectal cancer (EXPERT-C). J Clin Oncol 2012;30:1620-1627.
21. Helbling D, Bodoky G, Gautschi O, et al. Neoadjuvant chemoradiotherapy with or without panitumumab in patients with wild-type KRAS, locally advanced rectal cancer (LARC): a randomized, multicenter, phase II trial SAKK 41/07. Ann Oncol 2013;24:718-725.
22. Bosset JF, Calais G, Mineur L, et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. Lancet Oncol 2014;15:184-190.
23. Hayden DM, Pinzon MC, Francescatti AB, et al. Hospital readmission for fluid and electrolyte abnormalities following ileostomy construction: preventable or unpredictable? J Gastrointest Surg 2013;17:298-303.
24. Goldberg RM, Sargent DJ, Morton RF, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 2004;22:23-30.
25. Cercek A, Goodman KA, Hajj C, et al. Neoadjuvant chemotherapy first, followed by chemoradiation and then surgery, in the management of locally advanced rectal cancer. J Natl Compr Canc Netw 2014;12:513-519.
26. Sloothaak DA, Geijsen DE, van Leersum NJ, et al. Optimal time interval between neoadjuvant chemoradiotherapy and surgery for rectal cancer. Br J Surg 2013;100:933-939.
27. Francois Y, Nemoz CJ, Baulieux J, et al. Influence of the interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter-sparing surgery for rectal cancer: the Lyon R90-01 randomized trial. J Clin Oncol 1999;17:2396.
28. Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg 2004;240:711-717; discussion 717-718.

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The emerging role of neoadjuvant chemotherapy for rectal cancer

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Abstract: Locally advanced rectal cancer remains a substantial public health problem. Historically, the disease has been plagued by high rates of both distant and local recurrences. The standardization of pre-operative chemoradiation and transmesorectal excision (TME) have greatly lowered the rates of local recurrence. Efforts to improve treatment through use of more effective radiosensitizing therapies have proven unsuccessful in rectal cancer. Presently, due to improved local therapies, distal recurrences represent the dominant problem in this disease. Adjuvant chemotherapy is currently of established benefit in colorectal cancer. As such, adjuvant chemotherapy, consisting of fluoropyrimidine and oxaliplatin, represent the standard of care for many patients. However, after pre-operative chemoradiotherapy and rectal surgery, the administration of highly effective chemotherapy regimens has proven difficult. For this reason, novel neoadjuvant approaches represent appealing avenues for investigation. Strategies of neoadjuvant chemotherapy alone, neoadjuvant chemotherapy followed by chemoradiation and neoadjuvant chemoradiation followed by chemotherapy are under investigation. Initial encouraging results have been noted, though definitive phase III data is lacking.

Keywords: Rectal cancer; neoadjuvant; adjuvant; chemotherapy; chemoradiation

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Introduction

In 2014 it is estimated that there will be more than 136,000 new cases of colorectal cancer diagnosed as well as greater than 50,000 colorectal cancer associated deaths in the United States. Approximately 40,000 patients will be diagnosed with rectal cancer (1). National uptake of screening via colonoscopy has markedly increased in the last decade, with a corresponding decrease in the incidence of colorectal cancer over this time. In contrast, among individuals under the age of 50, a slight rise in the rates of distal colon and rectal cancers has been observed in the US, as recently reported in Norway (2). Over the last three decades, outcomes of patients with rectal cancer have substantially improved stage for stage, likely attributable to improvements in therapy (3). Prior to the standard use of radiotherapy, systemic therapy, and transmesorectal excision (TME) surgery, both local and distant recurrences represented major problems in the treatment of rectal cancer. Unacceptably high rates of devastating local recurrences prompted multiple efforts to improve local control. In the ensuing years, the benefit of peri-operative radiotherapy, specifically 5-FU based chemoradiation, was established to improve outcomes in patients with rectal cancer (4-7). The primary benefit seen is in reduced local recurrence rates, with a less consistent impact on disease free and overall survival. Moreover, this benefit is demonstrated to be greater with the use of pre-operative rather than post-operative chemoradiation (4). This has led to the incorporation of neoadjuvant 5-FU-based chemoradiation into the standard treatment paradigm for locally advanced rectal cancer.

Notably, since the initial trials of chemoradiation, surgical approaches for rectal cancer evolved significantly, with TME becoming the standard of care. This technique involves *en bloc* removal of the mesorectum, including the primary tumor and the associated perirectal lymph nodes via meticulous dissection so as not to disrupt the mesorectal plane. The advent of TME brought single-institution reports of local recurrence rates as low as 4-9%, compared with

rates of 32-35% through use of conventional surgery (8). Of course, these vast surgically mediated improvements in local control brought into question by some the necessity of pre-operative radiotherapy; as noted, the benefit most consistently observed with chemoradiation has been the reduction in local recurrence rates. For the most part, the pivotal trials evaluating the benefit of adding of radiotherapy to surgery incorporated a suboptimal, but formerly standard non-TME surgical approach. However, the Dutch neoadjuvant trial of short course pre-operative radiotherapy (5×5 Gy) utilized the modern surgical approach, TME, and yet demonstrated a consistent benefit of improved local control (9). Outcomes appear comparable with the two techniques: short course pre-operative radiotherapy and 5-FU based neoadjuvant chemoradiation, though the former has not been widely adopted in the US to date (10,11). Given the bulk of the data supporting pre-operative chemoradiation, as well as demonstration of improved outcomes with TME, utilization of both modalities is currently the standard approach for locally advanced rectal cancer (T3, T4 or node positive disease). Most guidelines also support the addition of post-operative adjuvant chemotherapy, which is administered for the majority of patients (12).

While the data for adjuvant chemotherapy in rectal cancer treated via multimodality therapy is less robust, it is generally accepted that adjuvant chemotherapy is a necessary part of therapy. GITSG protocol 7175 closed early following interim analysis and demonstrated improvements in recurrence rates and disease free survival (DFS) with the use of adjuvant chemotherapy, with or without radiotherapy (13). A survival benefit was not established here. However, the subsequently published NSABP R-01 study, utilizing adjuvant 5-FU based chemotherapy (5-FU, semustine, and vincristine), and the NCCTG study which added 5-FU and methyl-CCNU to radiotherapy both demonstrated that post-operative chemotherapy improves survival (14,15). Of course, refinements in these regimens followed. These chemotherapy choices do not represent the standard for colorectal cancer today. Through investigation, the options of infusional 5-FU or bolus 5-FU and leucovorin were established as the optimal regimens (16,17). The non-inferiority of capecitabine was subsequently confirmed (18). Further building upon this, the MOSAIC trial and NSABP C-07 demonstrated an additional improvement in DFS with the addition of oxaliplatin to 5-FU based adjuvant therapy for colon cancer (19,20). This has led to the routine offering of 5-FU based chemotherapy, typically FOLFOX to stage III and high risk stage II colon cancer patients. A Cochrane meta-analysis of 21 randomized controlled trials supports this practice in rectal cancer, demonstrating a 25% reduction in risk of recurrence for rectal cancer patients treated with adjuvant 5-FU based regimens (21).

On the other hand, long term results of EORTC 22921 were recently reported (22). This trial employed a 2×2 factorial design to assess the value of adding chemotherapy (5-FU and leucovorin) to preoperative radiotherapy concurrently, post-operatively or in both settings. The addition of chemotherapy, either concurrently with radiotherapy or post-operatively, clearly increased local control rates. However, there was no apparent impact of adjuvant chemotherapy on disease-free or overall survival (22). While these results are in some ways disappointing, it is important to note the very poor rates of adherence to chemotherapy: 82% pre-operatively and just 42.9% post-operatively (5). Both the poor compliance rates and the lack of use of a now standard oxaliplatin-based regimen have caused many to view these negative trial results with skepticism. Regardless, conclusive data is lacking, leaving room for debate as to the optimal incorporation of chemotherapy in rectal cancer.

Multiple investigations have been carried out to improve upon the gains described above, including the incorporation of additional radiosensitizing agents to 5-FU. Though irinotecan, oxaliplatin, bevacizumab, and anti-EGFR therapies have improved survival in the metastatic setting, none have yet proved superior as a radiosensitizer when compared to 5-FU-based chemoradiation (23-25). In addition, apart from oxaliplatin, none of these has conclusively improved outcomes in the adjuvant setting for early stage colorectal cancer (26). The testing of new agents in the adjuvant setting and the development of improved radiosensitizing agents may yet provide gains. However, toxicity appears to be greater with post-operative chemotherapy as well as post-operative chemoradiation, leading to delays in therapy as well as premature discontinuation, undermining its potential benefit. The CAO/ARO/AIO-94 trial demonstrated that post-operative as compared to pre-operative chemoradiation increased rates of grade 3/4 acute (40% *vs.* 27%) and long term adverse events (24% *vs.* 14%) (27). Full dose radiation and chemotherapy were administered in just 54% and 50% of post-operatively treated patients as opposed to 92% and 89% of pre-operatively treated patients (27).

Of importance, as highlighted by the results of EORTC 22921, tolerance and compliance with post-

operative chemotherapy is consistently dismal, possibly accounting for its inability to demonstrate benefit (5). In fact, greater than one in three patients do not receive post-operative chemotherapy, for a variety of reasons, as recently reported (28). Even in those who ultimately receive chemotherapy, post-operative complications are linked to delays in the initiation of adjuvant chemotherapy and linked to worsened survival (29). Given the lesser toxicity and improved compliance with therapy in the pre-operative setting, there is a growing interest in developing further neoadjuvant treatment strategies for locally advanced rectal cancer. The remainder of this paper will focus on review of recent data and ongoing neoadjuvant therapy efforts. The three major strategies of focus include neoadjuvant chemoradiation followed by chemotherapy, induction chemotherapy followed by chemoradiation, and neoadjuvant chemotherapy alone.

Neoadjuvant chemotherapy alone

As current surgical techniques achieve very good local control rates and the majority of recurrences represent distant metastatic disease, there is a strong argument to be made for turning our focus to improving the delivery of systemic therapy. The current treatment paradigm utilizes nearly 6 weeks of neoadjuvant chemoradiation, 6-8 weeks of recovery prior to surgery, and another 4 weeks of recovery prior to consideration of adjuvant therapy. As such, the standard approach delays the time to initiation of full dose systemic therapy for 4 months, at a minimum. Beginning chemotherapy sooner provides the theoretical advantage of treating micro-metastatic disease earlier, in hope of reducing the incidence of distant recurrence. In addition, as radiotherapy has not improved survival in the vast majority of the studies published, it is possible the added toxicities of this modality may be obviated through use of chemotherapy alone. Radiation related toxicities are not insignificant; there is a substantial incidence of fecal incontinence and sexual dysfunction which tend to be worse with chemoradiation as opposed to radiation alone (30). Patients treated with chemoradiation as compared with surgery alone note worsening of altered bowel habits: more frequent bowel movements per day, more frequent nighttime movements, and a greater incidence of occasional or frequent incontinence necessitating a pad (31).

However, radiotherapy has an established role in this disease. In addition, the MRC CR07/NCIC-CTG C016 comparing pre-operative short course radiotherapy with selective post-operative chemoradiotherapy demonstrated inferior local recurrence rates and DFS with the selective use of chemoradiation, suggesting that we may not be able to pick and choose the patients in whom to administer radiotherapy (32). In subset analysis, the benefit of radiation was maintained in those patients who underwent TME, but TME was not standard in this trial. Also, less than 50% of patients received any chemotherapy. Both of these factors limit the applicability of these results to the current patient population (32,33). Potentially further alleviating this concern, recent updated results of the MERCURY study suggest that pre-operative magnetic resonance imaging (MRI) assessment of the circumferential margin may be very helpful in predicting those patients who will have clear circumferential margins, with a 94% negative predictive value (34). Such assessments may aid in tailoring therapy, limiting the potential harms of withholding any valuable components.

The experience with neoadjuvant chemotherapy as the sole modality is very limited when compared to other approaches. However, initial results are encouraging. A single institutional study of neoadjuvant IFL (weekly irinotecan, 5-FU and leucovorin) was carried out in the early 2000's in Stage II & III rectal cancers. After 2 months of therapy, 15 of 26 (58%) patients achieved tumor downstaging with one (4%) pathologic complete response (pCR) achieved. A 5-year DFS of 75% was achieved, though there were three pelvic recurrences (35). Importantly, irinotecan is not of proven benefit in adjuvant therapy, and the majority of other efforts focused on oxaliplatin-based therapies. A recent multi-institutional Japanese study evaluated the use of four cycles of neoadjuvant CAPOX (capecitabine + oxaliplatin) and bevacizumab in high risk rectal cancer prior to surgery (T4 in 59.4%, <5 cm from anal verge in 50%). In this 32-patient study, the scheduled chemotherapy was completed by 91% of patients with an R0 resection rate of 90%. pCR was noted in 13% of patients with a total of 37% experiencing good tumor regression (36). A second effort was recently reported from a different group in Japan also utilizing CAPOX and bevacizumab in high risk patients: those with T4 or node positive rectal cancers. Twenty five patients were evaluated, though seven discontinued therapy after 2-3 cycles. One patient (4%) achieved a pCR, and the vast majority were downstaged. Ninety-two percent of patients underwent resection, all with R0 resections. However, post-operative complications were observed in 26% of patients, and at a median follow-up of 31 months, there have been five

Table 1 Studies of neoadjuvant chemotherapy alone in rectal cancer

Study	Key inclusion criteria	#pts	Treatment	pCR rate	Outcomes
Ishii, *et al.* (35)	T3 or T4	26	Irinotecan, 5-FU, Leucovorin ×8 weeks	3.8%	5-year DFS—74% 5-year OS—84%
Uehara, *et al.* (36)	MRI-defined poor risk: T4, N2, CRM ≤1 mm, extramural invasion >5 mm	32	CAPOX, bevacizumab ×12 weeks	13%	R0 resection rate—90%
Hasegawa, *et al.* (37)	T4 or N+	25	CAPOX, bevacizumab ×12 weeks	4%	R0 resection rate—92% DFS at 31 months—68%
Cercek, *et al.* (38)	No radiation, resected primary	20	FOLFOX +/– bevacizumab	35%	N/A
Schrag, *et al.* (39)	T3	32	FOLFOX + bevacizumab ×8 weeks	25%	R0 resection rate—100% 4-year LR—0% 4-year DFS—84%

pCR, pathologic complete response; DFS, disease free survival; OS, overall survival; CRM, circumferential resection margin; LR, local recurrence.

distant recurrences, including one with accompanying local recurrence (37). While neoadjuvant chemotherapy may be beneficial for high risk rectal cancer, the small numbers and poorer prognosis limit interpretation of the outcomes achieved. There is good reason to proceed with caution in eliminating local therapies for those patients at highest risk of local recurrence.

Average risk patients have also been evaluated through such an approach. A review from Memorial Sloan Kettering of 20 patients with colorectal cancer who were treated initially with FOLFOX +/– bevacizumab demonstrated an impressive pCR rate of 35% (38). Similar results were noted by the same group in a prospective evaluation of rectal cancer patients with standard risk (T3 or N+) tumors >5 cm from the anal verge and without bulky nodes. T4 tumors were not permitted. Thirty two patients were treated with 6 cycles of FOLFOX and bevacizumab followed by TME. Radiation was to be utilized for those without response. In this study, all patients demonstrated tumor regression with a 100% R0 resection rate and a 25% pCR rate. At a mean 53 months follow-up, the local recurrence rate is 0% with a 4-year DFS of 84% (39). While these results are encouraging, the small number of patients significantly hampers our ability to estimate the true benefit of this approach. A summary of select neoadjuvant chemotherapy studies is available in *Table 1*.

Appropriately, these encouraging results have prompted a prospective randomized trial evaluating this approach: the PROSPECT trial (NCT01515787). The PROSPECT trial is a phase II/III trial from the Alliance for Clinical Trials in Oncology, "The Alliance", examining the efficacy of 6 cycles of preoperative FOLFOX with the selective use of chemoradiation in patients with non-bulky Stage II/III rectal cancer. Patients are being randomized to pre-operative FOLFOX versus pre-operative chemoradiation, with post-operative treatment left to the discretion of the individual investigator. In the chemotherapy only arm, the use of chemoradiation will be limited to the pre-operative setting in those having less than a 20% reduction in their rectal tumor and the post-operative setting for those patients with positive circumferential margins. MRI will be utilized to guide therapy, with a primary end-point of DFS (*Figure 1*).

Similar studies evaluating pre-operative chemotherapy are ongoing on overseas. The BACCHUS trial is a medium sized phase II trial evaluating the efficacy and toxicity of 6 cycles of FOLFOX + bevacizumab versus 6 cycles of FOLFOXIRI (5-FU, leucovorin, oxaliplatin, irinotecan), with bevacizumab held in the final cycle for both (NCT01650428). Chemoradiation will only be selectively utilized and the primary outcome is pCR rate. There is also an ongoing 3-arm, randomized phase II trial in China evaluating 4 cycles of pre-operative FOLFOX versus FOLFOX followed by FOLFOX-based chemoradiation versus chemoradiation with 5-FU alone (NCT01211210). The primary end-point is 3-year DFS.

The results from the aforementioned trials will be important in the coming years in shaping the face of rectal cancer therapy, though at present neoadjuvant chemotherapy remains investigational given the limited

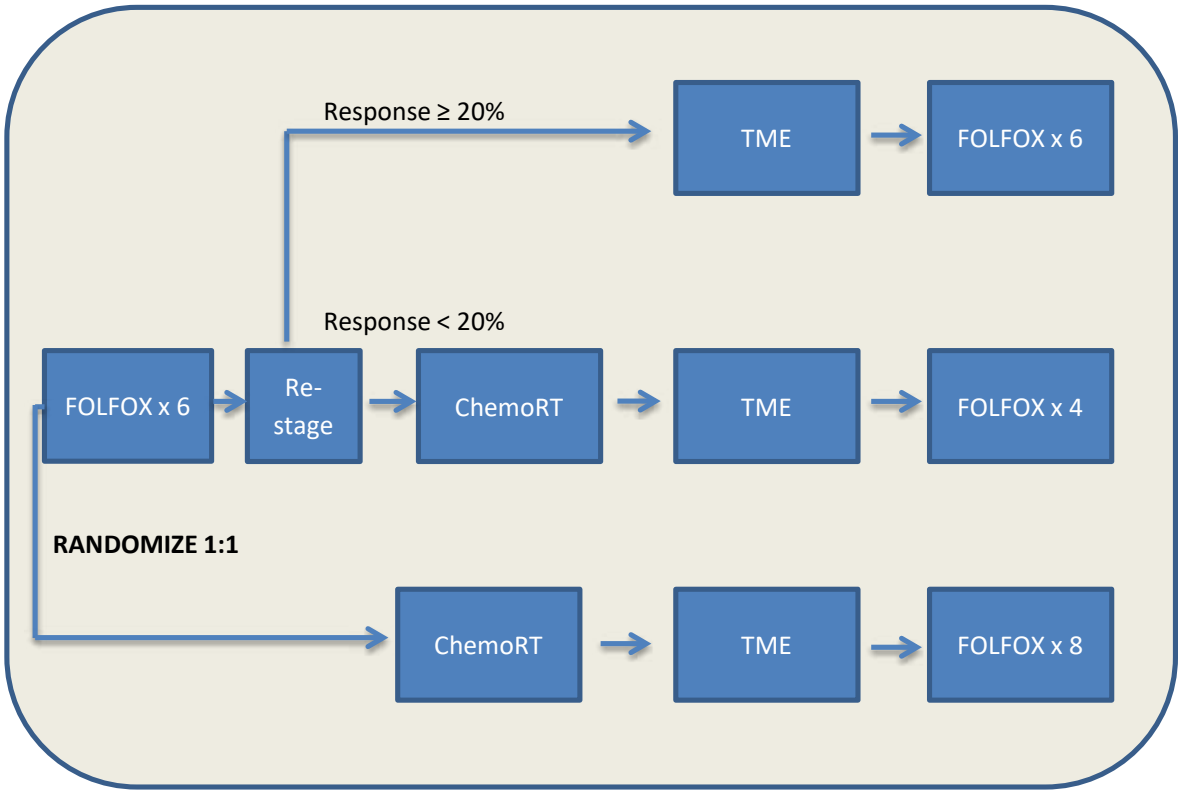

Figure 1 PROSPECT schema. ChemoRT, chemoradiation with 5-FU or capecitabine. Post-operative chemotherapy regimens are suggested, but left to the discretion of the investigator.

experience, coupled with the lack of data to predict which locally advanced patients may forgo radiotherapy.

Neoadjuvant chemotherapy followed by chemoradiation

Perhaps the most frequently explored tactic, induction chemotherapy followed by chemoradiation represents an attractive approach. With recognition that distant metastases largely remain the major risk, early systemic therapy is maintained. Still, a positive circumferential margin places patients at greatest risk for local recurrence and a using a combined approach may provide even greater benefit for those patients at elevated risk (distal tumors, >5 mm extramural spread, T4, or bulky nodal disease). As demonstrated in advanced disease, combination chemotherapy with FOLFOX or FOLFIRI induces response in 50-60% of patients with colorectal cancer (40). In sum, induction chemotherapy may allow for early treatment of micrometastatic disease and initial downstaging of the primary tumor. In turn, by following this immediately with chemoradiation, optimal local control may be attained, with the hope of increased complete response rates. It should be noted that this approach, however, has not shown benefit to date in other tumors, such as anal cancer, lung cancer or head and neck cancer. In addition, there is a theoretical risk of selecting for radio-resistant clones by the administration of chemotherapy prior to radiotherapy.

There have been reports on the results of induction chemotherapy followed by chemoradiation in several sizeable trials to date. The EXPERT and GCR-3 studies both examined 12 weeks of induction CAPOX (capecitabine + oxaliplatin) followed by chemoradiation (41,42).The EXPERT trial enrolled 104 patients who were treated with this approach as well as 12 weeks of adjuvant capecitabine. Ninety seven patients underwent resection and 20% of all patients were noted to have a pCR. In this high risk group, 3-year progression free survival (PFS) was 68%, with a 74% 3-year relapse free rate in those patients who underwent resection (41). The Spanish GCR-3 study randomized 108 locally advanced patients to induction CAPOX followed by chemoradiation versus a strategy of chemoradiation

followed by post-surgical adjuvant CAPOX. This was also a high risk population. Patients were deemed locally advanced on the basis of MRI; inclusion criteria included involvement of or threated circumferential resection margin (CRM), tumor ≤6 cm from anal verge, resectable cT4 tumors and node positivity. Outcomes between the two arms were comparable, with a pCR rate of 13% *vs.* 14% (42). Recently with updated follow-up, there is comparable 5-year DFS (60.7% *vs.* 64.3%) without a significant difference in local relapse (7.1% *vs.* 1.9%, P=0.36) (43). It is notable that acute grade 3/4 toxicity was observed in 19% of patients who received pre-operative chemotherapy versus 54% of post-operatively treated patients. Not surprisingly, the proportion of patients who completed all 4 cycles of chemotherapy was much improved when administered preoperatively: 94% *vs.* 57% (42). While not clearly improving outcomes, this supports the notion that a strategy of pre-operative as opposed to post-operative chemotherapy may decrease acute toxicity.

More protracted as well as abridged courses of neoadjuvant therapy have been examined, producing similar results. The CONTRE trial utilized a longer course of 8 cycles of FOLFOX prior to chemoradiation. In a preliminary report, an impressive pCR rate of 33% was demonstrated, albeit in a cohort of just 30 patients (44). Two cycles of CAPOX prior to chemoradiation was evaluated by a Danish Group, producing encouraging results in a phase II study of 85 patients with poor risk rectal cancer. A pCR rate of 25% was obtained, with 5-year for DFS and overall survival (OS) of 63% and 67%, respectively (45). Additionally, a randomized phase II trial utilizing 2 cycles of FOLFOX followed by chemoradiation with chemoradiation alone was also conducted in Belgium. After 57 patients had been enrolled, the trial was closed early for futility based on identical rates of major downstaging (34.5% and 32.1% achieving ypT0-1). Greater grade 3/4 toxicity was seen with induction chemotherapy (46). Finally, utilization of 1 cycle of CAPOX prior to chemoradiation with CAPOX has produced similarly encouraging tumor downstaging rates, pCR rates (23%), and R0 resection rates (98%) (47). Again, it remains difficult to compare merit of the various approaches given substantial issues with patient selection and small numbers.

Additional studies have evaluated the benefit of adding targeted therapies to this treatment paradigm, most notably the EXPERT-C and AVACROSS trials. The EXPERT-C trial compared treatment with four cycles of neoadjuvant CAPOX followed by chemoradiation with or without the addition of cetuximab to the entire pre-operative course. One hundred and sixty five patients with MRI-defined high risk rectal cancer were enrolled. After conception, data emerged supporting cetuximab use only in KRAS wild-type patients. As such, the primary endpoint of complete response was analyzed for the 90 KRAS wild-type patients. Cetuximab increased response rate (95% *vs.* 73% post-chemoradiation), but complete response rates were similar with or without cetuximab (11% *vs.* 9%), and there was no difference observed in PFS (48). In a recent follow-up, after a median follow-up of 63.8 months, an exploratory analysis including expanded RAS testing (KRAS non-exon 2 and NRAS) revealed no significant differences in outcomes. However, there was a hint of activity with trends toward improved complete response (15.8% *vs.* 7.5%, P=0.31), 5-year PFS (78.4% *vs.* 67.5%, P=0.17) and 5-year OS (83.8% *vs.* 70%, P=0.20) with cetuximab (49). The AVACROSS trial, demonstrated encouraging results in a poor risk patient population. CAPOX and bevacizumab were used as induction therapy and afterwards radiosensitizers through a multimodality neoadjuvant approach. Though almost all 47 patients (98%) underwent R0 resections and demonstrated a pCR rate of 36%, post-operative complications were abundant. Eleven (24%) patients required repeat surgical interventions (50). Similarly high complication rates have been reported by other groups utilizing neoadjuvant bevacizumab in this manner (24). A summary of select studies utilizing neoadjuvant chemoradiation followed by chemotherapy is available in *Table 2*.

The verdict is out on whether there is any true improvement in pathologic response rates and more importantly, long term outcomes. As described, the current data comes largely from small phase II studies with great heterogeneity in the proportion of patient with T4 tumors, the dose of radiotherapy administered and timing of surgery. All of these factors may have a substantial impact on pCR rates. The conduct of randomized phase III studies is needed to definitively evaluate this approach. Fortunately, this is an area of active research. The French phase III randomized PRODIGE 23 trial is evaluating a strategy of neoadjuvant FOLFIRINOX prior to chemoradiation versus standard chemoradiation in locally advanced rectal cancer, with plans to enroll 460 patients (NCT01804790). In addition, the ongoing UK COPERNICUS trial is evaluating the feasibility of administering 4 cycles of neoadjuvant FOLFOX prior to short course radiotherapy, followed immediately by surgery (NCT01263171).

Table 2 Studies of neoadjuvant chemotherapy followed by chemoradiation

Study	Key inclusion criteria	#pts	Treatment	pCR rate	Outcomes
EXPERT (41)	MRI-defined poor risk: T4, T3 at or below levators, N2, CRM ≤1 mm, extramural invasion >5 mm	77	CAPOX ×12 weeks → chemoRT with capecitabine → adjuvant capecitabine ×12 weeks	24% (16/67)	R0 resection rate—99% ORR—97% 1 year DFS—87% 1 year OS—93%
GCR-3 (42)	Tumor within 2 mm of CRM, T3 ≤6 cm from anal verge, T3N+, resectable T4	108	ChemoRT with capecitabine and oxaliplatin → surgery → adjuvant CAPOX	13%	R0 resection—87% Downstaging—58% 18 months DFS—82% 18 months OS—89%
			CAPOX → chemoRT with capecitabine and oxaliplatin → surgery	14%	R0 resection—86% Downstaging—43% 18 months DFS—76% 18 months OS—91%
CONTRE (44)	T3, T4 or N+	36	FOLFOX ×16 weeks → chemoRT with capecitabine or 5-FU	29% (6/21)	R0 resection—100%
Maréchal, *et al.* (46)	T2-T4N+	57	Chemoradiation with 5-FU	28%	ypT0-1—34.5% Downstaging—72% CRM + (≤1 mm)—14%
			FOLFOX ×4 weeks → Chemoradiation with 5-FU	25%	ypT0-1—32.1% Downstaging—61% CRM + (≤1 mm)—4%
EXPERT-C (48)	T3 at or below levators, T4, CRM ≤1 mm, extramural extension ≥5 mm, extramural venous invasion	165	CAPOX + cetuximab × 12 weeks → chemoRT with capecitabine + cetuximab	11%*	R0 resection—92%* Response rate—84% (93%*)
			CAPOX ×12 weeks → chemoRT with capecitabine	9%*	R0 resection—92%* Response rate—76% (75%*)
AVACROSS (50)	T3 low rectal, mid rectum with CRM ≤2 mm, N+ with CRM ≤2 mm, operable T4, T3N+	47	CAPOX + bevacizumab × 12 weeks → chemoRT with capecitabine + bevacizumab	35% (16/45)	R0 resection—98% DFS at 32 months—84%

*, results for analysis of KRAS wild-type population; pCR, pathologic complete response; CRM, circumferential resection margin; ORR, objective response rate; DFS, disease free survival; OS, overall survival.

Neoadjuvant chemoradiation followed by chemotherapy

A strong argument can be made for the approach of initial chemoradiation followed by chemotherapy, though this has been the least fully explored to this point. Chemoradiation remains the standard neoadjuvant treatment with established benefit. Initial utilization of this modality minimizes risk of interruption due to complications induced by other modalities. As this may be definitive treatment, itself, any detrimental effect that initial chemotherapy may induce is avoided. Moreover, as interest grows in the potential of non-surgical management of rectal cancer, data have suggested that an increased interval between the completion of chemoradiation and surgical evaluation may allow for improved response, namely increased pCR rates, as seen in anal cancer (51). Further validation is needed, and there is potential for worsened fibrosis and more a difficult surgical intervention with prolonged delays between radiotherapy and surgery. Arguing against this approach, the delivery of pelvic radiation may hamper the subsequent ability to deliver full dose chemotherapy, potentially lessening its impact. Further, the response to chemotherapy may not be fully appreciated when chemoradiation is first administered.

Studies of long course chemoradiation followed by pre-operative chemotherapy for locally advanced rectal cancer have been conducted by several groups. Two groups have conducted studies evaluating initial chemoradiation with capecitabine followed by an addition 2-4 weeks of capecitabine prior to surgery. These demonstrated feasibility, without marked increase in acute toxicity or post-operative complications (52,53). At this point, the pCR rates are comparable to other techniques and long term outcome data has not matured. A trial from Italy which used chemoradiation followed by two 3-week cycles of capecitabine (1,250 mg/m^2 bid) revealed more encouraging long term follow-up. The pathologic response rate was 18%, with a 5-year DFS of 85.4%. For those patients with tumors ≤6 cm from the anal verge, sphincter preservation rate was 62%. There was a low prevalence of T4 tumors or other high risk features in this study, perhaps accounting for the favorable long term outcomes (54).

As with other approaches, fluoropyrimidine and oxaliplatin based combinations have also been attempted. In a recent study of high risk locally advanced rectal cancer patients, 1 cycle of CAPOX was administered following chemoradiation with CAPOX. pCR was observed in 13 (36.1%) of the 36 patients enrolled (55). An intriguing Dutch report of 50 patients with metastatic, but resectable rectal cancer evaluated a strategy of short course radiotherapy (5×5 Gy) followed by 6 cycles of CAPOX + bevacizumab, which was initiated within 2 weeks of radiotherapy completion. Radical surgical resection was ultimately possible for 72% of all patients treated. The primary rectal tumor was resected in 43 (90%) patients, though a suboptimal R1 resection was achieved in four. In those undergoing primary resection, downstaging was evident in 47% with a pCR rate of 26%. Local recurrence after R0 resection was noted in just 2 (6%) patients (56). Thus, in the metastatic setting, this appears to be a viable approach. At times, short course radiotherapy is not embraced due to the perceived lesser rates of down-staging. The strategy of short course radiotherapy followed immediately by full-dose systemic therapy may allow for optimal downstaging with use of the 5×5 schema, and only minimally delay systemic therapy.

A larger experience has been reported utilizing long-course chemoradiation. In a non-randomized multicenter US study, 144 patients with stage II and III rectal cancer were assigned to one of two study groups. Both received initial 5-FU based chemoradiation. The first group had surgery within 6-8 weeks of completion. The second group was reassessed at 4 weeks and if with evidence of clinical response, patients were treated with two cycles of FOLFOX, followed by surgery 3-5 weeks after completion. Overall pathologic response rates were improved in the group with additional chemotherapy (and delayed surgical intervention), though differences in the pCR rate did not reach significance: 18% *vs.* 25%, respectively. Importantly, while there was a slight increase in pelvic fibrosis seen, the complication rates were not different between the two groups (51). From this same data set, preliminary results which include a third group of 48 patients have also been reported. In group 3, where two further cycles of FOLFOX were delivered, delaying surgery 4 further weeks, pCR rates increased to 31%, without increased complication rates (57). Thus initial chemoradiation followed by pre-operative chemotherapy appears at least as promising as the other strategies described. A summary of selected studies utilizing this approach is available in *Table 3*.

Multiple trials are ongoing with this approach. The Polish Colorectal Cancer Study Group is conducting a phase III study comparing short-course preoperative radiotherapy followed by three cycles of FOLFOX with conventional chemoradiation to 50.4 Gy with concurrent 5-FU (NCT00833131). The accrual goal is

Table 3 Studies of neoadjuvant chemoradiation followed by chemotherapy

Study	Key inclusion criteria	# pts	Treatment	pCR rate	Outcomes
Zampino, *et al.* (54)	T3, T4 or N+	51	ChemoRT with capecitabine → capecitabine ×6 weeks	18% (9/50)	R0 resection—100% 5-year DFS—85.4%
Gao, *et al.* (55)	T4, bulky (>5 cm), <6 cm from anal verge, N+, elevated CEA	36	ChemoRT with CAPOX → CAPOX ×3 weeks	36%	R0 resection—100% Downstaged—81%
van DijK, *et al.* (56)	Metastatic rectal cancer	50	Short course radiation → CAPOX + bevacizumab for up to 18 weeks	26% (11/43)	R0 resection of primary—91% (39/43) 2-year OS—80% LR rate after R0 resection—6% (2/36)
Garcia-Aguilar, *et al.* (51)	T3, T4 or N+	144	Chemoradiation with 5-FU Chemoradiation with 5-FU → FOLFOX ×4 weeks	18% 25%	R0 resection—97% R0 resection—96%

pCR, pathologic complete response; DFS, disease free survival; CEA, carcino-embryonic antigen; LR, local recurrence.

540 patients and positive results could be practice changing for both radiation and medical oncologists in the United States. An interim analysis revealed no major differences in acute toxicity or local efficacy, with a trend toward improved pCR rates in the short-course radiotherapy group: 21% *vs.* 9% (58). Equally important is the phase III RAPIDO study which is very similar in design, though goes further in moving the entire current treatment regimen to the pre-operative setting (NCT01558921). Only patients who are deemed high risk by MRI are to be included. In this study, a strategy of short course chemoradiation followed by 6 cycles of CAPOX will be compared with long course chemoradiation. Post-operative adjuvant chemotherapy is left up to the individual investigator.

Conclusions

Outcomes continue to improve in colorectal cancer as affected patients are discovered earlier in the disease process, largely attributable to increased screening efforts. Improved surgical technique, incorporation of pre-operative radiotherapy and the use of adjuvant chemotherapy all appear to confer additional benefit for a large portion of patients. Recent efforts to build upon 5-FU based chemoradiation regimens have yielded negative results. In the meantime, adjuvant colorectal cancer chemotherapy has not progressed further beyond the fluoropyrimidine and oxaliplatin based combination. In rectal cancer, neoadjuvant treatment offers a unique opportunity to improve the current paradigm. There is opportunity to both improve disease free and overall survival outcomes through the differential layering of therapy, as well as to reduce toxicity through the selective use of therapeutic modalities. Selection of the optimal patient population for each paradigm may prove critical in affecting the results and applicability of ongoing studies. Beyond clinical criteria, further biomarker validation may allow for the additional tailoring of therapy moving forward. As always, the support of clinical investigation remains paramount in improving future outcomes for our patients.

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Footnote

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

References

1. American Cancer Society: Cancer Facts and Figures 2014. [cited 2014 March 5]; Available online: http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2014/index
2. Siegel R, Desantis C, Jemal A. Colorectal cancer statistics, 2014. CA Cancer J Clin 2014;64:104-117.
3. Rutter CM, Johnson EA, Feuer EJ, et al. Secular trends in colon and rectal cancer relative survival. J Natl Cancer Inst 2013;105:1806-1813.
4. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94

randomized phase III trial after a median follow-up of 11 years. J Clin Oncol 2012;30:1926-1933.
5. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006;355:1114-1123.
6. Folkesson J, Birgisson H, Pahlman L, et al. Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. J Clin Oncol 2005;23:5644-5650.
7. Gérard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. J Clin Oncol 2006;24:4620-4625.
8. Havenga K, Enker WE, Norstein J, et al. Improved survival and local control after total mesorectal excision or D3 lymphadenectomy in the treatment of primary rectal cancer: an international analysis of 1411 patients. Eur J Surg Oncol 1999;25:368-374.
9. van Gijn W, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol 2011;12:575-582.
10. Ngan SY, Burmeister B, Fisher RJ, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. J Clin Oncol 2012;30:3827-3833.
11. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg 2006;93:1215-1223.
12. Khrizman P, Niland JC, ter Veer A, et al. Postoperative adjuvant chemotherapy use in patients with stage II/III rectal cancer treated with neoadjuvant therapy: a national comprehensive cancer network analysis. J Clin Oncol 2013;31:30-38.
13. Prolongation of the disease-free interval in surgically treated rectal carcinoma. Gastrointestinal Tumor Study Group. N Engl J Med 1985;312:1465-1472.
14. Fisher B, Wolmark N, Rockette H, et al. Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP protocol R-01. J Natl Cancer Inst 1988;80:21-29.
15. Krook JE, Moertel CG, Gunderson LL, et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. N Engl J Med 1991;324:709-715.
16. Wolmark N, Rockette H, Fisher B, et al. The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: results from National Surgical Adjuvant Breast and Bowel Project protocol C-03. J Clin Oncol 1993;11:1879-1887.
17. O'Connell MJ, Martenson JA, Wieand HS, et al. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. N Engl J Med 1994;331:502-507.
18. Hofheinz RD, Wenz F, Post S, et al. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial. Lancet Oncol 2012;13:579-588.
19. Yothers G, O'Connell MJ, Allegra CJ, et al. Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. J Clin Oncol 2011;29:3768-3774.
20. André T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol 2009;27:3109-3116.
21. Petersen SH, Harling H, Kirkeby LT, et al. Postoperative adjuvant chemotherapy in rectal cancer operated for cure. Cochrane Database Syst Rev 2012;3:CD004078.
22. Bosset JF, Calais G, Mineur L, et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. Lancet Oncol 2014;15:184-190.
23. Horisberger K, Treschl A, Mai S, et al. Cetuximab in combination with capecitabine, irinotecan, and radiotherapy for patients with locally advanced rectal cancer: results of a Phase II MARGIT trial. Int J Radiat Oncol Biol Phys 2009;74:1487-1493.
24. Dipetrillo T, Pricolo V, Lagares-Garcia J, et al. Neoadjuvant bevacizumab, oxaliplatin, 5-fluorouracil, and radiation for rectal cancer. Int J Radiat Oncol Biol Phys 2012;82:124-129.
25. Aschele C, Cionini L, Lonardi S, et al. Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. J Clin Oncol 2011;29:2773-2780.
26. de Gramont A, Chibaudel B, Bachet JB, et al. From chemotherapy to targeted therapy in adjuvant treatment for stage III colon cancer. Semin Oncol 2011;38:521-532.
27. Sauer R, Becker H, Hohenberger W, et al. Preoperative

versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731-1740.
28. Haynes AB, You YN, Hu CY, et al. Postoperative chemotherapy use after neoadjuvant chemoradiotherapy for rectal cancer: Analysis of Surveillance, Epidemiology, and End Results-Medicare data, 1998-2007. Cancer 2014;120:1162-1170.
29. Tevis SE, Kohlnhofer BM, Stringfield S, et al. Postoperative complications in patients with rectal cancer are associated with delays in chemotherapy that lead to worse disease-free and overall survival. Dis Colon Rectum 2013;56:1339-1348.
30. Brændengen M, Tveit KM, Bruheim K, et al. Late patient-reported toxicity after preoperative radiotherapy or chemoradiotherapy in nonresectable rectal cancer: results from a randomized Phase III study. Int J Radiat Oncol Biol Phys 2011;81:1017-1024.
31. Kollmorgen CF, Meagher AP, Wolff BG, et al. The long-term effect of adjuvant postoperative chemoradiotherapy for rectal carcinoma on bowel function. Ann Surg 1994;220:676-682.
32. Sebag-Montefiore D, Stephens RJ, Steele R, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet 2009;373:811-820.
33. Quirke P, Steele R, Monson J, et al. Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. Lancet 2009;373:821-828.
34. Taylor FG, Quirke P, Heald RJ, et al. Preoperative magnetic resonance imaging assessment of circumferential resection margin predicts disease-free survival and local recurrence: 5-year follow-up results of the MERCURY study. J Clin Oncol 2014;32:34-43.
35. Ishii Y, Hasegawa H, Endo T, et al. Medium-term results of neoadjuvant systemic chemotherapy using irinotecan, 5-fluorouracil, and leucovorin in patients with locally advanced rectal cancer. Eur J Surg Oncol 2010;36:1061-1065.
36. Uehara K, Hiramatsu K, Maeda A, et al. Neoadjuvant oxaliplatin and capecitabine and bevacizumab without radiotherapy for poor-risk rectal cancer: N-SOG 03 Phase II trial. Jpn J Clin Oncol 2013;43:964-971.
37. Hasegawa J, Nishimura J, Mizushima T, et al. Neoadjuvant capecitabine and oxaliplatin (XELOX) combined with bevacizumab for high-risk localized rectal cancer. Cancer Chemother Pharmacol 2014;73:1079-1087.
38. Cercek A, Weiser MR, Goodman KA, et al. Complete pathologic response in the primary of rectal or colon cancer treated with FOLFOX without radiation. J Clin Oncol 2010;28:abstr 3649.
39. Schrag D, Weiser MR, Goodman KA, et al. Neoadjuvant chemotherapy without routine use of radiation therapy for patients with locally advanced rectal cancer: a pilot trial. J Clin Oncol 2014;32:513-518.
40. Tournigand C, André T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 2004;22:229-237.
41. Chau I, Brown G, Cunningham D, et al. Neoadjuvant capecitabine and oxaliplatin followed by synchronous chemoradiation and total mesorectal excision in magnetic resonance imaging-defined poor-risk rectal cancer. J Clin Oncol 2006;24:668-674.
42. Fernández-Martos C, Pericay C, Aparicio J, et al. Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo cancer de recto 3 study. J Clin Oncol 2010;28:859-865.
43. Fernandez-Martos C, Pericay C, Aparicio J, et al. Chemoradiation (CRT) followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant CRT and surgery for locally advanced rectal cancer: Results of the Spanish GCR-3 randomized phase II trial after a median follow-up of 5 years. J Clin Oncol 2014;32:abstr 383.
44. Perez K, Pricolo V, Vrees M, et al. A phase II study of complete neoadjuvant therapy in rectal cancer (CONTRE): The Brown University Oncology Group. J Clin Oncol 2013;31:abstr 335.
45. Schou JV, Larsen FO, Rasch L, et al. Induction chemotherapy with capecitabine and oxaliplatin followed by chemoradiotherapy before total mesorectal excision in patients with locally advanced rectal cancer. Ann Oncol 2012;23:2627-2633.
46. Maréchal R, Vos B, Polus M, et al. Short course chemotherapy followed by concomitant chemoradiotherapy and surgery in locally advanced rectal cancer: a randomized multicentric phase II study. Ann Oncol 2012;23:1525-1530.
47. Koeberle D, Burkhard R, von Moos R, et al. Phase II

study of capecitabine and oxaliplatin given prior to and concurrently with preoperative pelvic radiotherapy in patients with locally advanced rectal cancer. Br J Cancer 2008;98:1204-1209.
48. Dewdney A, Cunningham D, Tabernero J, et al. Multicenter randomized phase II clinical trial comparing neoadjuvant oxaliplatin, capecitabine, and preoperative radiotherapy with or without cetuximab followed by total mesorectal excision in patients with high-risk rectal cancer (EXPERT-C). J Clin Oncol 2012;30:1620-1627.
49. Sclafani F, Gonzalez D, Cunningham D, et al. RAS mutations in EXPERT-C, a randomized phase II trial of neoadjuvant capecitabine and oxaliplatin (CAPOX) and chemoradiotherapy (CRT) with or without cetuximab (C) in MRI-defined, high-risk rectal cancer (RC). J Clin Oncol 2014;32: abstr 489.
50. Nogué M, Salud A, Vicente P, et al. Addition of bevacizumab to XELOX induction therapy plus concomitant capecitabine-based chemoradiotherapy in magnetic resonance imaging-defined poor-prognosis locally advanced rectal cancer: the AVACROSS study. Oncologist 2011;16:614-620.
51. Garcia-Aguilar J, Smith DD, Avila K, et al. Optimal timing of surgery after chemoradiation for advanced rectal cancer: preliminary results of a multicenter, nonrandomized phase II prospective trial. Ann Surg 2011;254:97-102.
52. Lee KH, Song MS, Park JB, et al. A Phase II Study of Additional Four-Week Chemotherapy With Capecitabine During the Resting Periods After Six-Week Neoadjuvant Chemoradiotherapy in Patients With Locally Advanced Rectal Cancer. Ann Coloproctol 2013;29:192-197.
53. Zhu J, Gu W, Lian P, et al. A phase II trial of neoadjuvant IMRT-based chemoradiotherapy followed by one cycle of capecitabine for stage II/III rectal adenocarcinoma. Radiat Oncol 2013;8:130.
54. Zampino MG, Magni E, Leonardi MC, et al. Capecitabine initially concomitant to radiotherapy then perioperatively administered in locally advanced rectal cancer. Int J Radiat Oncol Biol Phys 2009;75:421-427.
55. Gao YH, Zhang X, An X, et al. Oxaliplatin and capecitabine concomitant with neoadjuvant radiotherapy and extended to the resting period in high risk locally advanced rectal cancer. Strahlenther Onkol 2014;190:158-164.
56. van Dijk TH, Tamas K, Beukema JC, et al. Evaluation of short-course radiotherapy followed by neoadjuvant bevacizumab, capecitabine, and oxaliplatin and subsequent radical surgical treatment in primary stage IV rectal cancer. Ann Oncol 2013;24:1762-1769.
57. J. Garcia-Aguilar, J. Marcet, T. Coutsoftides, et al. Impact of neoadjuvant chemotherapy following chemoradiation on tumor response, adverse events, and surgical complications in patients with advanced rectal cancer treated with TME. J Clin Oncol 2011;29:abstr 3514.
58. Bujko K, Nasierowska-Guttmejer A, Wyrwicz L, et al. Neoadjuvant treatment for unresectable rectal cancer: an interim analysis of a multicentre randomized study. Radiother Oncol 2013;107:171-177.

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Novel radiation techniques for rectal cancer

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Abstract: The concepts for management of rectal cancer have changed drastically over the past few years. Through national bowel cancer screening programmes in the Western countries and the increasing use of endoscopic procedures as diagnostic tool, there has been an increase in detection of rectal cancer in early stages. There is increase in the ageing population worldwide but more so in Western countries. In addition, there is recognition of harm from extirpative surgical procedures which were directed towards managing advanced rectal cancer in the past. The increasing cost of health care has also led investigators to seek alternative treatment options which are effective, safe and economical. There are several modern radiation techniques which fit this bill and we need to be aware of newer radiation techniques to fill this gap.

Keywords: Early rectal cancer; X-ray contact; complete clinical response brachytherapy

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Background

The concept for management of rectal cancer has changed significantly in the past decade. There are several reasons for this. Many western countries have set up national bowel cancer screening programs which have targeted earlier stage rectal tumors compared with the more advanced staged cancers which were only diagnosed when they become symptomatic. Therefore, the surgical techniques that were aimed at treating advanced rectal tumours should not apply to the earlier stage disease. There is also recognition of surgical mortality and morbidity, especially in the elderly cohort (1). Many rectal cancer trials now include a wait and watch approach for those who achieved a complete clinical response. This allows organ preservation which has less detrimental effect on bowel function. Moreover, several clinical trials have shown improved disease free survival for those who achieved a complete response (2). In addition, there is evidence from the population-based statistics of an increase in rectal cancer in the ageing population worldwide with the average age of patients with rectal cancer predicted to rise from 65 to above 75 years within the next decade. The recent economic down turn across the world also has highlighted the financial burden of cancer care on the health care providers and many are seeking alternative strategies to keep the cost down without compromising outcomes. Radiotherapy is cheap compared to other treatment modalities. Novel radiation techniques have been developed which are attractive as alternatives to currently available radiotherapy options especially in treatment of early rectal cancer in the elderly.

Dose escalation to improve outcomes

There is evidence for dose response in rectal tumours and radiotherapy dose escalation could improve local control and other outcomes. However, there is a limit to how much radiation dose can be safely delivered using external beam alone without causing undue toxicity to the normal surrounding tissues. The dose escalation trial from Princess Margaret Hospital has shown that although higher rates of pathological responses can be achieved, the toxicity also increases, which negates the therapeutic ratio (3). The addition of chemotherapy does improve pathological complete response (pCR) rates (*Table 1*) and chemo radiotherapy has now become the standard of care in rectal cancer management (4). Traditionally, 5FU based regimes were used but oral capecitabine, which is much more convenient to use, has

Table 1 Comparative complete pathological response following chemo radiotherapy

	n	Dose (Gy)	pCR (%)
ACCORD	598	44-50	11-25
STAR	720	46	16
NSABP-4	1,608	50	20
CAO-4	1,265	50	13-17
PETTAC-6	1,094	44	11-13

pCR, pathological complete response.

replaced this and has become the standard of care. The addition of oxaliplatin to capecitabine has not kept up with earlier expectations. Both the French ACCORD (5) and the Italian STAR (6) trials have not shown benefit from the addition of oxaliplatin to either capecitabine or 5FU. However, the addition of irinotecan has shown some benefits and there are ongoing trials evaluating the role of irinotecan combined with capecitabine as in the UK lead ARISTOTLE trial.

Brachytherapy in rectal cancer

Over the years investigators have evaluated the role of brachytherapy to assess whether deliver of higher dose of radiation using brachytherapy as a boost improve outcomes. There are three types of brachytherapy:

(I) Contact X-ray brachytherapy (Papillon);
(II) High dose rate (HDR) intra luminal rectal brachytherapy;
(III) Interstitial rectal brachytherapy implant.

Contact X-ray brachytherapy (Papillon)

Low energy (50 KV) X-rays are used to deliver contact X-ray brachytherapy. It has been in clinical use for the past 80 years. However, very few centres around the world have continued to use this technique. There are several reasons for this. Firstly, the numbers of cases suitable for this type of treatment are small. There is development of newer competing surgical techniques e.g., Trans anal Endoscopic Micro Surgery (TEMS), Trans anal Endoscopic Operation (TEO) and Trans Anal Minimally Invasive Surgery (TAMIS) which are currently being used more for patients with early small rectal cancers. Only very few patients who are not fit for general anesthesia are referred for brachytherapy. Secondly, there were no replacement machines for the obsolete Philips 50 KV machines, which have been out of production since the mid 70's. Recently, there has been a revival of interest in contact X-rays brachytherapy and there are at least two companies Ariane (Derby, UK) and Xsoft (Axxend, CA) which have manufactured modern machines to produce 50 KV X-rays for use in contact X-ray brachytherapy.

The principle of contact X-ray brachytherapy consists of delivering high dose (30 Gy) of low energy (50 KV) X-rays applied straight on to the tumour under direct vision. This minimizes the chance of geographic miss. The dose falls off rapidly. The 100% dose is prescribed at the surface and the dose falls to 60% at 5 mm depth. Tumour size <3 cm can be offered X-ray contact radiotherapy initially. The treatment is given every 2 weeks which allows recovery of normal tissues in between treatments. As it is an orthovoltage radiation, the biological equivalent dose (EQD) is high at 1.4-1.6. Therefore, the total radiation dose delivered is above 40 Gy given in just over a minute instead of the usual protracted small doses of radiation given over 4-5 weeks. The applicator size use depends on the size of the tumour ranging from 30-22 mm. The patient is usually treated in knee chest position traditionally but can be treated in lithotomy position depending on the location of the tumour. The treatment can be delivered as an out-patient without the need for general anesthesia.

Assessment after two treatments is crucial to differentiate the good responders from the poor responders. If the response is favorable, further X-ray contact brachytherapy is offered to a total of four treatments (*Figure 1*). The radiation dose is usually 90-110 Gy in three to four fractions given every 2 weeks. For tumors which are initially staged as T2 or early T3, the risk of lymph node spread is high (20-30%). External beam chemo radiotherapy 45 Gy or its radiobiological equivalent should be offered to sterilize the lymph nodes. For bulky tumors >3 cm the treatment starts with external beam chemo radiotherapy. The response is assessed within 2-3 weeks after the completion of treatment. For good responders (tumour regresses >80%), this can be followed by X-ray contact radiotherapy to improve local control and increase the chance of a complete clinical response (7). This assumption will be evaluated in a clinicaltrial (OPERA) in which patients will be randomised to standard chemoradiotherapy against standard CRT and contact X-ray radiotherapy boost. This trial is planned to start early next year. If the response is poor (<80% regression) then patients are advised to accept immediate salvage surgery, provided the patient is fit and agreeable for surgery that involves a stoma.

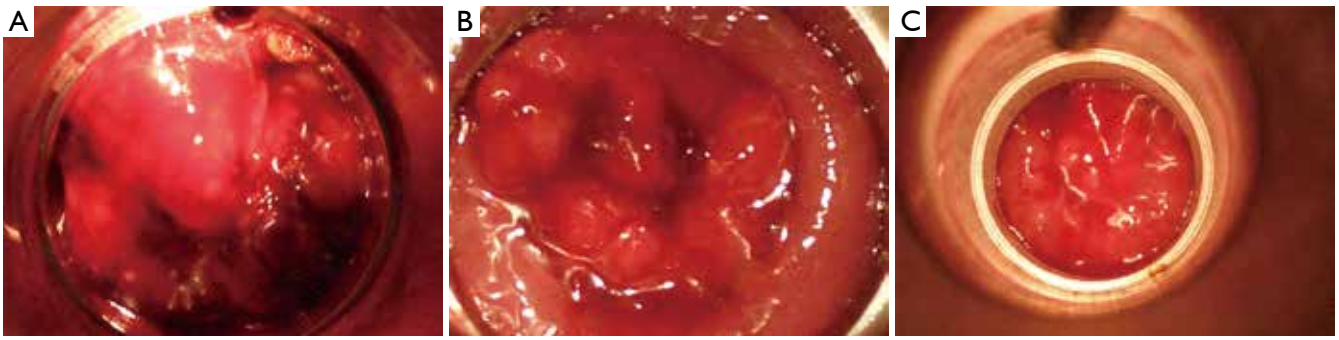

Figure 1 (A) Showing polypoidal tumour pre-treatment (day 1); (B) showing regression of tumour after one fraction (day 14); (C) showing complete regression of tumour after two fractions (day 28). Example of a good responder.

HDR rectal brachytherapy

HDR intra luminal rectal brachytherapy uses either Ir^{192} or Co^{60}. There are several commercially available remote after loaders. A number of different rectal applicators can be used depending on the system selected:

(I) Multiple channel rectal applicator (OncoSmart®, Elekta);
(II) Rectal/vagina rigid single line applicator Elekta/Eckert & Ziegler (Bebig);
(III) Rectal/vagina rigid single line applicator with variable central shielding Elekta/Eckert & Ziegler (Bebig);
(IV) Single line flexible endo-bronchial source (Elekta).

Multi channel rectal brachytherapy applicator

This rectal applicator has the advantage of using the channels close to where the tumour is situated and thus spare the contra lateral rectal mucosa (*Figure 2*). A balloon can be used to push the normal rectal mucosa away from the treatment source. Central shielding to minimize the dose to contra later rectal mucosa has also been investigated. It is suitable for any height of rectal tumour either low, mid or upper. It is a flexible applicator and more comfortable for the patient. It can be applied without general anesthesia (8) (*Figure 3*).

Rectal/vaginal rigid single line brachytherapy applicator

This type of applicator is suitable for low rectal tumors which occupy more than 50% of the rectal wall. It is not suitable for mid to high rectal tumors. There are different diameter applicators and stenosing tumors may need a defunctioning stoma before brachytherapy. This applicator is much easier to use.

Rectal/vagina rigid single line applicator with variable central shielding

This type of rectal applicator is suitable for smaller low rectal tumors which occupy less than half the circumference. Central shielding can be used to protect the contra lateral uninvolved rectal mucosa (9).

Rectal brachytherapy procedure

Endoscopy is carried out initially to assess the position and length of the rectal tumour. Marker seeds are inserted at the lower end of the tumour to locate it on the radiographs. The rectal brachytherapy applicator is inserted via the anus into the rectum either under general or local anesthesia. The position of the rectal applicator is checked on the fluoroscopy and adjusted as necessary. Once the position is satisfactory it is secured in place by clamps or strings tight to the corset. The patient treatment position is shown in *Figure 3*. The patient is then scanned on the CT simulator. The tumour position is outlined based on the information from the digital examination (lower rectal tumour), endoscopy and MRI. The dose is prescribed to cover the PTV (CTV + margin). The dose given depends on whether brachytherapy is given as monotherapy or as a boost after external beam chemo radiotherapy (10). Although the dose for monotherapy (26 Gy given over 4 daily treatments) is now fairly standard based on extensive experience from McGill University (8) much work is still needed to be done to determine dose for the brachytherapy boost.

Interstitial rectal implant using rectal template

For rectal tumors which extend into the anal canal, none of the above brachytherapy techniques are suitable. However, an interstitial implant using a rectal/anal jig can

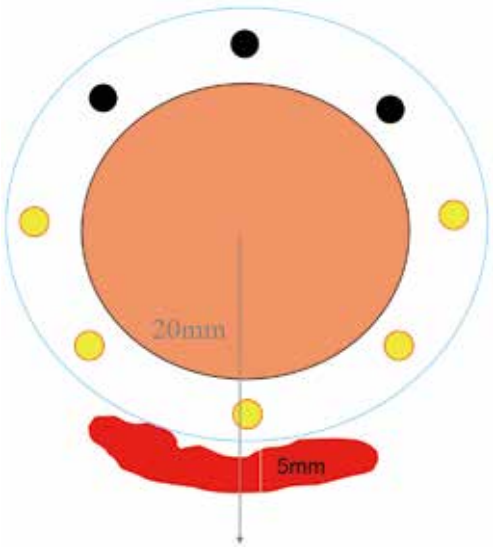

Figure 2 Showing multiple channels in flexible rectal applicator. Treatment is loaded towards residual tumour thus sparing the contra lateral uninvolved rectal mucosa.

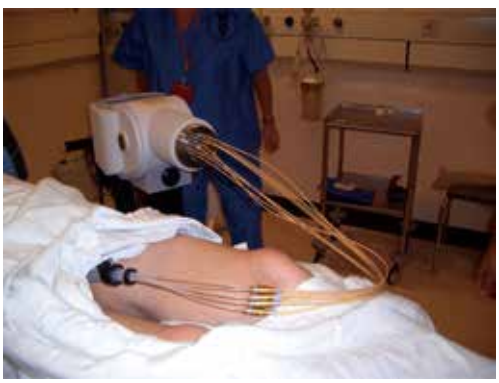

Figure 3 Showing treatment position for high dose rate (HDR) rectal brachytherapy.

be performed if there is residual tumour following external beam chemo radiotherapy. Most centres use a template with needles which are implanted through the perineum and into the tissues outside the wall of rectum. The iridium wires which were formerly used have now been replaced by fractionated HDR brachytherapy. The dose given varies but the usual schedule is 5-7 Gy in 3 fractions over 24 hours.

Selection of type of brachytherapy

Whether we should use contact X-ray brachytherapy or HDR isotope brachytherapy is determine by the morphology and the stage of rectal cancer. Exophytic usually sessile rectal cancers confined to the bowel wall are best treated by X-ray brachytherapy as the maximum dose of radiation is applied on to the surface of the rectal wall.

There is very little penetration and it is not useful for a tumor that penetrates much beyond the rectal wall. Therefore, tumors that infiltrate beyond the rectal wall are not suitable for contact X-ray brachytherapy. The exophytic component that protrudes from the rectal wall into the lumen gets a much higher dose due to the inverse square law. The tumour is shaved off layer by layer with each application of the contact X-ray brachytherapy until it regressed down to the surface of the rectal mucosa. The shrinkage is centripetal and the tumor regresses back to the site of origin in the case of a small rectal tumor. At the end of treatment, there may be a small superficial ulcer with smooth edge or a supple mucosa with no indurations beneath its base. This usually heals within 3-6 months if there is no residual tumour. However, those with residual tumour (if viable) can grow back within this period. Contact X-ray brachytherapy is therefore only suitable for T1/early T2 tumors that have not penetrated much into the muscularis propria. However, it is often very difficult to differentiate between T1 and early T2 tumors with the currently available radiological techniques.

HDR isotope brachytherapy is used when the tumour penetrates beyond the rectal wall (T3). This penetration can be readily seen on the MRI and EUS. It can be used as monotherapy or as a boost after external beam chemo radiotherapy when the residual tumour extends beyond the rectal wall. The radiation dose required to sterilize and kill off the residual tumour after external beam chemo radiotherapy is still under investigation and is not yet fully established. The dose currently in use is either 5-10 Gy in single fraction or 7-10 Gy per fraction in 3 weekly fractions. The volume irradiated is slightly larger, resulting in greater mucosal toxicity compare to contact X-ray brachytherapy.

Side effects

There is no reported mortality associated with rectal brachytherapy. No perforation or uncontrolled bleeding has been reported immediately following brachytherapy in experienced hands. The late toxicity is mainly bleeding which occurs in 26% of cases but usually resolves after 6-12 months. However, bleeding can be troublesome in 5% of patients

who are on anti-platelet medications e.g., warfarin or clopidrogel. Argon plasma coagulation is necessary in about 5% of patients if bleeding is troublesome (11). Endoluminal stricturing occurs in about 1%, usually in cases following surgical resection. Stricturing can also occur if there is residual tumour growing extra luminally. MRI can be difficult to interpret when attempting to differentiate the two processes. Surgical intervention may be necessary to establish the underlying pathology.

Discussion

The standard of care is surgery even for early rectal cancers, resulting in a permanent stoma for about a third of patients. The population is ageing and it is predicted that the majority of patients with rectal cancer will be above 75 years in the next decade. The mortality and morbidity is high for elderly patients and it is best to reserve surgery for those with advanced disease. Increased use of endoscopy to investigate bowel symptoms and screening programmes for asymptomatic patients have led to an increase in the diagnosis of early stage rectal cancer. These should be treated differently from advanced stage disease. There are now a number of alternative treatment options available to manage early rectal cancer.

Many novel radiation techniques in brachytherapy are now available and these may be more suitable for patients with early stage disease. All cases should be discussed in a multidisciplinary team meeting following diagnosis so that the optimal plan of management can be offered to the patients for best possible outcome. Difficult cases should be referred to centres of excellence and experience so that optimal treatments including brachytherapy can be offered as appropriate without compromising their chance of cure. Many centres have HDR brachytherapy facility for gynecological malignancies and these centres should look into setting up a rectal brachytherapy facility. Those centres with surgical expertise offering TEMS, TEO or TAMIS should consider introducing contact X-ray brachytherapy to compliment their services as not all patients referred will be fit for general anesthesia. Team work is important for successful outcomes and centres with expert multidisciplinary teams should consider expanding their services to include rectal brachytherapy facilities with both contact X-ray and HDR brachytherapy to improve the range of options they could offer for properly selected patients in the management of their rectal cancer.

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Footnote

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

References

1. Rutten H, den Dulk M, Lemmens V, et al. Survival of elderly rectal cancer patients not improved: analysis of population based data on the impact of TME surgery. Eur J Cancer 2007;43:2295-2300.
2. Patel UB, Taylor F, Blomqvist L, et al. Magnetic resonance imaging-detected tumor response for locally advanced rectal cancer predicts survival outcomes: MERCURY experience. J Clin Oncol 2011;29:3753-3760.
3. Wiltshire K, Brierley J, Cummings B, et al. Preoperative radiation with concurrent chemotherapy for resectable rectal cancer: effect of dose escalation on pathological complete response, local recurrence free survival and disease free survival. Int J Radiat Oncol Biol Phys 2004; 60. ASTRO proc 46: abstract 1061.
4. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006;355:1114-1123.
5. Gerard J, Azria D, Gourgou-Bourgade S, et al. Randomized multicenter phase III trial comparing two neoadjuvant chemoradiotherapy (CT-RT) regimens (RT45-Cap versus RT50-Capox) in patients (pts) with locally advanced rectal cancer (LARC): Results of the ACCORD 12/0405 PRODIGE 2. J Clin Oncol 2009;27:abstr LBA4007.
6. Aschele C, Pinto C, Cordio S, et al. Preoperative fluorouracil (FU)-based chemoradiation with and without weekly oxaliplatin in locally advanced rectal cancer: Pathologic response analysis of the Studio Terapia Adiuvante Retto (STAR)-01 randomized phase III trial. J Clin Oncol 2009;27:abstr CRA4008.
7. Sun Myint A, Grieve RJ, McDonald AC, et al. Combined modality treatment of early rectal cancer: the UK experience. Clin Oncol (R Coll Radiol) 2007;19:674-681.
8. Vuong T, Devic S, Podgorsak E. High dose rate endorectal brachytherapy as a neoadjuvant treatment for patients

with resectable rectal cancer. Clin Oncol (R Coll Radiol) 2007;19:701-705.
9. Jakobsen A, Mortensen JP, Bisgaard C, et al. Preoperative chemoradiation of locally advanced T3 rectal cancer combined with an endorectal boost. Int J Radiat Oncol Biol Phys 2006;64:461-465.
10. Sun Myint A, Lee CD, Snee AJ, et al. High dose rate brachytherapy as a boost after preoperative chemoradiotherapy for more advanced rectal tumours: the Clatterbridge experience. Clin Oncol (R Coll Radiol) 2007;19:711-719.
11. Sun Myint A, Whitmarsh K, Perkins K, et al. A preliminary report on toxicity of contact radiotherapy in first 100 patients treated by the new RT50 Papillon machine. Colorectal Disease 2013;15:Abst. P081.

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Radiomics for rectal cancer

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Abstract: Diagnosis and treatment of locally advanced rectal cancer is mainly based on multimodal approach for staging, planning and treatment. The modern radiological and imaging techniques offer, day after day, the possibility to characterize tumor lesions in a more precise and prognostically valuable way. In rectal cancer, extending often the characterization to colon cancer, literature offers some evidences that quantitative and "radiomics" analysis of tumor images might improve the prognostic evaluation of the tumor and the patients' characterization. Unfortunately, as in other fields of radiomics, the rise of new evidence and models based on single institution case series don't offer the practical chance to apply them universal data set. Greater efforts in the direction of model evaluation and validation, above all using an external validation approach, are expected to be shown in the coming years for validation of methodology.

Keywords: Rectal cancer; colorectal cancer; radiomics; image analysis; MR; CT; PET; numerical analysis

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Introduction

Rectal cancer malignancies represent one of the most challenging aspects in modern oncology, because of the complex intersection among different specialties needed to treat this kind of cancer. The treatment workflow involves mainly surgeons (at diagnosis and surgical treatment time), radiation oncologists (for neoadjuvant treatment management) and clinical medical oncologists (for managing chemotherapy administration during radiation treatment delivery and/or distant metastases therapy). In each treatment step, the involvement of diagnostic findings and imaging contribution for characterization of malignant tumors represent key factors to direct patients to the optimal treatment pathway. At this moment, only "qualitative" imaging features and simple findings related to tumor infiltration characteristics, as anatomic involvement of pelvic structures (for pelvis limited tumors), are being used as validated standards. Novel aspects of imaging, such as the "quantitative" imaging and the radiomics approach, are being included in the tumor characterization to better direct patients to a more appropriate and tailored clinical pathway. Currently there is a lack of shared solutions to be considered as "standard" for the characterization of radiomics for rectal cancer. One of the most exciting aspects of tumor characterization is the definition of "biomarkers" able to correlate with defined outcome [e.g., survival or tumor regression grade (TRG) (1) after neoadjuvant treatment]. The ability to biologically characterize the tumor is improving due the discovery of different genetic pathways involved in tumor progression and coupling with possible contributions offered by modern imaging

techniques. "Radiomics" represents the high-throughput extraction of large amounts of image features from radiographic images and is one of the approaches that hold great promises but need further validation in multi-centric settings and in the laboratory (2) for a wide shared application. Image heterogeneity is now considered a potential biomarker regarding multiple clinical settings and a recent review has been conducted to investigate the use and performance of different heterogeneity imaging biomarkers extracted from diagnostic tumor images (3). One of the most important issues in radiomics analysis is the availability of wide series of features to be correlated to a given number of observed cases. This situation can raise the need to adopt "alternative" model fitting procedures that primarily have to solve the features selection process in order to finalize the modeling process. Interesting tools adopted in this scenario can be for example the "elastic net" (4) or unsupervised clustering (5). This interesting perspective is being applied also to rectal cancer, starting from the need to characterize the features of primary lesions and is being moved to nodal and metastases classification and definition.

Definition of primary tumor and treatment monitoring

The study of primary rectal cancer in radiomics literature has often been dealt analyzing at the same time rectal *and* colon cancer patients. These two kinds of malignancies are completely different, because of the different treatment pathways that usually involve these patients: rectal cancer is often treated by using chemo-radiotherapy, more often in neoadjuvant setting, and subsequently by surgery that is performed trying to remove the residual tumor (if any), and trying to spare (if possible) the anal sphincter complex to avoid the abdominal-perineal amputation (6). On the other hand the treatment of colon cancer is mostly performed by surgery (as primary treatment) and subsequently (if required) adjuvant chemotherapy (7). For this reason the oncologist's and radiation oncologist's perspectives in tumor characterization about rectal and colon cancer can differ significantly. This scenario, containing some "blurred" aspects and overlaps between these two kinds of tumor has to be clearly taken into account in almost all papers that will be shown in this review. Starting from the definition of the primary tumor the literature already offers some interesting proofs that radiomics can be helpful in describing the pathological characterization of the lesions: Song and collaborators (8) created an interesting modeling procedure using a machine learning approach in order to distinguish among benign and malignant lesions in CT colonography exams. The performance of their model is fair with an AUC of the ROC (9,10) of 0.8525, but we have to consider, as a limitation in this paper, the lack of an external validation of the model [hopefully needed in all modeling works (11)] and subsequently the potential enhancement of overfitting issues typical of machine learning techniques as support vector machine (12) used in this paper. Regarding the primary tumor characterization, it is very interesting to observe the contribution of textural analysis as implemented by Ng *et al.* (13) and its correlation with the overall survival outcome. In this paper the authors studied the contribution of CT scan with contrast medium in order to characterize the tumor. They used different levels of filtration of the raw images, implementing the Laplacian of Gaussian (LoG) filter in order to smooth the high frequency noise and enhance the variation of values among adjacent pixels in the images. LoG filter can return images with different appearance according the value of σ parameter that is used in LoG filter Eq. [1]:

$$LoG(x,y) = -\frac{1}{\pi\sigma^4}\left[1-\frac{x^2+y^2}{2\sigma^2}\right]e^{-\frac{x^2+y^2}{2\sigma^2}} \quad [1]$$

This formula returns the values of a *convolution kernel* that is a matrix with values that have to be convolved above the initial pixels values of an image. The returned values of a convolution kernel matrix are similar to the *Table 1*, where x and y represent the coordinates respect to the target pixel (the center grey colored one) and σ=1.

The shape of the LoG filter convolution matrix is similar to a "reversed Mexican hat" as shown in *Figure 1*.

An example of the result of application of LoG filter on a rectal cancer CT scan is given in *Figure 2*. The upper line shows the initial CT scan over five different levels of the tumor. The second line shows the delineated gross tumor volume (GTV), the following lines show the appearance of processed images using LoG filter at different values of σ (0.5, 1.0, 1.5 and 2.0 pixels). It is evident, with growing the σ value, the appearance of the texture shows larger variations as the σ value grows up. It is interesting to understand as the use of filtering process can be an important prerequisite to achieve significant result in radiomics analysis. In this paper, indeed, only LoG processed images returned significant correlations with observed outcome while raw images didn't: the features that showed significant prediction value for overall survival after Cox multivariate analysis

Table 1 Convolution kernel of a LoG filter with σ=1. The grey cell represents the target pixel (the center one). The coordinates of surrounding pixels are provided respect to the target one

Pixel coordinate	*x*–3	*x*–2	*x*–1	*x*	*x*+1	*x*+2	*x*+3
y–3	0.000314	0.002632	0.008579	0.012376	0.008579	0.002632	0.000314
y–2	0.002632	0.01749	0.039193	0.043079	0.039193	0.01749	0.002632
y–1	0.008579	0.039193	0	–0.09653	0	0.039193	0.008579
y	0.012376	0.043079	–0.09653	–0.31831	–0.09653	0.043079	0.012376
y–1	0.008579	0.039193	0	–0.09653	0	0.039193	0.008579
y+2	0.002632	0.01749	0.039193	0.043079	0.039193	0.01749	0.002632
y+3	0.000314	0.002632	0.008579	0.012376	0.008579	0.002632	0.000314

LoG, Laplacian of Gaussian.

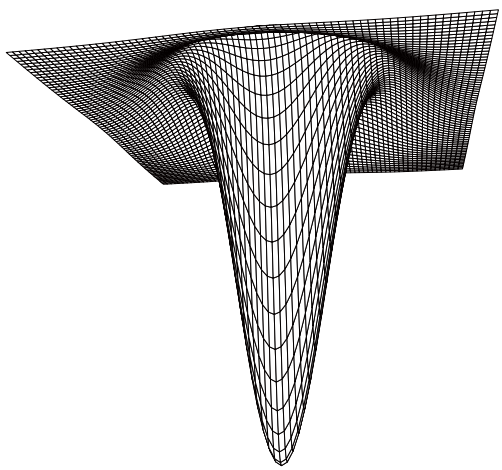

Figure 1 The shape of LoG filter convolution matrix as 3D plot. LoG, Laplacian of Gaussian.

were entropy, kurtosis, uniformity, skewness and standard deviation (SD) of pixel distribution histogram: among these features, entropy, kurtosis and skewness are mathematically invariant for pixels values when these are scaled linearly. This characteristic will show its value in the analysis of MR images, as it will be shown hereafter.

The application of MR for radiomics has always been considered affected by many issues due to the intrinsic difficulty in generalizing the analysis of signal in MR images because of the problem of normalization and regularization of MR images (14). On the other hand the characterization of primary tumor given by MR has been treated in literature starting from the early 1990's up to our days (15-19), so the application of radiomics could result in interesting outcome if applied. One of the most important outcomes considered in the treatment of rectal cancer is the pathological complete response (pCR). It has been proven that patients showing pCR usually show better survival outcome than others (1). MR has been already used for determining the probability of pCR by comparing pre-treatment staging MR and pre-surgery (after chemoradiotherapy) MR (20) but without using a proper "radiomics" approach. In a small cohort of patients, De Cecco *et al.* (21), using a 3T MR device, showed that texture parameters and their changes during treatment could predict histopathological tumour response (P values respectively 0.016 and 0.038). Heterogeneity (kurtosis, skewness, entropy and mean value of positive pixels, MPP) was assessed using histogram parameters extracted from T2 weighted MRI pre-treatment and mid-treatment studies, computed with and without LoG image filtration. In our experience (22) we used the textural analysis of pre-treatment T2 high resolution MR scans (performed with a 1.5T MR scanner) in order to predict the probability of PCR in a cohort of 173 patients. Analysis and models have been obtained by using in-house radiomics analysis software (23). The final model returned a good discrimination capability (AUC of ROC 0.73) and at the same time an optimal prediction accuracy (mean prediction absolute error =0.018). In this radiomics model the use of cited features (skewness, entropy) that are invariant for different scaling factor in the overall signal of MR has been proven to be able (coupled with clinical T stage) in predicting PCR. Maybe such kind of models will result in effective and reliable prediction for future tailoring of patients' treatments. Much work will be necessary to create MR radiomics models able to be applied on patients coming from environments different from the ones where the models have been created: this seems to be one of the most important challenges for future directions in radiomics applied on MR imaging. Regarding PET-CT, it is extensively used for staging and response monitoring in rectal

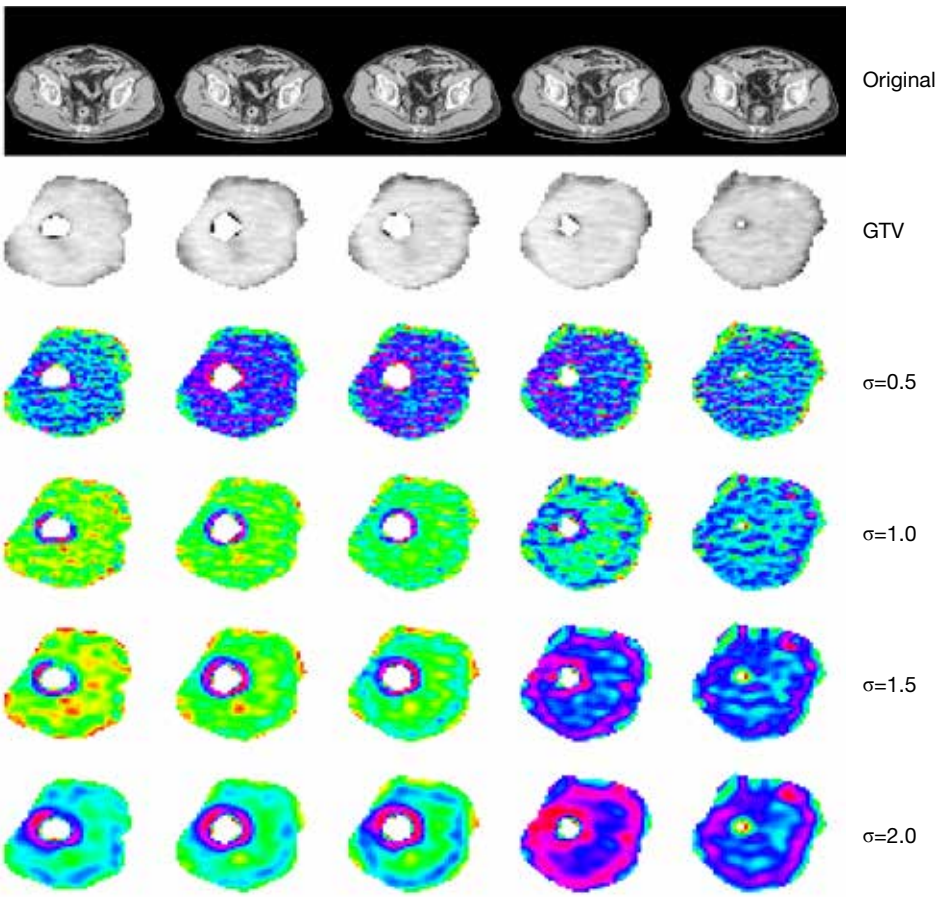

Figure 2 Application of LoG filter on a rectal cancer CT study: the upper line shows the original CT scan; the second line shows the delineated gross tumor volume (GTV); the four lines below show the effect of different values of σ applying a LoG filter over the original GTV delineated structure: it is evident the effect of higher coarseness due to higher value of σ that smoothes the high frequency noise and enhances the larger pixels values variations. LoG, Laplacian of Gaussian.

cancer (24-31). From the radiomics perspective PET-CT was also used in order to extract predictive features: Bundschuh *et al.* (32) evaluated the correlation between pathological response and textural features obtained from 18F-FDG PET/CT examinations. In 27 patients, conventional and textural parameters (coefficient of variation COV, calculated by dividing SD for the mean value of the activity, skewness and kurtosis), changes of the parameters during and after neoadjuvant chemoradiotherapy (nCRT—early response) before surgery (late response) were extracted from pre-therapeutic co-registered PET/CT images: the COV showed a statistically significant predictive capability regarding pre-therapeutic response (AUC =0.73) and in the assessment of early response (AUC =0.89). In late response COV, skewness, and kurtosis showed statistically significant predictive capabilities (with an AUC of respectively 0.89, 0.74 and 0.74). In 74 patients diagnosed with rectal cancer Bang *et al.* (33) calculated metabolic and textural features from pre-treatment 18F FDG PET/CT scans. Response to nCRT was assessed by TRG after surgery. Textural parameters from histogram-based and co-occurrence analysis were significantly correlated with TRG, however with no significance after multivariate analysis.

Definition of primary lymph nodes and distant metastases

Quantitative analysis has been reported improving the prediction of nodal status in rectal cancer: Cui *et al.* (34) evaluated contrast enhanced CT scans in 228 patients with newly diagnosed rectal cancer, and showed that fractal dimension obtained by the Minkowski box-counting approach

was higher in malignant nodes than in benign nodes, and there was a significant difference in heterogeneity between metastatic and not-metastatic lymph nodes (model accuracy =88%). For distant metastases special attention was placed over liver metastases: several studies showed that texture analysis of an apparently metastases free-area of the liver in patients with colorectal cancer correlates with hepatic hemodynamic and metabolism, indirectly revealing metastatic status also in the absence of any visible morphological changes. Hepatic metastases are known to be associated with changes in hepatic blood flow in adjacent apparently disease-free areas of the liver, determining both reduced portal perfusion and pro-angiogenic changes with increased arterial perfusion. Ganeshan *et al.* (35) demonstrated that textural parameters obtained during the portal phase of contrast enhanced CT (derived from perfusion dynamic study) correlate with patients hepatic perfusion index (HPI, ratio of arterial flow to total blood flow) and patients survival. The best correlation values where obtained by entropy values after image filtration, inversely correlated with HPI and directly correlated with survival; an entropy value lower than 2.0 provided a diagnostic threshold that identified patients who died within 36 months with 100% sensitivity and 65% specificity. This fact could be explained by the reduced portal flow in presence of micro-metastases, resulting in lower portal veins enhancement with consequent reduced entropy on filtered images as opposite to higher HPI. Moreover the same authors (36) showed that changes in hepatic entropy and uniformity measurements during the arterial phase of contrast enhanced CT scans (derived from perfusion dynamic study) are tumor-related. Indeed apparently disease-free areas of liver in patients with hepatic metastases from colorectal cancer demonstrated significantly increased uniformity and decreased entropy values during arterial phase compared with patients with no evidence of tumor. Greater uniformity, and the opposite reduced entropy, could relate to vascular dilatation (reduced number of vascular "spot" from small vessels) and/or increased enhancement of the hepatic parenchyma, also in the presence of tumors too small to be directly visualized. Also Rao *et al.* (37) found higher entropy and corresponding lower uniformity in the not-diseased part of the liver of patients with synchronous metastatic disease as compared to those without. The Authors explained the results with higher heterogeneity due to both the presence of micro-metastases and induced vascular changes. These conflicting results could derive from: (I) different imaging protocol used (phase derived from perfusion dynamic study *vs.* standard contrast enhanced protocol) with different contrast doses and injection rates, resulting in variable timing of portal venous phase; (II) assessment of mid-liver axial section (35) or whole volume of the liver (37); (III) differences in study group characteristics. Ganeshan *et al.* (35) included patients during surveillance after primary rectal resection, while Rao *et al.* (37) included patients at the time of primary staging (before any treatment). Presence *vs.* absence of the primary tumor or chemotherapy could result in variable hepatic hemodynamic: it's important however to underline that textural parameters derived from dynamic contrast-enhanced CT could offer additional parameter apart that of perfusion (38). An interesting result is that texture analysis in non-contrast enhanced CT is also useful in revealing changes in apparently disease-free areas of metastatic liver, as demonstrated by different value in patients with hepatic metastases compared to patients with no tumor (entropy) and patients with extra-hepatic disease (uniformity) (39). The use of non-contrast enhanced images could avoid variability related to technical or patient factors affecting contrast enhancement. Moreover it could allow the evaluation in patients with contra-indication to contrast medium administration. Ganeshan *et al.* (40) also supposed a relation between textural parameter of portal contrast enhanced CT with glucose metabolism, and consequent liver fat content. Colorectal cancer patients have documented insulin resistance independent of patient weight that is reversed by removal of the tumor. On the other hand it is well recognized that tumors exhibit increased glucose metabolism, even microscopically. Lubner *et al.* (41) showed that in patients with untreated liver metastases from colon-rectal cancer entropy, mean positive pixels (MPP) and SD of pixel distribution histogram were negatively associated with tumor grade, moreover skewness was negatively associated with KRAS mutation. This is another biological correlate, suggesting that tumors that are more homogeneous (less entropy, smaller SD, higher in attenuation/higher mean of positive pixels) are potentially more aggressive in their biology.

Conclusions

The use of radiomics for analysis and characterization of tumors is a "trend topic" that is being increasingly explored in modern oncological and radiological sciences. The literature gives a wide and fragmented series of publications dealing mainly with the need to assess what are the technical pathways to be defined and used for creating

a reliable "radiomics workflow". An important issue about these workflows is the need to assess the external validation, applicability and re-usability of a given radiomics model. If many efforts have been already done in terms of basic research and exploratory findings, now the time for seeking shared confirmations that can establish the "rules" in the radiomics field. This step is not trivial at all: the intrinsic value of clinical prediction model is mainly based on the possibility to apply externally the model itself, as recently established in the TRIPOD publication (11). In the radiomics of rectal cancer, we do not have any model published with a reliable external validation process yet. Hopefully in the coming years we will see new publications able to create a more reproducible workflow that will offer the chance to apply worldwide the potential of radiomics findings in the classification and categorization of cancer patients. Another key point will be the possibility of using MR data for radiomics research. Great efforts have to be made to create valid external validation processes. The role of MR certainly will increase, since this imaging modality already proven its validity in the characterization of tumor in more traditional fashion, as stated before. The first findings in MR radiomics topic seem promising so our expectation is that MRI will provide the first reliable results in this field, being sure that they will exploit the potential of radiomics in rectal cancer better than traditional CT scan made in the recent past.

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Footnote

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References

1. Vecchio FM, Valentini V, Minsky BD, et al. The relationship of pathologic tumor regression grade (TRG) and outcomes after preoperative therapy in rectal cancer. Int J Radiat Oncol Biol Phys 2005;62:752-760.
2. Lambin P, Rios-Velazquez E, Leijenaar R, et al. Radiomics: extracting more information from medical images using advanced feature analysis. Eur J Cancer 2012;48:441-446.
3. Alic L, Niessen WJ, Veenland JF. Quantification of heterogeneity as a biomarker in tumor imaging: a systematic review. PLoS One 2014;9:e110300.
4. Zou H, Hastie T. Regularization and variable selection via the elastic net. J R Statist Soc B 2005;67:301-320.
5. Aerts HJ, Velazquez ER, Leijenaar RT, et al. Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach. Nat Commun 2014;5:4006.
6. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol 2012;30:1926-1933.
7. André T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol 2009;27:3109-3116.
8. Song B, Zhang G, Lu H, et al. Volumetric texture features from higher-order images for diagnosis of colon lesions via CT colonography. Int J Comput Assist Radiol Surg 2014;9:1021-1031.
9. Bradley AP. The use of the area under the ROC curve in the evaluation of machine learning algorithms. Pattern Recognit 1997;30:1145-1159.
10. Fawcett T. An introduction to ROC analysis. Pattern Recognit Lett 2006;27:861-874.
11. Moons KG, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med 2015;162:W1-73.
12. Cawley GC, Talbot NL. On over-fitting in model selection and subsequent selection bias in performance evaluation. J Mach Learn Res 2010;11:2079-2107.
13. Ng F, Ganeshan B, Kozarski R, et al. Assessment of primary colorectal cancer heterogeneity by using whole-tumor texture analysis: contrast-enhanced CT texture as a biomarker of 5-year survival. Radiology 2013;266:177-184.
14. Collewet G, Strzelecki M, Mariette F. Influence of MRI acquisition protocols and image intensity normalization methods on texture classification. Magn Reson Imaging 2004;22:81-91.
15. Allen SD, Padhani AR, Dzik-Jurasz AS, et al. Rectal carcinoma: MRI with histologic correlation before and after chemoradiation therapy. AJR Am J Roentgenol 2007;188:442-451.
16. Brown G, Richards CJ, Newcombe RG, et al. Rectal carcinoma: thin-section MR imaging for staging in 28 patients. Radiology 1999;211:215-222.
17. Vliegen RF, Beets GL, Lammering G, et al. Mesorectal

fascia invasion after neoadjuvant chemotherapy and radiation therapy for locally advanced rectal cancer: accuracy of MR imaging for prediction. Radiology 2008;246:454-462.
18. Kuo LJ, Chern MC, Tsou MH, et al. Interpretation of magnetic resonance imaging for locally advanced rectal carcinoma after preoperative chemoradiation therapy. Dis Colon Rectum 2005;48:23-28.
19. de Lange EE, Fechner RE, Edge SB, et al. Preoperative staging of rectal carcinoma with MR imaging: surgical and histopathologic correlation. Radiology 1990;176:623-628.
20. Barbaro B, Fiorucci C, Tebala C, et al. Locally advanced rectal cancer: MR imaging in prediction of response after preoperative chemotherapy and radiation therapy. Radiology 2009;250:730-739.
21. De Cecco CN, Ganeshan B, Ciolina M, et al. Texture analysis as imaging biomarker of tumoral response to neoadjuvant chemoradiotherapy in rectal cancer patients studied with 3-T magnetic resonance. Invest Radiol 2015;50:239-245.
22. Dinapoli N, Barbaro B, Gatta R, et al. MR radiomics predicting complete response in radiochemotherapy (RTCT) of rectal cancer (LARC). ESTRO 2016;35:E35-0909.
23. Dinapoli N, Alitto AR, Vallati M, et al. Moddicom: a complete and easily accessible library for prognostic evaluations relying on image features. Conf Proc IEEE Eng Med Biol Soc 2015;2015:771-4.
24. Capirci C, Rubello D, Pasini F, et al. The role of dual-time combined 18-fluorodeoxyglucose positron emission tomography and computed tomography in the staging and restaging workup of locally advanced rectal cancer, treated with preoperative chemoradiation therapy and radical surgery. Int J Radiat Oncol Biol Phys 2009;74:1461-1469.
25. Chennupati SK, Quon A, Kamaya A, et al. Positron emission tomography for predicting pathologic response after neoadjuvant chemoradiotherapy for locally advanced rectal cancer. Am J Clin Oncol 2012;35:334-339.
26. Maffione AM, Ferretti A, Grassetto G, et al. Fifteen different 18F-FDG PET/CT qualitative and quantitative parameters investigated as pathological response predictors of locally advanced rectal cancer treated by neoadjuvant chemoradiation therapy. Eur J Nucl Med Mol Imaging 2013;40:853-864.
27. Huh JW, Min JJ, Lee JH, et al. The predictive role of sequential FDG-PET/CT in response of locally advanced rectal cancer to neoadjuvant chemoradiation. Am J Clin Oncol 2012;35:340-344.
28. Capirci C, Rampin L, Erba PA, et al. Sequential FDG-PET/CT reliably predicts response of locally advanced rectal cancer to neo-adjuvant chemo-radiation therapy. Eur J Nucl Med Mol Imaging 2007;34:1583-1593.
29. Li C, Lan X, Yuan H, et al. 18F-FDG PET predicts pathological response to preoperative chemoradiotherapy in patients with primary rectal cancer: a meta-analysis. Ann Nucl Med 2014;28:436-446.
30. Maffione AM, Chondrogiannis S, Capirci C, et al. Early prediction of response by 18F-FDG PET/CT during preoperative therapy in locally advanced rectal cancer: a systematic review. Eur J Surg Oncol 2014;40:1186-1194.
31. Maffione AM, Marzola MC, Capirci C, et al. Value of (18) F-FDG PET for Predicting Response to Neoadjuvant Therapy in Rectal Cancer: Systematic Review and Meta-Analysis. AJR Am J Roentgenol 2015;204:1261-1268.
32. Bundschuh RA, Dinges J, Neumann L, et al. Textural Parameters of Tumor Heterogeneity in ¹⁸F-FDG PET/CT for Therapy Response Assessment and Prognosis in Patients with Locally Advanced Rectal Cancer. J Nucl Med 2014;55:891-897.
33. Bang JI, Ha S, Kang SB, et al. Imaging biomarker for predicting neoadjuvant radiation chemotherapy response and survival using pretreatment F-18 FDG PET/CT scan in locally advanced rectal cancer. J Nucl Med 2015;56:576.
34. Cui C, Cai H, Liu L, et al. Quantitative analysis and prediction of regional lymph node status in rectal cancer based on computed tomography imaging. Eur Radiol 2011;21:2318-2325.
35. Ganeshan B, Miles KA, Young RC, et al. Hepatic enhancement in colorectal cancer: texture analysis correlates with hepatic hemodynamics and patient survival. Acad Radiol 2007;14:1520-1530.
36. Ganeshan B, Miles KA, Young RC, et al. Hepatic entropy and uniformity: additional parameters that can potentially increase the effectiveness of contrast enhancement during abdominal CT. Clin Radiol 2007;62:761-768.
37. Rao SX, Lambregts DM, Schnerr RS, et al. Whole-liver CT texture analysis in colorectal cancer: Does the presence of liver metastases affect the texture of the remaining liver? United European Gastroenterol J 2014;2:530-538.
38. Ganeshan B, Burnand K, Young R, et al. Dynamic contrast-enhanced texture analysis of the liver: initial assessment in colorectal cancer. Invest Radiol 2011;46:160-168.
39. Ganeshan B, Miles KA, Young RC, et al. Texture analysis in non-contrast enhanced CT: impact of malignancy on texture in apparently disease-free areas of the liver. Eur J Radiol 2009;70:101-110.
40. Ganeshan B, Miles KA, Young RC, et al. In search of

biologic correlates for liver texture on portal-phase CT. Acad Radiol 2007;14:1058-1068.
41. Lubner MG, Stabo N, Lubner SJ, et al. CT textural analysis of hepatic metastatic colorectal cancer: pre-treatment tumor heterogeneity correlates with pathology and clinical outcomes. Abdom Imaging 2015;40:2331-2337.

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Results of intraoperative electron beam radiotherapy containing multimodality treatment for locally unresectable T4 rectal cancer: a pooled analysis of the Mayo Clinic Rochester and Catharina Hospital Eindhoven

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Background: The aim of this study is to analyse the pooled results of intraoperative electron beam radiotherapy (IOERT) containing multimodality treatment of locally advanced T4 rectal cancer, initially unresectable for cure, from the Mayo Clinic, Rochester, USA (MCR) and Catharina Hospital, Eindhoven, The Netherlands (CHE), both major referral centers for locally advanced rectal cancer. A rectal tumor is called locally unresectable for cure if after full clinical work-up infiltration into the surrounding structures or organs has been demonstrated, which would result in positive surgical margins if resection was the initial component of treatment. This was the reason to refer these patients to the IOERT program of one of the centers.

Methods: In the period from 1981 to 2010, 417 patients with locally unresectable T4 rectal carcinomas at initial presentation were treated with multimodality treatment including IOERT at either one of the two centres. The preferred treatment approach was preoperative (chemo) radiation and intended radical surgery combined with IOERT. Risk factors for local recurrence (LR), cancer specific survival, disease free survival and distant metastases (DM) were assessed.

Results: A total of 306 patients (73%) underwent a R0 resection. LRs and metastases occurred more frequently after an R1-2 resection (P<0.001 and P<0.001 respectively). Preoperative chemoradiation (preop CRT) was associated with a higher probability of having a R0 resection. Waiting time after preoperative treatment was inversely related with the chance of developing a LR, especially after R+ resection. In 16% of all cases a LR developed. Five-year disease free survival and overall survival (OS) were 55% and 56% respectively.

Conclusions: An acceptable survival can be achieved in treatment of patients with initially unresectable T4 rectal cancer with combined modality therapy that includes preop CRT and IOERT. Completeness of the resection is the most important predictive and prognostic factor in the treatment of T4 rectal cancer for all outcome parameters. IOERT can reduce the LR rate effectively, especially in R+ resected patients.

Keywords: T4 rectal cancer; intraoperative irradiation; re-irradiation; pooled results

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Introduction

Treatment of rectal cancer changed significantly over the past decades. The introduction of total mesorectal excision (TME) (1), the evaluation of the circumferential margin (CRM) status (2), the introduction of neoadjuvant (chemo) radiation and adjuvant therapy have improved the prognosis of patients with rectal cancer (3,4).

Rectal carcinomas are considered locally advanced when infiltrating through the enveloping mesorectal fascia or ingrowth into adjacent structures (5). These carcinomas are sub classified as T4b when they adhere to or invade into the surrounding structures or organs according to the TNM classification. The idea of treating patients with these T4 rectal carcinomas that may be locally unresectable for cure at initial presentation has changed from a merely palliative setting to a more aggressive multimodality treatment combining neoadjuvant (chemo) radiation with extended surgery. As a result of this approach the survival also changed from almost no long-term survivors to a reported 5-year survival rate up to 67% (6).

A number of factors appear to influence survival in the treatment of patients with T4b rectal tumors. Among these are the ability to achieve an R0 resection (6-9), and the use of neoadjuvant external beam irradiation therapy (EBRT) or concurrent chemoradiation (CRT) to achieve downsizing and downstaging of the tumour, which may improve the probability of performing a R0 resection. Furthermore neoadjuvant EBRT or CRT improves local control and in some series survival (5,10). However the dose tolerance of normal tissue limits the dose of EBRT that can be delivered safely. The addition of concurrent chemotherapy to the neoadjuvant radiation has improved local control, time to treatment failure, and cancer-specific survival (CSS) *vs.* EBRT alone in a phase III Norwegian trial of patients with locally unresectable rectal cancer (5).

Intra-operative irradiation therapy with either electrons (IOERT) or high dose brachytherapy (HDR-IORT) can provide a solution to overcome the problem of EBRT dose limitations. With IORT a boost can be delivered to the area of highest risk, i.e., the region where the tumor was initially fixed or most adherent to adjacent structures on clinical exam and confirmed on pelvic imaging and the risk of a close margin or even an R1 or R2 resection is highest. Dose limiting surrounding structures can be removed or shielded from the IORT boost. IORT has become an integral part of multimodality treatment of locally unresectable T4 rectal cancer in a number of institutions worldwide (6,11-30). The combination of EBRT and IORT may result in a tumorcidal dose equivalent to 80–90 Gy in 2 Gy fractions (12).

Two major tertiary referral centres practicing IOERT-containing multimodality treatment in the treatment of locally unresectable primary T4 rectal carcinomas, the Mayo Clinic in Rochester, Minnesota, USA (MAYO) and the Catharina Hospital in Eindhoven, The Netherlands (CHE), pooled their data. The aim of this study was to analyse the patient and treatment factors influencing local recurrence (LR), distant metastases (DM) and survival in uni and multivariate analyses.

Methods

Patients

At the MAYO the IOERT program started in 1981 and since then MAYO has been a leader in the field of treating patients with locally unresectable and recurrent rectal carcinoma (11,13,14,27). The Catharina Hospital Eindhoven (CHE) joined the Mayo Clinic in an IOERT program for rectal cancer in 1994 with the same treatment protocol (15-17).

The clinical stage of all patients was assessed by abdomen-pelvic computed tomography (CT) and or magnetic resonance imaging (MRI) in most patients, demonstrating loss of a fat plane relative to critical organs or structures, and the inability to perform an upfront R0 resection. In addition, patients had routine labs and chest film or CT, and many had endoscopic ultrasound to evaluate depth of invasion.

The data of the patients of the Mayo Clinic and the Catharina Hospital have been pooled from the beginning of their IOERT-program until 2010. Patients with primary T4b rectal cancer, locally unresectable for cure at initial presentation, without pre-operative DM were selected. Patients with a good response to neoadjuvant treatment not necessitating IOERT during surgery were excluded from this analysis resulting in a pooled group of 417 patients. The mean follow up time was 52 months (range, 0–234 months).

Treatment

In *Table 1* the similarities and differences between the institutions are shown. Patients in the MAYO cohort were significantly younger (mean 56 *vs.* 62 years in the CHE cohort, P<0.001) and had a longer mean follow up (57 *vs.* 48 months in the CHE, P=0.009). The preferred

Table 1 Patient characteristics—Mayo Clinic Rochester (MAYO) and Catharina Hospital Eindhoven (CHE)

Characteristic	All (N=417)	CHE (N=242)	MAYO (N=175)	P value
Age (years), mean [range]	59.2±12.2 [19–89]	62.3±10.2 [19–89]	56.4±13.7 [19–89]	<0.0001
FU (mo), mean [range]	51.8±38.1 [1–234]	48.2±33.7 [1–158]	56.8±43.1 [1–234]	0.024
Gender, n (%)				
Male	248 (60.0)	140 (58.0)	108 (62.0)	0.428
Female	169 (40.0)	102 (42.0)	67 (38.0)	
Preop Rx, n (%)				
None	13 (3.1)	0 (0.0)	13 (7.4)	<0.0001
EBRT	79 (18.9)	54 (22.3)	25 (14.3)	
ChemoRT	325 (77.9)	188 (77.7)	137 (78.3)	
Waiting time* (weeks), n (%)				<0.0001
0.1–2	47 (11.6)	3 (1.2)	44 (27.2)	
2.1–4	34 (8.4)	8 (3.3)	26 (16.0)	
4.1–6	62 (15.3)	14 (5.8)	48 (29.6)	
6.1–8	68 (16.8)	47 (19.4)	21 (13.0)	
8.1–10	79 (19.6)	69 (28.5)	10 (6.2)	
10.1–12	55 (13.6)	53 (21.9)	2 (1.2)	
>12	43 (10.6)	39 (16.1)	4 (2.4)	
Missing	16 (4.0)	9 (3.7)	7 (4.3)	
Total	404 (100.0)	242 (100.0)	162 (100.0)	
Adjuv chemo^, n (%)				0.635
No	346 (83.1)	199 (82.2)	147 (84.0)	
Yes	71 (17.0)	43 (17.8)	28 (16.0)	
Postop EBRT^, n (%)				<0.0001
No	390 (94.5)	238 (98.3)	152 (86.9)	
Yes	27 (5.5)	4 (1.7)	23 (13.1)	

*, stratified for radicality of resection (dependent variable); ^, postoperative treatment shown but not included in multivariate analyses; yr, year; Preop Rx, preoperative treatment; EBRT, external beam irradiation; ChemoRT, chemoradiotherapy; waiting time, interval from end of preoperative therapy to surgery; adjuv chemo, adjuvant chemotherapy; postop, postoperative.

treatment approach was preoperative (chemo) radiation, an intended radical resection followed by an IOERT boost at the area of risk, however in the early phase of the MAYO cohort 13 of 175 patients (7.4%) had an irradical surgical resection (R1 or R2) as the initial component of treatment. Over the years, the adjuvant and neoadjuvant treatment schemes have changed in both centers. However, the basic treatment principle (radiotherapy with concurrent 5-fluorouracil or capecitabine, followed by resection and an IOERT boost) remained the same. Treatment methods from both institutions have been described in detail in prior manuscripts and will only be summarized here (13-17,27).

The majority of the patients received preoperative radiotherapy combined with 5-FU based chemotherapy, and this percentage was comparable in both centers (MCR: 79% *vs.* CHE: 78%). The preoperative EBRT-dose ranged from 45–54 Gy in fractions of 1.8 to 2.0 Gy.

The waiting period between the finishing of the preoperative (chemo) radiotherapy and surgery ranged from 1 day to more than 12 weeks. At MAYO, the waiting time was significantly shorter than at CHE with a waiting time interval of 6 weeks or less in 73% *vs.* 10% of patients and an interval of 8 weeks or less in 86% *vs.* 30%. All patients were re-evaluated, with either a pelvic MRI and/or a CT thorax/abdomen/pelvis, after finishing neoadjuvant therapy and before proceeding to surgery/IOERT.

Performing surgery in these patients constitutes a challenge, given the fact that the tumors were beyond their natural anatomical borders and often required an extra-anatomical resection. IORT was delivered as an electron boost at both institutes. Currently, both centers have a dedicated linear accelerator in the operating theatre. The IOERT dose and energy were comparable and were usually 10 to 12.5 Gy after an R0 or R1 resection (15 Gy or higher in the few patients with R2 resection), with electron energies ranging from 8 to 12 MEV and the most commonly used diameter of the bevelled applicator was 6 cm.

All patients referred for treatment for a T4b carcinoma were discussed in a multidisciplinary setting in both centers. Data of all patients treated for T4 carcinomas are prospectively collected in a database.

Statistical analysis

Statistical analysis was performed using SPSS package (SPSS 20.0 for Windows; SPSS Inc., Chicago, IL). The *t*-tests and chi-square tests were used to compare individual variables. The LR rate, DM rate, CSS, relapse-free survival (RFS) and overall survival (OS) were estimated using the Kaplan-Meier (KM) method. CSS was defined as the time between rectal cancer surgery and death caused by rectal cancer. Differences were assessed using the Log-Rank test. P values were two-sided and considered statistically significant at a value of 0.05 or less. For determination of risk factors, first univariate analyses were performed by analyzing the effect of the covariates in a univariate Cox regression (CR). Covariates with trend-significant effects (P value <0.10) were selected for multivariate analysis, using stepwise Cox proportional hazards regression modeling. Stepwise regression was used and a two-sided P value of less than 0.05 was considered significant. Forest plots were implemented using Comprehensive Meta-Analysis version 2.0.

In this group of 417 patients only seven R2 resections occurred and therefore, R1 and R2 were combined as R+ in most statistical analyses.

The Mayo Clinic institutional review board and the Catharina Hospital review board approved this study.

Results

Radicality of the resection

Overall, 306 patients of the 417 patients (73%) underwent a complete resection without tumor cells at the surgical resection margins (R0 resection). *Table 2* shows the influence of preoperative parameters on the radicality of the resections. In the group of patients who had no preoperative treatment the R0 rate was 54%, while this ranged from 67% after preoperative radiotherapy and 76% after preoperative chemoradiotherapy (P=0.026). Furthermore it was found that the waiting time between the last day of the neoadjuvant radiotherapy and the day of surgery had a significant effect on the margin status of the resection. In the group of patients who waited less than 57 days (the median number of days waiting time), 69% of patients underwent a R0 resection opposed to 80% in the group of patients who had a longer waiting period (P=0.014). *Figure 1A* shows the effect of the waiting time on the percentage of R0 resections.

The LR

In 66 of 417 patients a LR developed (19.3% 5-year LR rate). After univariate analysis (*Table 3*) the risk factor associated with LR were margin status of the resection (P<0.001) and interval from completion of preoperative therapy to resection (waiting time; P=0.037). Subtotal resection resulted in 3- and 5-year LR rates of 27% and 40% for R1 resection and 43% for R2 resections, while this was 10% and 13% after R0 resection (P<0.001).

As waiting time was correlated with radicality of resection, the influence of waiting time on the development of LR was stratified for radicality of resection. After univariate analyses a significant increase in LR was found with a waiting time of >8 *vs.* ≤8 weeks or less (KM, P=0.037) leading to a risk reduction of 42% (CR, HR: 0.58; CI: 0.35–0.97, P=0.039).

After multivariate analyses with waiting time and radicality of resection included, a significant risk reduction of 41% (CR, HR: 0.59; CI: 0.35–0.99, P=0.044) and 70% (CR, HR: 0.30; CI: 0.18–0.51, P<0.0001) was found for waiting time and radicality of resection respectively. The most prominent risk reduction of almost 60% was seen in the R+ resected group. *Figure 1B* demonstrates the effect of waiting time on 3 years LR rate in R0 and R+ resected patients. *Figure 1C* shows the different effect of waiting time on radically resected patients and incomplete resected patients. In R+ patients, the 3-year local relapse rate was 43% *vs.* 18% with waiting time of >8 *vs.* ≤8 weeks (P=0.018).

A lower risk of LR was observed at 5 years in patients receiving neoadjuvant therapy, although this effect did not reach statistical significance since 97% of patients received preoperative therapy. No effect of adjuvant chemotherapy was found on the development of a LR.

Table 2 Preoperative variables influencing radicality of resection in pooled analysis

Characteristic	Resection R0 (%)	R1/R2 (%)	All (%)	Univariate P value	Multivariate P value (R0 *vs*. R1/R2)
Age, years					
≤69	243 (74.3)	84 (25.7)	327 (100.0)	0.412	
≥70	63 (70.0)	27 (30.0)	90 (100.0)		
Gender					
Male	178 (71.8)	70 (28.2)	248 (100.0)	0.368	
Female	128 (75.7)	41 (24.3)	169 (100.0)		
Preop Rx					
None	7 (53.8)	6 (46.2)	13 (100.0)	0.026	0.339
EBRT	53 (67.1)	26 (32.9)	79 (100.0)		
ChemoRT	246 (75.7)	79 (24.3)	325 (100.0)		
Waiting time* (weeks)				<0.0001	<0.0001
0.1–2	24 (53.3)	21 (46.7)	45 (100.0)		
2.1–4	21 (56.8)	16 (43.2)	37 (100.0)		
4.1–6	48 (70.6)	20 (29.4)	68 (100.0)		
6.1–8	59 (85.5)	10 (14.5)	69 (100.0)		
8.1–10	68 (86.1)	11 (13.9)	79 (100.0)		
10.1–12	40 (80.0)	10 (20.0)	50 (100.0)		
>12	34 (70.8)	14 (29.2)	48 (100.0)		
Total	294 (74.2)	102 (25.8)	396 (100.0)		
Adjuv chemo^				0.042	
No	247 (71.4)	99 (28.6)	346 (100.0)		
Yes	59 (83.1)	12 (16.9)	71 (100.0)		
Postop EBRT^				0.086	
No	290 (74.4)	100 (25.6)	390 (100.0)		
Yes	16 (59.3)	11 (40.7)	27 (100.0)		

*, stratified for radicality of resection (dependent variable); ^, postoperative treatment shown but not included in multivariate analyses; yr, year; Preop Rx, preoperative treatment; EBRT, external beam irradiation; ChemoRT, chemoradiotherapy; waiting time, interval from end of preoperative therapy to surgery; adjuv chemo, adjuvant chemotherapy; postop, postoperative.

The DM

The 5-year DM free survival was 64%. Only an incomplete resection was associated with a higher risk for DM, as shown in *Table S1*, with 3- and 5-year DM free survival of 76% and 69%, 59% and 47%, and 33% and 33% for R0, R1 and R2 resected patients respectively (P=0.001). When investigating factors influencing the development of metastases, no influence was found of adjuvant therapy in this analysis. *Figure 2* shows the effect of an R0 and R+ resection on the development of metastases and other oncological outcome parameters.

CSS and relapse-free survival (RFS)

CSS was 64.6% after 5 years; the main factor associated with CSS after univariate analysis was margin status (*Table 4*). R1-R2 resections were associated with a 3- and 5-year CSS of 69% and 44%, and 40% and 20% respectively, compared to 82% and 73% after R0 surgery (P<0.001). After univariate analysis of factors influencing CSS it was found that receiving preoperative chemoradiotherapy or radiotherapy decreased the chance of dying of the cancer (P=0.036), which did not reach statistical significance on multivariate analysis.

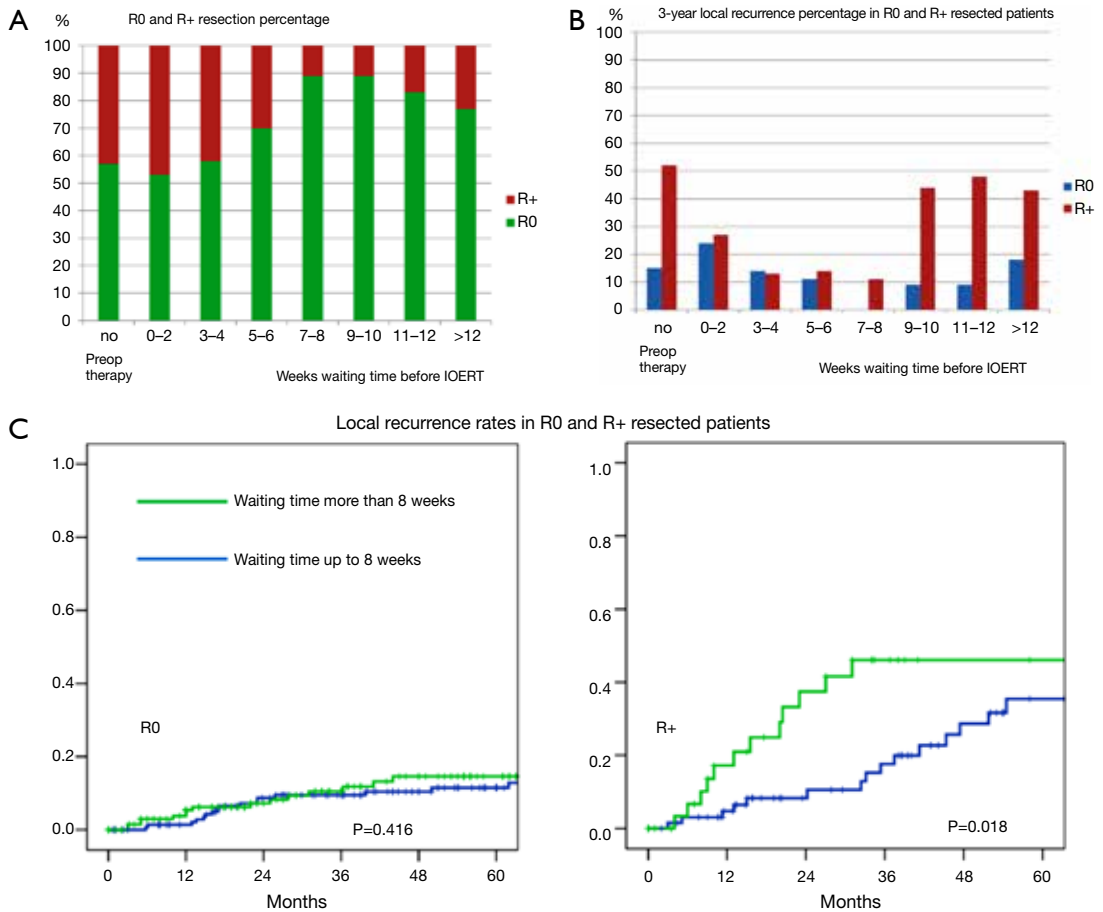

Figure 1 Influence of waiting time (interval from end of preoperative therapy to surgery). (A) Rate of R0 resections—increases with a 7–10 weeks waiting time; (B) local recurrence (LR) rates at 3 years—if relatively short waiting time (3–8 weeks), 3 years LR is statistically reduced; when >8 weeks, 3 years LR similar in R+ patients to those with no preoperative treatment; (C) LR rates in R0 and R+ resected patients.

Five-year RFS was 55.1%. RFS was significantly influenced by the margin status (P<0.001, *Table S2*). A trend towards improved RFS is observed after neoadjuvant therapy (5-year RFS of 56% *vs.* 30%, with *vs.* without neoadjuvant therapy; P=0.148). The RFS was not influenced by adjuvant therapy.

OS

The 3- and 5-year OS estimates were 73% and 56%. When an R0 resection was achieved, these percentages were 77% 3-year and 64% 5-year OS. In patients with R1-R2 resection the 3 and 5 years OS were 60% and 35%, and 29% and 14% respectively (P<0.001). Factors influencing OS after uni- and multivariate analysis were age (P<0.001) and margin status (P<0.001) (*Table 5*). The different types of neoadjuvant therapy had no significant effect on survival but the fact that patients did or did not receive neoadjuvant therapy showed a trend towards better survival in patients treated with neoadjuvant therapy (5-year OS of 46% with no preop therapy *vs.* 57% with preop CRT). Adjuvant chemotherapy resulted in a trend for improved 5-year OS (70% *vs.* 53%) that did not reach statistical significance (P=0.101). Postoperative radiotherapy was not correlated with OS nor with other oncological outcome parameters

Discussion

In this study the pooled results of the IOERT containing multimodality treatment in two major centers are presented in 417 patients with T4 rectal carcinomas that were locally unresectable for cure at initial presentation. The pooling

Table 3 Uni and multivariate analysis of variables influencing local recurrence rates

Parameter	3–5 years (%)	P value (KM)	Univariate analyses			Multivariate analyses		
			CR HR	CI	P value	CR HR	CI	P value
Age, years		0.470			0.480			
≤69	13–18		1					
≥70	19–24		1.244	0.687–2.250				
Gender					0.936			
Male	13–20		1					
Female	17–19		0.980	0.598–1.606				
Preop Rx		0.846			0.861			
None	19–32		1					
EBRT	16–18		0.703	0.198–2.494				
ChemoRT	14–19		0.715	0.233–2.293				
Waiting time* (weeks)		0.037			0.039			0.044
>8	17–21		1			1		
≤8	12–18		0.579	0.345–0.972		0.589	0.352–0.985	
Radicality		<0.0001						
R0	10–13		1		<0.0001	1		<0.0001
R1	27–40		3.082	1.880–5.053	<0.0001	3.324	1.981–5.576	<0.0001
R2	43–43		3.384	0.811–14.117	0.094	2.627	0.351–19.666	0.347
Adjuv chemo		0.873						
No	15–19		1					
Yes	13–22		0.948	0.946–1.813				
Postop EBRT		0.923			0.923			
No	15–19		1					
Yes	23–23		1.046	0.420–2.603				

*, stratified for radicality of resection (dependent variable); ^, postoperative treatment shown but not included in multivariate analyses; yr, year; KM, Kaplan Meier; Preop Rx, preoperative treatment; EBRT, external beam irradiation; ChemoRT, chemoradiotherapy; waiting time, interval from end of preoperative therapy to surgery; adjuv chemo, adjuvant chemotherapy; postop, postoperative; CR, cox regression; HR, hazard ratio; CI, confidence interval.

of this large cohort of patients with sufficient follow up allowed in-depth statistical analysis. However, combining the data from different centers may also introduce some bias. Therefore the treatment protocols of both centers were compared to evaluate if the groups of patients were comparable and to detect differences, which could be used for analytical purposes. Furthermore the pre-treatment staging and the TNM classification were compared to evaluate if the groups were similar. All patients had a T4b tumor as staged prior to initiation of treatment. The percentage of patients receiving neoadjuvant therapy was comparable in both centers (100% *vs.* 93%): however, 13 of 175 patients (7.3%) in the early part of the MAYO cohort had an irradical (R1 or R2) resection as the initial component of treatment. Finally specialists of both centers visited each other and observed treatment of patients in the collaborating center. It was concluded that both the patient groups and method of treatment were quite comparable before the pooled analysis was started. Other limitations of the analysis include changes in treatment protocol over time especially with regard to concurrent chemotherapy during EBRT and maintenance postoperative chemotherapy (utilization, which drugs, method of administration, intensity, duration, etc.).

The major difference in the treatment approach at MAYO and CHE was the interval from completion of

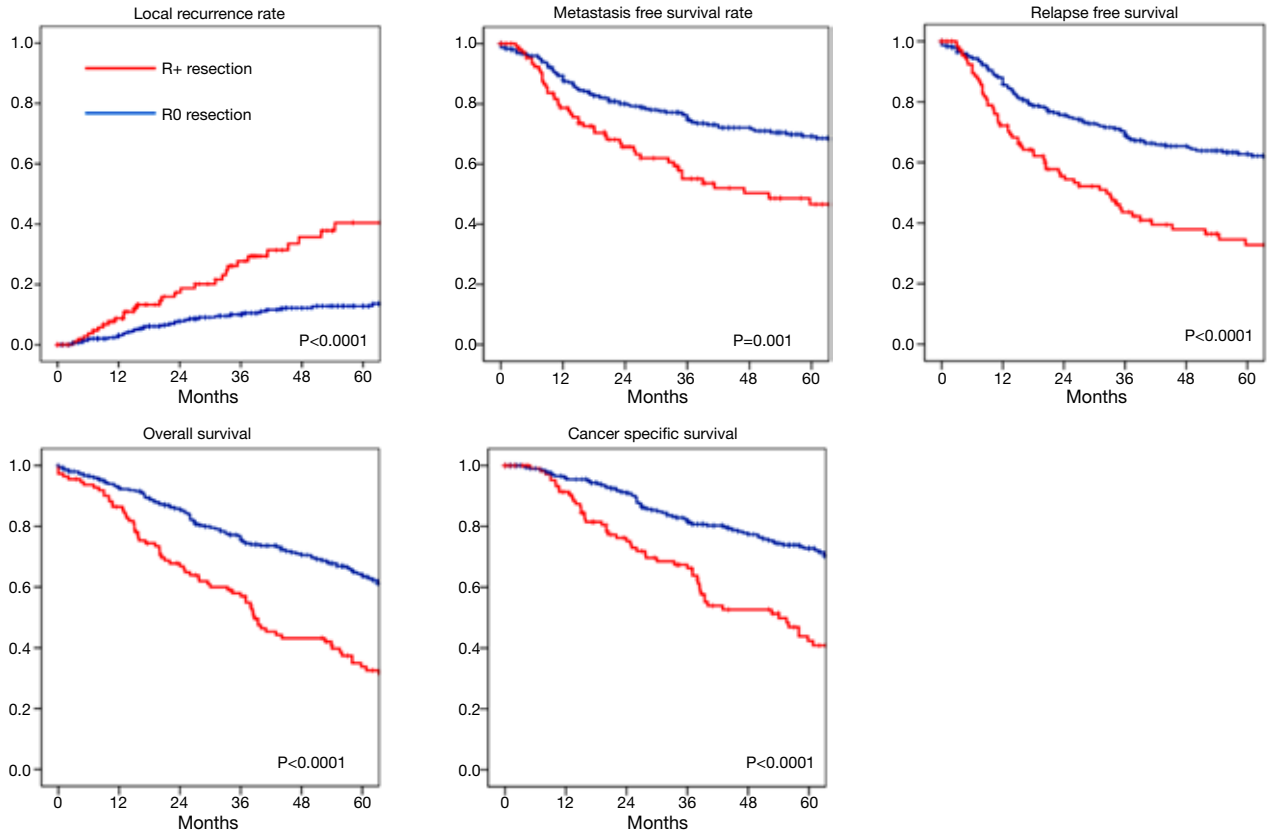

Figure 2 Influence of radicality of resection (R0 *vs.* R+) on all oncological outcome parameters.

neoadjuvant therapy to radical resection plus IOERT. At MAYO, the waiting time was 6 weeks or less in 73% of patients *vs.* 10% at CHE and 8 weeks or less in 86% *vs.* 30%. The MAYO preferred interval of ≤6 weeks was chosen to obtain an additive effect of the EBRT and IOERT components of treatment by reducing the total duration of irradiation, in an attempt to maximize local control of disease. CHE preferred an interval of 8–10 weeks in order to achieve maximum tumor shrinkage from preoperative therapy and optimize the rate of R0 resection.

The treatment protocols in the current pooled analysis have succeeded in achieving an increased 5-year OS of 56% for patients with T4 rectal carcinomas that were locally unresectable for cure at time of initial presentation because of tumor fixation. The distant metastasis free survival was 64% and CSS was 65% after 5 years. These results compare well with the outcome of rectal cancer treatment in general, when considering that all these patients had 'locally unresectable' T4 tumors. Other IOERT series published survival figures ranging from 52% to 67% (6,14,18-20), however some of those studies included T1–T3 tumours (18-20).

In the current pooled analysis the LR rate was 16% (3-year LR: R0—10%, R1—27% and R2—43%). In other IOERT studies similar rates have been reported. Kusters *et al.* found a LR rate of 12% in a pooled analysis of the results of four European tertiary referral IORT centers treating T4 tumours and T3 tumours with a threatened CRM (6). Mathis *et al.* analyzed a Mayo IOERT series of 146 patients with unresectable T4 colorectal cancers of which 106 were rectal; the LR rate was 14% (14).

Impact of IOERT on outcomes

It is difficult to assess the effect of adding IOERT to the treatment approach for patients with LARC with regard to increased survival. One would assume that the combination of improved components of the treatment will improve both local control and survival over time, but it is challenging to determine which part of the improvement can be contributed to IOERT. However, in a non-IORT series from MAYO by Schild *et al.* (24), 17 rectal cancer patients with irradical resection (R1—10 pts, R2—7) received

Table 4 Uni and multivariate analysis of variables influencing cancer specific survival

Parameter	3–5 years (%)	P value (KM)	Univariate analyses			Multivariate analyses		
			CR HR	CI	P value	CR HR	CI	P value
Age, years		0.121			0.122			
≤69	80–66		1					
≥70	74–57		1.370	0.919–2.043				
Gender		0.429			0.430			
Male	81–66		1					
Female	76–63		1.142	0.882–1.587				
Preop Rx		0.086						
None	69–46		1		0.094	1		0.235
EBRT	73–63		0.578	0.274–1.219	0.150	0.629	0.297–1.332	0.226
ChemoRT	80–66		0.483	0.244–0.954	0.036	0.599	0.282–1.108	0.096
Waiting time* (weeks)		0.674			0.674			
>8	77–67		1					
≤8	81–65		0.925	0.644–1.330				
Radicality		<0.0001						
R0	82–73		1		<0.0001	1		<0.0001
R1	69–44		2.344	1.661–3.281	<0.0001	2.273	1.614–3.203	<0.0001
R2	40–20		3.092	1.131–8.547	0.028	3.085	1.114–8.399	0.03
Adjuv chemo		0.869			0.869			
No	78–73		1					
Yes	81–71		0.964	0.621–1.496				
Postop EBRT		0.730			0.731			
No	77–65		1					
Yes	84–62		1.109	0.614–2.005				

*, stratified for radicality of resection (dependent variable); ^, postoperative treatment shown but not included in multivariate analyses; yr, year; KM, Kaplan Meier; Preop Rx, preoperative treatment; EBRT, external beam irradiation; ChemoRT, chemoradiotherapy; waiting time, interval from end of preoperative therapy to surgery; adjuv chemo, adjuvant chemotherapy; postop, postoperative; CR, cox regression; HR, hazard ratio; CI, confidence interval.

postoperative EBRT or CRT with 3- and 5-year OS of only 24% *vs.* 5-year OS of 52% in the MAYO IOERT series reported by Mathis *et al.* (14) and 5-year OS of 56% in the current analysis. In the MAYO non-IORT series of 17 patients, LR occurred in 76% of patients (3 and 5-year LR: resection R1—70%; R2—86%). In the MAYO IOERT series of 146 patients, 3- and 5-year LR rates were 10% and 14%. In the current pooled IOERT analysis, the 5-year LR rate was 19%.

A separate Mayo analysis by Schild *et al.* was performed regarding outcomes in 103 patients with locally advanced colon cancer treated with EBRT or CRT alone or plus IOERT as a supplement to maximal surgical resection (25). Outcomes at 5-year based on radicality of resection were as follows: LR, resection R0—10%, R1—54%, R2—79% (P<0.0001); 5-year OS, R0—66%, R1—47%, R2—23% (P=0.0009). Patients with R1 or R2 resection who received IOERT plus EBRT/CRT as a component of treatment had better outcomes than those who had only EBRT or CRT: LR—11% *vs.* 82% (P=0.02); 5-year OS 76% *vs.* 26% (P=0.04).

In a recent systematic review and meta-analysis evaluating IORT in the treatment of colorectal cancer by Mirnezami *et al.*, it was concluded that IORT may improve oncological outcome in patient treated for LARC (21). The meta-analysis of outcomes for locally advanced primary and recurrent rectal cancer showed a significant effect of IORT for both local control (pooled odds ratio of 0.22, P=0.03)

Table 5 Uni and multivariate analysis of variables influencing overall survival

Parameter	3–5 years (%)	P value (KM)	Univariate analyses			Multivariate analyses		
			CR HR	CI	P value	CR HR	CI	P value
Age, years		<0.0001			<0.0001			<0.0001
≤69	76–60		1			1		
≥70	58–43		1.986	1.461–2.698		1.982	1.458–2.694	
Gender		0.808			0.808			
Male	73–55		1					
Female	69–56		1.035	0.783–1.369				
Preop Rx		0.171						
None	69–46		1		0.176			
EBRT	64–54		0.741	0.372–1.474	0.393			
ChemoRT	74–57		0.601	0.317–1.142	0.120			
Waiting time* (weeks)		0.300			0.301			
>8	68–54		1					
≤8	76–58		0.854	0.632–1.153				
Radicality		<0.0001						
R0	77–64		1		<0.0001	1		<0.0001
R1	60–35		2.053	1.532–2.750	<0.0001	2.049	1.529–2.745	<0.0001
R2	29–14		3.039	1.336–6.912	0.008	3.047	1.338–6.939	0.008
Adjuv chemo		0.101			0.103			
No	70–53		1					
Yes	80–70		0.710	0.470–1.072				
Postop EBRT		0.973			0.973			
No	70–56		1					
Yes	81–60		0.991	0.585–1.678				

*, stratified for radicality of resection (dependent variable); ^, postoperative treatment shown but not included in multivariate analyses; yr, year; KM, Kaplan Meier; Preop Rx, preoperative treatment; EBRT, external beam irradiation; ChemoRT, chemoradiotherapy; waiting time, interval from end of preoperative therapy to surgery; adjuv chemo, adjuvant chemotherapy; postop, postoperative; CR, cox regression; HR, hazard ratio; CI, confidence interval.

and 5-year OS (HR =0.51, P=0.009) in patients with R0, R1 and R2 resection.

There are no large randomized controlled trials (RCT's) comparing treatment with or without IOERT in the treatment of T4 rectal cancer that observed a survival benefit for IOERT. Two RCT's failed to show benefit of the addition IOERT to the treatment of LARC. However in both RCT's T3 tumors were included, in whom the additional effect of IOERT would theoretically be minimal (18,21,28).

In an analysis from Massachusetts General Hospital (MGH) by Willett *et al.*, outcomes were compared after R0 resection in 20 patients with and 18 patients without IOERT. There was no difference in 5 years disease free survival, but an improved local control rate was found with IOERT (5-year LC of 88% *vs.* 67%) (22). The improvement in local control with IOERT has been confirmed in a series by Valentini *et al.* of 78 patients with preoperative chemoradiation (preop CRT) and R0 resection for T4 rectal cancers; 29 had IOERT after resection (29). Local control at 5-year was best in those with IOERT as a component of treatment (100% *vs.* 81%, P=0.014). On multivariate analysis, IOERT was the only variable with a positive predictive value.

In a separate MGH series by Willett *et al.*, 47 patients with locally advanced rectal cancer had preop CRT and R0 resection, but IOERT was not given (good tumor response or not technically feasible) (30). In patients with a pathological CR or ypT2N0 disease, 5-year LR was only

13%, but in those with ypT3N0 or nodal disease, 5-year LR was 68%. In a subsequent analysis by Willett *et al.*, 95 patients with T4 rectal cancer had preop EBRT/CRT followed by complete resection; 40 had IOERT and 55 did not (favorable tumor response or IOERT not feasible technically) (31). Local control was better in IOERT patients, in both responders (100% *vs.* 84%) and non-responders (88% *vs.* 73%). In view of these findings, the authors recommended that IORT should be delivered, if technically feasible, independent of the extent of tumor downstaging after preoperative treatment.

In the aforementioned study by Kusters it was found that 55% of patients treated with IOERT for positive resection margins had no LR. A similar observation was noted by Mathis *et al.*, who found that only 2% of subsequent LRs were located in the IOERT field (14). When an R0 resection is not feasible, Ferenschild *et al.* found an improved local control rate and OS with the addition of HDR-IORT with 5-year local control of 58% *vs.* 0% (23).

In a recent Memorial Sloan Kettering HDR-IORT analysis by Terezakis *et al.*, 89 patients with T4 rectal cancer had preoperative chemoradiation followed by R0 or R1 resection and HDR-IORT (HDR-IORT not feasible after R2 resection) (26). Outcomes were similar to IOERT series with 5-year LR of 23%, 26% and 17% for negative (n=58), close (2 mm or less; n=16) or positive R1 resection margins (n=16) and 5-year OS of 57%, 60% and 45% respectively.

All these observations may lead to the assumption that IORT with either electrons or HDR brachytherapy has an effect on residual tumor cells. This effect has the potential to impact both local control and survival.

Waiting time—impact on outcomes

A new finding in this pooled analysis was that a relatively short waiting time between the last day of preoperative radio (chemo) therapy and the administration of IOERT was important to reduce LR. Patients with a waiting time of >8 weeks had a higher rate of local relapse than those with a waiting time of 8 weeks or less (P=0.044, multivariate). The impact of waiting time on LR extended from 3 to 8 weeks following completion of neoadjuvant treatment. From a radio-biological point of view this finding seems logical: the longer the waiting time the more effective the repopulation of cancer cells in the previously irradiated tumor.

In a prospective randomized study evaluating the optimal waiting period in patients with rectal carcinomas (T2 to T3, NX, M0) after neoadjuvant radiation therapy it was concluded that a waiting period of 6 weeks is optimal, mainly because tumour downsizing was increased and no detrimental effects on toxicity and early clinical results was observed. No difference in LR or short-term survival was found in this study (32). However, in patients with locally unresectable rectal cancer, who are treated with neoadjuvant concurrent chemoradiation, no results of prospective studies evaluating the optimal waiting period are available. In patients with rectal carcinomas retrospective data is available on the subject of a longer waiting period after finishing the neoadjuvant chemoradiation. Results have been published that a longer period waiting after neoadjuvant chemoradiation accomplishes a higher level of pathological complete response (pCR) (33) or more downstaging (34,35), without an increase in complications. However an increase in disease free or OS has not been shown.

In LARC patients, an analysis by Tulchinsky *et al.* showed that an interval between neoadjuvant chemoradiation and surgery of more than 7 weeks was associated with higher rates of pCR and near pCR, decreased recurrence and disease free survival in 132 patients analysed (36). de Campos-Lobato *et al.* evaluated the same subject in LARC patients with an interval shorter or longer than 8 weeks. They also found a significant higher rate of complete response (P=0.03) and a (not significant) correlation with decreased LR (P=0.07) (37). Other studies confirmed the effect of longer waiting on downstaging, but did not find an effect on survival (34,38).

However, other studies did not find an effect of a longer waiting period. Stein *et al.* evaluated downstaging in LARC patients divided in two groups (a waiting time of 4–8 and 10–14 weeks) They found no influence of longer waiting on perioperative morbidity and downstaging (39). A similar outcome was found in a Korean study by Lim *et al.* which was performed to evaluate the optimal waiting time to LARC surgery after preoperative chemoradiation (CRT) to 50.4 Gy with resection 4–8 weeks later (40). There was no difference in pathologic or surgical outcomes in those who had surgery 28–41 d after CRT *vs.* 42–56 d (pCR—13.8% *vs.* 15.0%; downstaging—47.5% *vs.* 44.4%; sphincter preservation—83.9% *vs.* 82%) and both groups had similar local-recurrence free survival (P=0.1165).

In the current pooled analysis, longer waiting times did have a significant effect on the R0 rate, which was an important factor influencing LR, DM, CSS, RFS and OS. The highest radicality rate was achieved with the waiting period of 6–10 weeks (*Figure 1*). However, waiting times longer than eight weeks resulted in an increased

rate of LR in both univariate analyses (P=0.037) and multivariate analyses (P=0.044) which may indicate the lack of an additive effect of IOERT to preoperative EBRT or chemoradiation with the longer waiting times. In fact, waiting times longer than twelve weeks resulted in LR rates comparable to no preoperative radio (-chemo) therapy. Accordingly, in institutions without the capability of an IORT boost after radical resection, the waiting time can and perhaps should be tailored to the tumor characteristics in the individual patient. If a longer waiting is expected to create downsizing of the tumour leading to a situation in which a radical resection can be performed more easily, it may be preferable to wait longer than six weeks to get the maximum effect of the neoadjuvant therapy. However, in institutions with IORT capability, it may be preferable to perform the resection after a 3–8-week interval, to increase the likelihood of an additive effect of IORT plus EBRT in destroying residual tumour cells.

Adjuvant chemotherapy

In the current pooled analysis, 79 patients (19%) received post-op chemotherapy with no impact on disease relapse or survival. Previous reports on the role of adjuvant chemotherapy concluded that the addition of adjuvant chemotherapy in the treatment of patients with colorectal carcinoma is beneficial in selected patients (41,42). A more recent analysis of the phase III EORTC 2291 trial in 1,011 patients with stage II or III rectal cancer confirms the benefit of preoperative concurrent chemoradiation *vs.* preop EBRT alone with regard to improved local control, but no survival benefit was found for adjuvant postop chemotherapy (43,44).

Conclusions

In conclusion, an acceptable disease free and OS can be achieved in treatment of patients with locally unresectable T4b rectal cancer with a combined modality regimen that includes neoadjuvant chemoradiation, radical intent surgery and IORT. Radicality of the resection has a significant impact on all oncological outcome parameters. Early administration of an IORT boost in margin positive and probably also margin close patients may reduce the development of LRs by more than 50% and result in LR rates comparable to radically resected patients.

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Footnote

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

Ethical Statement: Both the Catharina Hospital and the Mayo Clinic did not require formal approval of the ethical committees nor informed consent because data collected and provided were completely anonymous and the study without intervention did not violate the privacy of individual patients.

References

1. Heald RJ. The 'Holy Plane' of rectal surgery. J R Soc Med 1988;81:503-508.
2. Glynne-Jones R, Mawdsley S, Novell JR. The clinical significance of the circumferential resection margin following preoperative pelvic chemo-radiotherapy in rectal cancer: why we need a common language. Colorectal Dis 2006;8:800-807.
3. Bosset JF, Calais G, Mineur L, et al. Enhanced tumorocidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: preliminary results--EORTC 22921. J Clin Oncol 2005;23:5620-5627.
4. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731-1740.
5. Braendengen M, Tveit KM, Berglund A, et al. Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. J Clin Oncol 2008;26:3687-3694.
6. Kusters M, Valentini V, Calvo FA, et al. Results of European pooled analysis of IORT-containing multimodality treatment for locally advanced rectal cancer: adjuvant chemotherapy prevents local recurrence rather than distant metastases. Ann Oncol 2010;21:1279-1284.
7. Nagtegaal ID, Quirke P. What is the role for the circumferential margin in the modern treatment of rectal cancer? J Clin Oncol 2008;26:303-312.
8. Trakarnsanga A, Gonen M, Shia J, et al. What is the significance of the circumferential margin in locally advanced rectal cancer after neoadjuvant

chemoradiotherapy? Ann Surg Oncol 2013;20:1179-1184.
9. Tilney HS, Rasheed S, Northover JM, et al. The influence of circumferential resection margins on long-term outcomes following rectal cancer surgery. Dis Colon Rectum 2009;52:1723-1729.
10. Aklilu M, Eng C. The current landscape of locally advanced rectal cancer. Nat Rev Clin Oncol 2011;8:649-659.
11. Gunderson LL, Haddock MG, Nelson H, et al. Locally recurrent colorectal cancer: IOERT and EBRT +/-5-FU and maximal resection. Front Radiat Ther Oncol 1997;31:224-228.
12. Willett CG, Czito BG, Tyler DS. Intraoperative radiation therapy. J Clin Oncol 2007;25:971-977.
13. Gunderson LL, Martin JK, Beart RW, et al. Intraoperative and external beam irradiation for locally advanced colorectal cancer. Ann Surg 1988;207:52-60.
14. Mathis KL, Nelson H, Pemberton JH, et al. Unresectable colorectal cancer can be cured with multimodality therapy. Ann Surg 2008;248:592-598.
15. Mannaerts GH, Martijn H, Crommelin MA, et al. Feasibility and first results of multimodality treatment, combining EBRT, extensive surgery, and IOERT in locally advanced primary rectal cancer. Int J Radiat Oncol Biol Phys 2000;47:425-433.
16. Rutten HJ, Mannaerts GH, Martijn H, et al. Intraoperative radiotherapy for locally recurrent rectal cancer in The Netherlands. Eur J Surg Oncol 2000;26 Suppl A:S16-20.
17. Mannaerts GH, Schijven MP, Hendrikx A, et al. Urologic and sexual morbidity following multimodality treatment for locally advanced primary and locally recurrent rectal cancer. Eur J Surg Oncol 2001;27:265-272.
18. Dubois JB, Bussieres E, Richaud P, et al. Intra-operative radiotherapy of rectal cancer: results of the French multi-institutional randomized study. Radiother Oncol 2011;98:298-303.
19. Sadahiro S, Suzuki T, Ishikawa K, et al. Preoperative radio/chemo-radiotherapy in combination with intraoperative radiotherapy for T3-4Nx rectal cancer. Eur J Surg Oncol 2004;30:750-758.
20. Diaz-Gonzalez JA, Calvo FA, Cortes J, et al. Prognostic factors for disease-free survival in patients with T3-4 or N+ rectal cancer treated with preoperative chemoradiation therapy, surgery, and intraoperative irradiation. Int J Radiat Oncol Biol Phys 2006;64:1122-1128.
21. Mirnezami R, Chang GJ, Das P, et al. Intraoperative radiotherapy in colorectal cancer: systematic review and meta-analysis of techniques, long-term outcomes, and complications. Surg Oncol 2013;22:22-35.
22. Willett CG, Shellito PC, Tepper JE, et al. Intraoperative electron beam radiation therapy for primary locally advanced rectal and rectosigmoid carcinoma. J Clin Oncol 1991;9:843-849.
23. Ferenschild FT, Vermaas M, Nuyttens JJ, et al. Value of intraoperative radiotherapy in locally advanced rectal cancer. Dis Colon Rectum 2006;49:1257-1265.
24. Schild SE, Martenson JA Jr, Gunderson LL, et al. Long-term survival and patterns of failure after postoperative radiation therapy for subtotally resected rectal adenocarcinoma. Int J Radiat Oncol Biol Phys 1989;16:459-463.
25. Schild SE, Gunderson LL, Haddock MG, et al. The treatment of locally advanced colon cancer. Int J Radiat Oncol Biol Phys 1997;37:51-58.
26. Terezakis S, Morikawa L, Wu A, et al. Long-Term Survival After High-Dose-Rate Brachytherapy for Locally Advanced or Recurrent Colorectal Adenocarcinoma. Ann Surg Oncol 2015;22:2168-2178.
27. Gunderson LL, Nelson H, Martenson JA, et al. Locally advanced primary colorectal cancer: intraoperative electron and external beam irradiation +/- 5-FU. Int J Radiat Oncol Biol Phys 1997;37:601-614.
28. Masaki T, Takayama M, Matsuoka H, et al. Intraoperative radiotherapy for oncological and function-preserving surgery in patients with advanced lower rectal cancer. Langenbecks Arch Surg 2008;393:173-180.
29. Valentini V, Coco C, Rizzo G, et al. Outcomes of clinical T4M0 extra-peritoneal rectal cancer treated with preoperative radiochemotherapy and surgery: a prospective evaluation of a single institutional experience. Surgery 2009;145:486-494.
30. Willett CG, Shellito PC, Gunderson LL. Primary colorectal EBRT and IOERT. Humana Press 1999;249-72.
31. Willett CG, Nakfoor BK, Daley W, et al. Pathological downstaging does not guide the need for IORT in primary locally advanced rectal cancer. Front Radiat Ther Oncol 1997;31:245-246.
32. Francois Y, Nemoz CJ, Baulieux J, et al. Influence of the interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter-sparing surgery for rectal cancer: the Lyon R90-01 randomized trial. J Clin Oncol 1999;17:2396.
33. Kalady MF, de Campos-Lobato LF, Stocchi L, et al. Predictive factors of pathologic complete response after neoadjuvant chemoradiation for rectal cancer. Ann Surg 2009;250:582-589.

34. Evans J, Tait D, Swift I, et al. Timing of surgery following preoperative therapy in rectal cancer: the need for a prospective randomized trial? Dis Colon Rectum 2011;54:1251-1259.
35. Garcia-Aguilar J, Smith DD, Avila K, et al. Optimal timing of surgery after chemoradiation for advanced rectal cancer: preliminary results of a multicenter, nonrandomized phase II prospective trial. Ann Surg 2011;254:97-102.
36. Tulchinsky H, Shmueli E, Figer A, et al. An interval >7 weeks between neoadjuvant therapy and surgery improves pathologic complete response and disease-free survival in patients with locally advanced rectal cancer. Ann Surg Oncol 2008;15:2661-2667.
37. de Campos-Lobato LF, Geisler DP, da Luz Moreira A, et al. Neoadjuvant therapy for rectal cancer: the impact of longer interval between chemoradiation and surgery. J Gastrointest Surg 2011;15:444-450.
38. Dolinsky CM, Mahmoud NN, Mick R, et al. Effect of time interval between surgery and preoperative chemoradiotherapy with 5-fluorouracil or 5-fluorouracil and oxaliplatin on outcomes in rectal cancer. J Surg Oncol 2007;96:207-212.
39. Stein DE, Mahmoud NN, Anne PR, et al. Longer time interval between completion of neoadjuvant chemoradiation and surgical resection does not improve downstaging of rectal carcinoma. Dis Colon Rectum 2003;46:448-453.
40. Lim SB, Choi HS, Jeong SY, et al. Optimal surgery time after preoperative chemoradiotherapy for locally advanced rectal cancers. Ann Surg 2008;248:243-251.
41. Collette L, Bosset JF, den Dulk M, et al. Patients with curative resection of cT3-4 rectal cancer after preoperative radiotherapy or radiochemotherapy: does anybody benefit from adjuvant fluorouracil-based chemotherapy? A trial of the European Organisation for Research and Treatment of Cancer Radiation Oncology Group. J Clin Oncol 2007;25:4379-4386.
42. Gray R, Barnwell J, McConkey C, et al. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. Lancet 2007;370:2020-2029.
43. Bosset JF, Calais G, Mineur L, et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. Lancet Oncol 2014;15:184-190.
44. Hong TS, Ryan DP. Adjuvant Chemotherapy for Locally Advanced Rectal Cancer: Is It a Given? J Clin Oncol 2015;33:1878-1880.

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Rectal cancer: do protons have prospects?

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Preoperative chemoradiation and preoperative short course radiotherapy have widely been accepted as standards of care for stage II and III rectal cancer. However, pelvic radiotherapy can lead to significant rates of acute and late toxicity. Advances in radiation therapy technique and newer radiation therapy modalities could potentially reduce acute and late toxicity rates, by limiting radiation exposure to normal tissues. In this issue, Colaco *et al.* report a dosimetric study comparing proton therapy with 3-dimensional conformal radiotherapy (3D-CRT) and intensity modulated radiation therapy (IMRT), in an effort to lower treatment-related toxicity (1).

Colaco *et al.* report that proton therapy reduced bone marrow exposure and small bowel exposure, compared to both IMRT and 3D-CRT. Proton therapy also reduced bladder exposure, compared to 3D-CRT, but not compared to IMRT. Their findings are similar to that reported by previous studies on proton therapy for rectal cancer, which also showed that proton therapy reduced normal tissue exposure compared to 3D-CRT and IMRT (2-4). However, all of these studies have been dosimetric analyses and not clinical evaluations. While proton therapy does appear to reduce normal tissue exposure, it remains unknown whether this reduction will lead to differences in acute and late toxicity.

Clinical studies, ideally prospective trials, will be necessary to evaluate the role of proton therapy in the neoadjuvant treatment of rectal cancer. However, it will be difficult to design such studies. Treatment-related toxicity in rectal cancer patients is multifactorial, arising from the combination of chemotherapy, radiation therapy and surgery. Hence, it may be difficult to discern the contribution of radiation therapy to toxicity. If the use of proton therapy leads to only a modest-sized reduction in toxicity, then a large sample size will be required to demonstrate the benefit of proton therapy. Furthermore, long follow-up will be required to evaluate late toxicity. Similar challenges have made it difficult to evaluate the role of IMRT for rectal cancer. While multiple dosimetric studies have shown that IMRT reduces normal tissue exposure, only a limited number of retrospective studies have shown reductions in acute toxicity; furthermore, a prospective study did not show a significant difference in acute toxicity with the use of IMRT compared to conventional radiotherapy (5-8).

Proton therapy for rectal cancer may be associated with certain technical challenges. For example, proton range is highly dependent on the stopping power of different substances; proton range is much higher in air than in tissue. Changes in rectal gas volume may therefore affect proton range, leading to either undercoverage of the target or overexposure of normal tissues. In Colaco *et al.*'s study, Hounsfield units were overridden for air in the rectum. Hence, this study did not account for uncertainties arising from rectal gas. Further studies are needed on such technical factors.

Proton therapy may have a potential role in some specific clinical situations. Proton therapy may reduce the risk of second malignancies in patients undergoing radiation therapy for rectal cancer at a young age. Proton therapy may also have a role in reirradiation for rectal cancer, in patients previously treated with pelvic radiation therapy. While it is difficult to develop clinical trials for such uncommon indications, retrospective studies may help us better understand the role of proton therapy in these situations.

Studies on proton therapy have explored one way of decreasing radiation-related toxicity: reduction in the dose

to normal tissues. However, another way of decreasing toxicity could be patient selection, i.e., reduction in the number of patients treated with radiation therapy. A large phase II/III trial (PROSPECT) is currently comparing standard preoperative chemoradiation versus induction chemotherapy and selective radiotherapy for rectal cancer. A prospective European trial (MERCURY) has indicated that MRI could be used to identify patients likely to have a good outcome with surgery alone without preoperative radiotherapy (9). In the future, more selective use of radiation may help lower treatment-related toxicity in rectal cancer patients.

In summary, Colaco *et al.* have presented an intriguing dosimetric study on the role of proton therapy for the treatment of rectal cancer. Clinical studies will be needed to further elucidate the potential role of proton therapy.

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Footnote

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References

1. Colaco RJ, Nichols RC, Huh S, et al. Protons offer reduced bone marrow, small bowel, and urinary bladder exposure for patients receiving neoadjuvant radiotherapy for resectable rectal cancer. J Gastrointest Oncol 2014;5:3-8.
2. Tatsuzaki H, Urie MM, Willett CG. 3-D comparative study of proton vs. x-ray radiation therapy for rectal cancer. Int J Radiat Oncol Biol Phys 1992;22:369-374.
3. Wolff HA, Wagner DM, Conradi LC, et al. Irradiation with protons for the individualized treatment of patients with locally advanced rectal cancer: a planning study with clinical implications. Radiother Oncol 2012;102:30-37.
4. Palmer M, Mok H, Ciura K, et al. Dose Reduction to Small Bowel and Other Relevant Structures in Rectal Carcinoma with Proton Therapy. Int J Radiat Oncol Biol Phys 2012;84:S846.
5. Mok H, Crane CH, Palmer MB, et al. Intensity modulated radiation therapy (IMRT): differences in target volumes and improvement in clinically relevant doses to small bowel in rectal carcinoma. Radiat Oncol 2011;6:63.
6. Samuelian JM, Callister MD, Ashman JB, et al. Reduced acute bowel toxicity in patients treated with intensity-modulated radiotherapy for rectal cancer. Int J Radiat Oncol Biol Phys 2012;82:1981-1987.
7. Garofalo M, Moughan J, Hong T, et al. RTOG 0822: A Phase II Study of Preoperative (PREOP) Chemoradiotherapy (CRT) Utilizing IMRT in Combination with Capecitabine (C) and Oxaliplatin (O) for Patients with Locally Advanced Rectal Cancer. Int J Radiat Oncol Biol Phys 2011;81:S3-S4.
8. Jabbour SK, Patel S, Herman JM, et al. Intensity-modulated radiation therapy for rectal carcinoma can reduce treatment breaks and emergency department visits. Int J Surg Oncol 2012;2012:891067.
9. Taylor FG, Quirke P, Heald RJ, et al. Preoperative high-resolution magnetic resonance imaging can identify good prognosis stage I, II, and III rectal cancer best managed by surgery alone: a prospective, multicenter, European study. Ann Surg 2011;253:711-719.

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Genomic predictor of complete response after chemoradiotherapy in rectal cancer

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Comment on: Sebio A, Salazar J, Páez D, *et al*. EGFR ligands and DNA repair genes: genomic predictors of complete response after capecitabine-based chemoradiotherapy in locally advanced rectal cancer. Pharmacogenomics J 2015;15:77-83.

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A multimodal approach to locally advanced (cT3, 4 and/or N+) rectal cancer, based on the use of concurrent chemo-radiotherapy followed by radical surgery with total mesorectal excision, has led to a significant improvement in oncologic outcomes (1,2). This therapeutic approach also improves tumor resectability and increases the chance to preserve anal sphincter (3,4). For these reasons, neoadjuvant chemoradiotherapy (nCRT) followed by surgery has become the standard treatment for locally advanced rectal cancer.

However, the response to nCRT varies substantially in each individual patient, which is considered as an important prognostic factor (5-8). Currently, there is no definite method to predict a tumor response to nCRT. Determination of factors predicting tumor regression after nCRT is important, which would permit tailored treatment strategies that include fewer invasive surgical approaches or intensified neoadjuvant treatment in patients with a lower likelihood of responding (9,10).

To date, multiple factors have been suggested as a putative predictive factor for tumor regression. Clinical factors include performance status, tumor stage, tumor mobility and circumference of the rectal wall involved by tumor (11). Treatment factors include radiation dose and time elapsed from radiation to surgery (12,13). Additionally, there are various biologic factors that may be involved in the tumor response process such as specific gene or protein expression and genetic mutation (14).

As a biologic factor, genetic polymorphisms have been investigated to reveal the association with tumor regression after nCRT. In the previous study, patients with specific thymidylate synthase (TS) single nucleotide polymorphism (SNP) showed significantly greater downstage of rectal cancer after nCRT (15). Also, polymorphisms in the *EGFR* gene have been investigated but the results were not confirmed as predictive markers of response (16).

A recent *The Pharmacogenomics Journal* paper entitled "EGFR ligands and DNA repair genes: genomic predictors of complete response after capecitabine-based chemoradiotherapy in locally advanced rectal cancer" investigated the association between tumor response to capecitabine-based nCRT and polymorphism in genes involved in the fluoropyrimidine metabolism (TS), the DNA repair (ERCC1, XPD, XRCC1) and the EGFR pathway (EGFR, EGF, *AREG* and EREG). A total of 84 patients with rectal cancer underwent capecitabine-based nCRT were included. Analyzing SNPs in the selected genes from blood samples by means of genotyping, the associations of pathological response to nCRT with each SNP were investigated. This study showed significant associations of two SNPs with pCR; rs11942466 C>A polymorphism in *AREG* gene and rs11615 C>T in *ERCC1* gene. Authors suggested these SNPs as a potential biomarker for pCR after capecitabine based chemoradiation.

The EGFR pathway and DNA repair mechanism were revealed to involve in the resistance to radiotherapy (17).

Several studies have found a relationship between the expression of these genes and tumor response after nCRT in rectal cancer (18). However, limited data are available on the polymorphisms in *AREG* or *ERCC1* genes and the radiotherapy response (19). Furthermore, in the field of specific haplotypes and genetic polymorphisms, the data for SNPs is limited and only a few genes have been the candidate for genotyping such as TS and EGFR. In this context, the result of this study has substantial clinical importance.

Genetic polymorphisms are promising predictive biomarker because drug resistance or severe toxicity might be related to genetic variations in tumor cells and/or to the genetic background of each patient. However, it requires higher levels of evidence before they can be considered clinically useful. Thus retrospective studies on large numbers of samples with detailed clinical data, and prospective pharmacogenetic-guided clinical trials, albeit challenging, are needed. These gene polymorphisms could be candidate markers for such further studies.

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References

1. Du CZ, Li J, Cai Y, et al. Effect of multidisciplinary team treatment on outcomes of patients with gastrointestinal malignancy. World J Gastroenterol 2011;17:2013-2018.
2. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001;345:638-646.
3. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus Postoperative Chemoradiotherapy for Rectal Cancer. N Engl J Med 2004;351:1731-1740.
4. Roh MS, Colangelo LH, O'Connell MJ, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. J Clin Oncol 2009;27:5124-5130.
5. Rödel C, Martus P, Papadoupolos T, et al. Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. J Clin Oncol 2005;23:8688-8696.
6. Eich HT, Stepien A, Zimmermann C, et al. Neoadjuvant radiochemotherapy and surgery for advanced rectal cancer: prognostic significance of tumor regression. Strahlenther Onkol 2011;187:225-230.
7. Fokas E, Liersch T, Fietkau R, et al. Tumor regression grading after preoperative chemoradiotherapy for locally advanced rectal carcinoma revisited: updated results of the CAO/ARO/AIO-94 trial. J Clin Oncol 2014;32:1554-1562.
8. Maas M, Nelemans PJ, Valentini V, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol 2010;11:835-844.
9. Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg 2004;240:711-717.
10. Smith FM, Waldron D, Winter DC. Rectum-conserving surgery in the era of chemoradiotherapy. Br J Surg 2010;97:1752-1764.
11. Janjan NA, Abbruzzese J, Pazdur R, et al. Prognostic implications of response to preoperative infusional chemoradiation in locally advanced rectal cancer. Radiother Oncol 1999;51:153-160.
12. Glimelius B, Isacsson U, Jung B, et al. Radiotherapy in addition to radical surgery in rectal cancer: evidence for a dose-response effect favoring preoperative treatment. Int J Radiat Oncol Biol Phys 1997;37:281-287.
13. Francois Y, Nemoz CJ, Baulieux J, et al. Influence of the interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter-sparing surgery for rectal cancer: the Lyon R90-01 randomized trial. J Clin Oncol 1999;17:2396.
14. Kim NK, Hur H. New Perspectives on Predictive Biomarkers of Tumor Response and Their Clinical Application in Preoperative Chemoradiation Therapy for Rectal Cancer. Yonsei Med J 2015;56:1461-1477.
15. Hur H, Kang J, Kim NK, et al. Thymidylate synthase gene polymorphism affects the response to preoperative 5-fluorouracil chemoradiation therapy in patients with rectal cancer. Int J Radiat Oncol Biol Phys 2011;81:669-676.
16. Molinari C, Matteucci F, Caroli P. Biomarkers and Molecular Imaging as Predictors of Response to Neoadjuvant Chemoradiotherapy in Patients With Locally Advanced Rectal Cancer. Clin Colorectal Cancer 2015;14:227-238.

17. Liang K, Ang KK, Milas L, et al. The epidermal growth factor receptor mediates radioresistance. Int J Radiat Oncol Biol Phys 2003;57:246-254.
18. Bertolini F, Bengala C, Losi L, et al. Prognostic and predictive value of baseline and posttreatment molecular marker expression in locally advanced rectal cancer treated with neoadjuvant chemoradiotherapy. Int J Radiat Oncol Biol Phys 2007;68:1455-1461.
19. Spindler KL, Nielsen JN, Lindebjerg J, et al. Prediction of response to chemoradiation in rectal cancer by a gene polymorphism in the epidermal growth factor receptor promoter region. Int J Radiat Oncol Biol Phys 2006;66:500-504.

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Neoadjuvant chemoradiation therapy for rectal cancer: current status and perspectives for the surgeon

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Abstract: Modern management of rectal cancer has become increasingly complex over the last decades. The introduction of neoadjuvant chemoradiation to the treatment strategy of locally advanced and distal rectal cancers has added numerous variables that may ultimately affect final surgical or even non-surgical management. Specific chemoradiation regimens, intervals after neoadjuvant treatment completion and tools for the assessment of tumor response may all affect final surgical decision and should be interpreted with care. The present study attempts to provide a review of commonly used neoadjuvant chemoradiation regimens, specific intervals and final surgical or non-surgical management of rectal cancer in current clinical practice.

Keywords: Rectal cancer; neoadjuvant therapy; total mesorectal excision (TME)

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Introduction

Significant changes in the clinical management of rectal cancer over the past 15 years have occurred. Prior perioperative chemotherapy or radiation therapy, recurrence rates could reach 40% in patients with locally advanced rectal cancers (1). Over the years, the increasing importance given to pre- and post-treatment staging, pre-operative multimodal treatment, new surgical techniques and detailed pathological analyses has contributed to improvement in the treatment and survival of these patients. Therefore, the management of patients with rectal cancer has become multidisciplinary requiring a coordinated effort from physicians and surgeons and with regular multidisciplinary requiring a coordinated effort from multiple specialties and with regular meetings as the best way to obtain synchronization (2).

The changes incorporated in the management of advanced rectal cancer have emphasized a more individualized approach aiming to provide oncological safety preserving functional outcomes and quality of life. Alongside with the establishment of total mesorectal excision (TME) (3), one of the most important interventions pertains the use of chemoradiation therapy (CRT), which has been part of the treatment of rectal cancer since the 1990s. Therefore, treatments potentially associated with decreased morbidity, improved functional and quality of life outcomes are of significant interest to patients and payer stakeholders (4).

In the following pages, we review the current evidence on the present and future use of CRT in the treatment of patients with locally advanced rectal cancer.

First things first: the role of TME

For patients with advanced rectal cancer, surgery remains the

pillar of curative treatment. Complete TME accomplished through an appropriate surgical technique is required to assure adequate oncological outcomes and minimize intra and postoperative complications (5,6). A precise dissection between the visceral mesorectal fascia and the parietal endopelvic fascia using a conventional or minimally invasive approach enables complete *en bloc* removal of the primary tumor and associated mesorectal lymph nodes. Proper TME also prevents autonomic nerve injuries and intraoperative bleeding. This operation should be conducted by experienced surgeons in the management of rectal cancer, with lower complication rates and improved survival (7).

One of the major determinants for local recurrence is the presence of neoplastic foci within parts of mesorectum left behind (non-resected) (5). Distal mesorectal spread often extends further than intramural spread, resulting in nests of cancer cells away from the primary tumor as far as 3 to 4 cm (8). Therefore, in upper rectal tumors, the mesorectal excision (also called tumor-specific or partial) should extend at least for 5 cm beyond the distal edge of the primary tumor, whereas TME is required mid and low rectal tumor (9). These issues were addressed by Heald *et al.* with the first description of TME reported in 1982 (3). TME alone in selected cases may provide rates of local recurrence as low as 5–10%.

Another crucial surrogate marker used for local control is obtaining an adequate circumferential radial margin (CRM). Addressed in the pre-treatment staging most commonly through dedicated high-resolution magnetic resonance, imaging studies are mandatory for TME planning and decision for the need of neoadjuvant therapy (10). A pathologically compromised (≤1 mm) circumferential resection margin [(+) CRM] is an independent predictor of local recurrence and decreased survival (5).

Neoadjuvant chemoradiation therapy (nCRT): since when and why?

Multimodality treatment, instead of surgery alone, was initially given postoperatively, for the curative treatment of locally advanced rectal cancer. Before broad adoption and practice of TME surgery, multimodality therapy had become standard for patients with locally advanced rectal cancers (2). The efficacy of postoperative CRT was demonstrated in the GTSG and NSABP R-01 trials (11,12). In the GTSG-7175 study, it was observed a significant decrease in the overall recurrence rate after adjuvant CRT when compared to the surgery alone group (33% *vs.* 55%) (11). Despite not showing a difference in overall survival (OS) among groups, the CRT group had a longer time to (tumor) recurrence. Conversely, in the NSABP R-01 trial, in which surgery alone was compared with surgery plus adjuvant radiation or plus adjuvant chemotherapy, patients treated with adjuvant chemotherapy had an improved disease-free survival (DFS), despite similar rates of local or distant recurrences (12). The results of these two studies formed the basis for the 1990 U.S. National Cancer Institute Consensus Statement, that recommended adjuvant therapy for stage II and III rectal cancer (13). It was not before 1991 that the first study reporting benefits of adjuvant CRT for decreasing local recurrence rates and prolonging 5-year overall and DFS was published (14).

The initial considerations among investigators regarding neoadjuvant CRT (nCRT) was based on its potential to promote primary tumor and lymph nodes downstaging in a more oxygenated and unscarred tumor tissue allowing easier resection and eventually increasing the chance of sphincter-preserving surgery. Additional benefits included decreased toxicity due to smaller volume of irradiated small bowel, and improved functional outcomes for not irradiating a low colorectal or coloanal anastomosis.

Neoadjuvant therapy for rectal cancer is accomplished more commonly by selecting one of two main strategies: preoperative short-course radiotherapy (SCRT), and long-course nCRT. The SCRT consists of 5 Grays (Gy) of external beam radiotherapy delivered daily for 5 days (5×5 Gy) without chemotherapy and surgery performed within 1 week. In the long-course nCRT, preoperative external beam RT using 1.8 to 2 Gy daily doses are delivered with concurrent administration of 5-fluorouracil-based chemotherapy over 5–6 weeks. The full dose reaches 45 to 50.4 Gy and is followed by radical surgery after 8–12 weeks of resting period.

The Swedish Rectal Cancer Trial reported that patients submitted to SCRT have a lower recurrence rate (11% *vs.* 27%), a higher 5-yr OS (58% *vs.* 48%; 75 months follow-up), and cancer-specific survival at 9 years (74% *vs.* 65%) when compared to patients without radiotherapy (15). Moreover, better long-term oncologic outcomes were confirmed in a later update (16). A survival benefit for rectal cancer patients assigned to preoperative SCRT remains exclusively associated with this trial. As TME was not the standard technique during this trial, the external validity of the Swedish trial is difficult to estimate, especially if we highlight a 27% local recurrence rate in the surgery alone group.

Meanwhile, the Dutch TME trial also demonstrated better local control after 2 and 10 years for tumors located below 10 cm from the anal verge, when comparing SCRT and TME alone (17,18). However no impact on OS was observed. Moreover, if we consider a subgroup analysis of patients with pathological stage III rectal cancer undergoing TME and negative CRM, survival was better after 10 years (50% *vs.* 40%; P=0.032) in the SCRT group.

The next logical step would be to verify the potential advantages of neoadjuvant compared to adjuvant CRT. The German trial randomized patients to nCRT and TME or TME followed by adjuvant CRT (19). The experimental group treatment consisted of 5,040 cGy, concurrently with infusional 5-FU. All patients underwent TME 6 weeks after the completion of CRT and had 4 additional cycles of adjuvant 5-FU, one month after TME. The control group had identical postoperative treatment, except for the delivery of a 540 cGy boost in this group. Those that received nCRT had significantly lowered 5-yr (6% *vs.* 13%; P=0.006) and 10-yr local recurrence rates (7% *vs.* 10%; P=0.048) (19,20). Distant recurrence, overall, and DFS rates were similar between the two groups. Downstaging was significantly more frequent in the preoperative group as expected. In the nCRT group, 8% had developed pathologic complete response (pCR), and 25% had positive lymph nodes (40% in the postoperative group). In addition to the benefits in final pathological staging, the preoperative group had a higher chance of completing the treatment than the control group.

Although two other trials aimed to compare nCRT with postoperative CRT in the U.S., both the Radiation Therapy Oncology Group and the National Surgical Adjuvant Breast and Bowel Project were prematurely terminated due to insufficient accrual.

Current evidence supports that, combined with radical surgery, nCRT for advanced rectal cancer, results in a statistically significant reduction in local recurrence rates. Additionally, long-course CRT may reduce the odds for a CRM+ and may positively impact the rates of sphincter-preserving operation even though there is still insufficient evidence to fully support this (21). Altogether, following the publication of the German Trial, long-course nCRT became the new standard of care for patients with advanced rectal cancer.

nCRT: how? Short- versus long-course nCRT

An alternative strategy to long-course nCRT is the use of SCRT for the treatment of patients with operable rectal cancer, as previously reported by the Swedish and Dutch studies. A shorter neoadjuvant approach at a reduced cost are main attractive when considering SCRT.

The comparison of clinical results between SCRT and nCRT was addressed in two main trials.

In the Polish trial, no difference regarding sphincter-preserving rates was observed between the two groups (respectively, 61.2% and 58%). However, long-course nCRT was associated with more tumor donwnstaging (pCR: 16.1% after nCRT *vs.* 0.7% after neoadjuvant SCRT) and a lower rate of (+) CRM (12.9% *vs.* 4.4%) (22). In the long-term follow-up no difference was observed between the groups regarding local recurrence and overall survival. It is important to notice though that this trial was designed to evaluate if long-course CRT could lead to more sphincter-preserving surgery, and was not properly powered to evaluate difference regarding recurrence and survival. Despite meaningful downsizing, long-course nCRT did not result in increased sphincter preservation rate. The issue of defining the type of operation to be performed based on pre-multimodality treatment tumor characteristics may have certainly contributed to the results of this trial.

In the Trans-Tasman Radiation Oncology Group (TROG) Trial, the main outcome was local recurrence after treatment. Also in this study no difference was observed among the two groups in local or distant recurrence rates and overall survival. Again, after long-course nCRT, tumor downstaging was more frequently observed. However, when Annual Percentage Rates (APRs) are considered in each treatment, as observed in the Polish trial, no benefit (79% *vs.* 77%) could be attributed to a long-course treatment (23).

According to the MERCURY trial, magnetic resonance imaging (MRI) may have established standards for the identification of patients with high-risk rectal cancers (24). For patients with clearly resectable cancers, TME alone may provide excellent local and systemic control. On the other hand, for patients harboring features associated with a high risk for local recurrence, long-course nCRT remains the preferred option. Finally, in an intermediate group, SCRT followed by immediate surgery is an undeniably clever strategy.

The main drawback for nCRT is treatment-related toxicity, especially in frail patients. The efforts in avoiding toxicity, by omitting chemotherapeutic agents may negatively affect efficacy. Ultimately, since there is significant morbidity associated with radical surgery for rectal cancer, complicated cases may not be fit enough

to receive adjuvant chemotherapy leading to low overall compliance rates.

Despite the disadvantages of long-course nCRT toxicity, SCRT is still not the new standard of care (25). In the currently ongoing RAPIDO trial, patients with high-risk rectal cancer as determined by MRI are randomized to nCRT (25×1.8 or 25×2 Gy with capecitabine) and selective postoperative adjuvant chemotherapy or SCRT (5×5 Gy) followed by full-dose chemotherapy (26). These results may significantly contribute to the understanding of current options in neoadjuvant therapy.

Optimal interval between nCRT and radical surgery: pursuing pCR

In an attempt to increase tumor response to nCRT and the rates of pCR, some groups proposed to increase the interval between CRT and radical surgery. Most commonly, TME has been recommended 6–8 weeks after CRT completion to maximize tumor regression and avoid extensive fibrosis (27-30). However, several studies have shown that longer intervals between CRT and surgery may increase the rates of pCR without increasing perioperative complications or worsening the oncologic outcomes (27,29,30). This is still a matter of debate in rectal management, without agreement over which is the best interval.

The issue concerning the interval between nCRT completion and radical operation exists for a long time. In the Lyon R90-01 Trial, patients were randomized to be operated after 2 or 6 weeks after CRT completion (31). Clinical response increased from 53.1% to 71.7% in the group randomized for longer interval. Since these results were published, 6 weeks become the standard of interval for operation after CRT.

However this interval did not seem enough. In 2004, Moore *et al.* have shown that the rate of pCR increased from 9% to 23% comparing patients operated before 6 weeks after nCRT completion and those that waited more than 7 weeks (27). A few years later, Tulchinsky *et al.* demonstrated that the pCR rates were higher after a longer (>7 *vs.* ≤7 weeks) interval between nCRT completion and surgery: 35% *vs.* 17% (P=0.03). And that those patients operated after 7 weeks had significantly better DFS (P=0.05) (28).

Habr-Gama *et al.* waited longer in their retrospective study comparing patients operated ≤12 weeks with those operated >12 weeks from nCRT completion (30). They observed similar rates of OS and DFS suggesting the safety of this approach. Also Kalady *et al.* observed higher rates of pCR when waiting longer than 8 weeks, and that these patients had better OS and local recurrence-free survival after 5 years than patients with incomplete response (32). Moreover, the local recurrence rate after 3 years was significant lower in the >8 weeks group (1.2% *vs.* 3.9%). Ultimately, the same group observed that the postoperative morbidity or mortality were similar between the two groups (29).

Probst *et al.* have published a retrospective observational study comprising information from the U.S. National Cancer Data Base (33). In this study, the association between interval time and pCR, surgical morbidity and tumor downstaging were evaluated in 17,255 patients using different cut-offs (<6, 6–8, >8 weeks). Longer interval was associated with higher pCR rates and tumor downstaging.

Even though a significant amount of retrospective studies supported the potential benefits of prolonged intervals between CRT completion and surgery, the recently reported results from the GRECCAR-6 study has reported rather disappointing outcomes. The comparison between 7 and 11 weeks after CRT completion and radical surgery not only resulted in no differences in pCR rates but also showed inferior outcomes for the 11 weeks interval group in terms of quality of the mesorectum and postoperative morbidity (34).

After standardization of multimodality treatment and proper TME surgery, the development of distant relapse became more relevant than local recurrence. Consequently, postoperative adjuvant chemotherapy should be recommended at least to some (if not all) patients treated with nCRT. However up to 27% of patients eligible to adjuvant chemotherapy never actually receive treatment as a significant amount of patients fail to receive the full-prescribed treatment due to postoperative complications or stoma closure. A systematic review including more than 15,000 patients demonstrated that a 4-week delay in treatment is correlated with a 14% decrease in OS (35). Moreover, the use of chemotherapy in the resting period between nCRT completion and response assessment could potentially increase rates of clinical complete response (cCR). Habr-Gama *et al.* added chemotherapy during this interval, demonstrating an increased rate of cCR. In this prospective study, 34 patients with rectal cancer underwent radiation and 5-fluorouracil-based chemotherapy every 21 days in six cycles (36). The complete response rate was 65% for at least 12 months after nCRT. The authors concluded, although in a preliminary basis, that the addition of chemotherapy during the resting period (also known as

"consolidation" chemotherapy) and after nCRT resulted in considerably high rates of complete response.

Patients harboring tumors that achieve a pCR after nCRT have a better prognosis than the non-responders. In these patients, local recurrence is uncommon and survival is excellent. However, response to chemoradiation is variable. Moreover, the proportion of patients achieving a pCR remains not only unpredictable, but small. Garcia-Aguilar *et al.* conducted a non-randomized trial adding cycles of mFOLFOX6 between nCRT and surgery (37). In the group without additional mFOLFOX6 cycles 18% of patients achieved pCR. In the groups of patients receiving two, four, or six cycles of mFOLFOX6 the pCR rates were 25%, 30%, and 38% respectively.

Current recommendation suggests surgery to be scheduled after 6 to 8 weeks following nCRT completion as the standard. Still, optimal timing of surgery remains controversial with evidence supporting that longer interval may increase tumor downsizing.

Complete clinical response after nCRT and the watch and wait (WW) strategy

nCRT for rectal cancer may result in significant primary tumor downstaging. In fact, the degree of tumor downstaging may lead to clinically relevant consequences in terms of long-term oncologic outcomes. Survival and local disease control seem to be directly related to tumor regression, while complete pathological response is clearly associated with improved oncological outcomes (38). Radical surgery remains the cornerstone of the treatment of patients with locally advanced rectal cancer. However, up to 33% of patients treated with nCRT exhibit a pCR at the time of surgical resection (31). In the setting of a pCR, local recurrence rates lower than 1% and 5-year survival rate higher than 95% lead us to question the true benefit of TME for these patients (38). Moreover, tumor downstaging and pCR may offer the possibility of sparing patients from significant postoperative morbidity associated with TME, avoidance of a definitive stoma or even the need of any surgical resection with an organ-preserving strategy. Also known as the WW approach, it was pioneered in an institutional level in Sao Paulo (39-42).

Regarding radical surgery for rectal cancer after nCRT, several perioperative complications, including vascular injury and presacral bleeding, infection, wound complications, ureteral injury, and both urinary and sexual dysfunction, are associated with this procedure (43). The Dutch TME trial observed in-hospital postoperative mortality and overall complication rates of 3% and 47%, respectively (17,44).

If there is not a viable cancer cell left after nCRT, then radical surgery may not add a clinical benefit at the expense of adding risk for increased morbidity (45). WW precludes pathologic confirmation of the primary tumor and lymph node response. As a result, a cCR is used as a surrogate for pCR. The determination of a cCR is defined after assessment through a combination of digital rectal examination, direct visualization by proctoscopy, and imaging studies with or without biopsy confirmation. The definition of a complete clinical response should be based on strict clinical and endoscopic findings. The finding of any residual superficial ulceration, irregularity, or nodule should prompt surgical attention, including transanal full-thickness excision or even a radical resection with TME. Standard or incisional biopsies should be avoided in this setting (46). Endorectal ultrasound (ERUS) imaging and MRI are useful techniques for rectal cancer staging. In one meta-analysis, ERUS was found to have increased sensitivity for perirectal tissue invasion in comparison with MRI (90% *vs.* 82%). However, regarding imaging of lymph node involvement, both methods had similar rates of sensitivity and specificity (66–67% and 76–78%, respectively) (47). In contrast to the results of baseline imaging evaluation, in a meta-analysis both techniques overstaged (73% and 66%) patients with pCR (ypT0), respectively (48), and also had a poor sensitivity (MRI, 15%; ERUS, 37%) but high specificity (95% for both). Moreover, the accuracy for nodal restaging for both MRI and ERUS has been reported to be approximately 72% (48).

The experience with WW for potentially curable advanced rectal cancer has evolved with time. Most patients in early studies were not staged or followed with modern imaging techniques, including MRI and ERUS, mainly because these techniques were not widely available. Therefore, the assessment of cCR was almost exclusively based on clinical/endoscopic examination. Habr-Gama *et al.* defined that the follow-up of cCR demands intensive follow-up evaluations every 8 weeks after nCRT completion (46). Moreover, a 1-year disease-free interval has been arbitrarily defined in earlier studies for the classification of a cCR in order to rule out early regrowths requiring immediate salvage procedures.

In an early publication, Habr-Gama *et al.* reported the outcomes of 265 patients with distal rectal adenocarcinoma treated with nCRT (5,040 cGy with infusional

5-fluorouracil) (40). Only 26.8% of patients had cCR, 2.8% of patients developed an endoluminal recurrence, successfully salvaged, and 4.2% metastatic disease (57 months follow-up). A larger report confirmed the safety of this approach (42).

Following the published experience regarding WW led by the group of Sao Paulo, other institutions have reported small series regarding multimodality treatment of locally advanced rectal cancer without immediate surgery. Maas *et al.* using MRI found that only 11% of patients were eligible for WW. These patients had a 2-year DFS (89% *vs.* 93%) and OS rates (100% *vs.* 91%) similar to pCR patients. Patients who were treated operatively had more bowel dysfunction.

Appelt *et al.* prospectively evaluated patients with resectable distal rectal adenocarcinoma (49). In this trial, patients underwent high-dose external beam radiation therapy (60 Gy with a 5-Gy endorectal boost) and oral tegafur-uracil. Seventy-eight percent of patients diagnosed with cCR were initially managed without radical surgery. Cumulative local recurrence rates were 15% and 26% for 1- and 2-year follow-up. All patients were surgically salvaged.

Smith *et al.* reported the outcomes of 32 patients with rectal cancer after a 28-month follow-up. Local recurrence for WW group was 21% versus 0% in patients with pCR treated at the same institution (50). Successful salvage surgery was performed on all patients with local failure and outcomes were similar between the groups. This updated data from 73 patients achieving cCR, showed local tumor regrowth in 26% (3.5 years follow-up) and almost all patients were surgically salvaged. Rectal preservation rate for the series was 77%. Overall and DFS were similar between groups.

Habr-Gama *et al.* published the results of 70 patients treated with extended nCRT (also referred to as consolidation nCRT) chemotherapy (51). Forty-seven out of 69 (68%) patients that completed the treatment had cCR 10 weeks after nCRT. Of these, 39 sustained cCR for 12 months. Four developed local recurrence more than one year after nCRT. Overall, 35 (50%) patients have not undergone surgery after a median follow-up of nearly 4 years.

A significant proportion of patients with initial cCR may still develop local failure during the first 12 months of follow-up meaning that significant improvements in appropriate identification of cCR are warranted.

More recently, the OnCoRe project evaluated the acceptance of WW in what they have called "a real world multicentric setting". In this trial, 109 patients who developed cCR after nCRT were managed with no immediate surgery and 109 patients were operated. Patients not operated on immediately had a slight difference in 3-year DFS (88% *vs.* 78 and better colostomy-free survival (74% *vs.* 47%).

Despite these favorable experiences with no immediate surgery after a complete clinical response following nCRT, two studies have been reported recently attempting to caution the use of this WW approach. By querying the National Cancer Database (NCDB) in the U.S., Ellis *et al.* have tried to correlate the absence of surgical resection after nCRT with low-volume centers, uninsured patients and worse long-term survival. However, these studies underscore the importance of restricting such approach only to highly selected patients with thorough assessment of response after nCRT and achieving a complete clinical response. In the NCDB, no information is available regarding tumor response and it is likely that patients in both studies never underwent surgery for reasons other than presenting a cCR. In other words, no surgery after nCRT is very different from no immediate surgery after complete clinical response following nCRT (52-55).

Finally, efforts have been made to minimize the use of neoadjuvant RT. After the experience with exclusively chemotherapy for metastatic disease, the PROSPECT study is investigating the impact of neoadjuvant chemotherapy alone for locally advanced rectal cancer. Patients that develop favorable response to chemotherapy alone may undergo radical surgery or even WW (if complete clinical response is achieved) while only poor responders to chemotherapy are still referred to further (standard) CRT. The idea of delivering upfront chemotherapy is to address micrometastatic disease in addition to avoid the potential disadvantages of radiation therapy to the pelvis. Preliminary data have reported promising outcomes with nearly 30% complete pathological response rate (56).

Conclusions

In conclusion, management of rectal cancer has evolved significantly over the past decades and requires a multidisciplinary approach. Even though local control is now more easily achieved with proper surgical resection, neoadjuvant approaches may provide significant tumor regression allowing for organ-preserving strategies, provided assessment of tumor response shows evidence of complete tumor regression. Future studies addressing

oncological and functional outcomes with these various treatment strategies are warranted to further optimize the roles of surgery, radiation and chemotherapy in this setting.

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Footnote

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References

1. Wanebo HJ, Koness RJ, Vezeridis MP, et al. Pelvic resection of recurrent rectal cancer. Ann Surg 1994;220:586-595; discussion 595-597.
2. Monson JR, Weiser MR, Buie WD, et al. Practice parameters for the management of rectal cancer (revised). Dis Colon Rectum 2013;56:535-550.
3. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery--the clue to pelvic recurrence? Br J Surg 1982;69:613-616.
4. Massarweh NN, Artinyan A, Chang GJ. Neoadjuvant treatment for rectal cancer-A value-based proposition. J Surg Oncol 2016;114:304-310.
5. Quirke P, Durdey P, Dixon MF, et al. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. Lancet 1986;2:996-999.
6. Martling AL, Holm T, Rutqvist LE, et al. Effect of a surgical training programme on outcome of rectal cancer in the County of Stockholm. Stockholm Colorectal Cancer Study Group, Basingstoke Bowel Cancer Research Project. Lancet 2000;356:93-96.
7. Read TE, Myerson RJ, Fleshman JW, et al. Surgeon specialty is associated with outcome in rectal cancer treatment. Dis Colon Rectum 2002;45:904-914.
8. Hida J, Yasutomi M, Maruyama T, et al. Lymph node metastases detected in the mesorectum distal to carcinoma of the rectum by the clearing method: justification of total mesorectal excision. J Am Coll Surg 1997;184:584-588.
9. Scott N, Jackson P, al-Jaberi T, et al. Total mesorectal excision and local recurrence: a study of tumour spread in the mesorectum distal to rectal cancer. Br J Surg 1995;82:1031-1033.
10. Nagtegaal ID, Quirke P. What is the role for the circumferential margin in the modern treatment of rectal cancer? J Clin Oncol 2008;26:303-312.
11. Prolongation of the disease-free interval in surgically treated rectal carcinoma. Gastrointestinal Tumor Study Group. N Engl J Med 1985;312:1465-1472.
12. Fisher B, Wolmark N, Rockette H, et al. Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP protocol R-01. J Natl Cancer Inst 1988;80:21-29.
13. NIH consensus conference. Adjuvant therapy for patients with colon and rectal cancer. JAMA 1990;264:1444-1450.
14. Krook JE, Moertel CG, Gunderson LL, et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. N Engl J Med 1991;324:709-715.
15. Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. N Engl J Med 1997;336:980-987.
16. Folkesson J, Birgisson H, Pahlman L, et al. Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. J Clin Oncol 2005;23:5644-5650.
17. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001;345:638-646.
18. van Gijn W, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol 2011;12:575-582.
19. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731-1740.
20. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol 2012;30:1926-1933.
21. Gerard JP, Rostom Y, Gal J, et al. Can we increase the chance of sphincter saving surgery in rectal cancer with neoadjuvant treatments: lessons from a systematic review of recent randomized trials. Crit Rev Oncol Hematol 2012;81:21-28.
22. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg 2006;93:1215-1223.

23. Ngan SY, Burmeister B, Fisher RJ, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. J Clin Oncol 2012;30:3827-3833.
24. MERCURY Study Group. Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. BMJ 2006;333:779.
25. Minsky BD. Short-course radiation versus long-course chemoradiation for rectal cancer: making progress. J Clin Oncol 2012;30:3777-3778.
26. Nilsson PJ, van Etten B, Hospers GA, et al. Short-course radiotherapy followed by neo-adjuvant chemotherapy in locally advanced rectal cancer--the RAPIDO trial. BMC Cancer 2013;13:279.
27. Moore HG, Gittleman AE, Minsky BD, et al. Rate of pathologic complete response with increased interval between preoperative combined modality therapy and rectal cancer resection. Dis Colon Rectum 2004;47:279-286.
28. Tulchinsky H, Shmueli E, Figer A, et al. An interval >7 weeks between neoadjuvant therapy and surgery improves pathologic complete response and disease-free survival in patients with locally advanced rectal cancer. Ann Surg Oncol 2008;15:2661-2667.
29. de Campos-Lobato LF, Geisler DP, da Luz Moreira A, et al. Neoadjuvant therapy for rectal cancer: the impact of longer interval between chemoradiation and surgery. J Gastrointest Surg 2011;15:444-450.
30. Habr-Gama A, Perez RO, Proscurshim I, et al. Interval between surgery and neoadjuvant chemoradiation therapy for distal rectal cancer: does delayed surgery have an impact on outcome? Int J Radiat Oncol Biol Phys 2008;71:1181-1188.
31. Francois Y, Nemoz CJ, Baulieux J, et al. Influence of the interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter-sparing surgery for rectal cancer: the Lyon R90-01 randomized trial. J Clin Oncol 1999;17:2396.
32. Kalady MF, de Campos-Lobato LF, Stocchi L, et al. Predictive factors of pathologic complete response after neoadjuvant chemoradiation for rectal cancer. Ann Surg 2009;250:582-589.
33. Probst CP, Becerra AZ, Aquina CT, et al. Extended Intervals after Neoadjuvant Therapy in Locally Advanced Rectal Cancer: The Key to Improved Tumor Response and Potential Organ Preservation. J Am Coll Surg 2015;221:430-440.
34. Lefevre JH, Mineur L, Kotti S, et al. Effect of Interval (7 or 11 weeks) Between Neoadjuvant Radiochemotherapy and Surgery on Complete Pathologic Response in Rectal Cancer: A Multicenter, Randomized, Controlled Trial (GRECCAR-6). J Clin Oncol 2016. [Epub ahead of print].
35. Biagi JJ, Raphael MJ, Mackillop WJ, et al. Association between time to initiation of adjuvant chemotherapy and survival in colorectal cancer: a systematic review and meta-analysis. JAMA 2011;305:2335-2342.
36. Habr-Gama A, Perez RO, Sabbaga J, et al. Increasing the rates of complete response to neoadjuvant chemoradiotherapy for distal rectal cancer: results of a prospective study using additional chemotherapy during the resting period. Dis Colon Rectum 2009;52:1927-1934.
37. Garcia-Aguilar J, Chow OS, Smith DD, et al. Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial. Lancet Oncol 2015;16:957-966.
38. Maas M, Nelemans PJ, Valentini V, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol 2010;11:835-844.
39. Habr-Gama A, de Souza PM, Ribeiro U Jr, et al. Low rectal cancer: impact of radiation and chemotherapy on surgical treatment. Dis Colon Rectum 1998;41:1087-1096.
40. Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg 2004;240:711-717; discussion 717-718.
41. Habr-Gama A, Perez RO, Nadalin W, et al. Long-term results of preoperative chemoradiation for distal rectal cancer correlation between final stage and survival. J Gastrointest Surg 2005;9:90-99; discussion 99-101.
42. Habr-Gama A, Perez RO, Proscurshim I, et al. Patterns of failure and survival for nonoperative treatment of stage c0 distal rectal cancer following neoadjuvant chemoradiation therapy. J Gastrointest Surg 2006;10:1319-1328; discussion 1328-1329.
43. Hendren SK, Morris AM. Evaluating patients undergoing colorectal surgery to estimate and minimize morbidity and mortality. Surg Clin North Am 2013;93:1-20.
44. Marijnen CA, Kapiteijn E, van de Velde CJ, et al. Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: report of a multicenter randomized trial. J Clin Oncol 2002;20:817-825.
45. Habr-Gama A, Perez RO. Immediate surgery or clinical

follow-up after a complete clinical response? Recent Results Cancer Res 2014;203:203-210.
46. Habr-Gama A, Perez RO, Wynn G, et al. Complete clinical response after neoadjuvant chemoradiation therapy for distal rectal cancer: characterization of clinical and endoscopic findings for standardization. Dis Colon Rectum 2010;53:1692-1698.
47. Bipat S, Glas AS, Slors FJ, et al. Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MR imaging--a meta-analysis. Radiology 2004;232:773-783.
48. Memon S, Lynch AC, Bressel M, et al. Systematic review and meta-analysis of the accuracy of MRI and endorectal ultrasound in the restaging and response assessment of rectal cancer following neoadjuvant therapy. Colorectal Dis 2015;17:748-761.
49. Appelt AL, Pløen J, Harling H, et al. High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study. Lancet Oncol 2015;16:919-927.
50. Smith JD, Ruby JA, Goodman KA, et al. Nonoperative management of rectal cancer with complete clinical response after neoadjuvant therapy. Ann Surg 2012;256:965-972.
51. Habr-Gama A, Sabbaga J, Gama-Rodrigues J, et al. Watch and wait approach following extended neoadjuvant chemoradiation for distal rectal cancer: are we getting closer to anal cancer management? Dis Colon Rectum 2013;56:1109-1117.
52. Ellis CT, Dusetzina SB, Sanoff H, et al. Long-term Survival After Chemoradiotherapy Without Surgery for Rectal Adenocarcinoma: A Word of Caution. JAMA Oncol 2017;3:123-125.
53. Ellis CT, Samuel CA, Stitzenberg KB. National Trends in Nonoperative Management of Rectal Adenocarcinoma. J Clin Oncol 2016;34:1644-1651.
54. Habr-Gama A, Perez RO. No Surgery After Chemoradiation Is Not Equal to Nonoperative Management After Complete Clinical Response and Chemoradiation. J Clin Oncol 2016. [Epub ahead of print].
55. Habr-Gama A, São Julião GP, Perez RO. Caution! Survival after chemoradiation for rectal without surgery when surgery is required is awful! JAMA Oncol 2016. [Epub ahead of print].
56. Schrag D, Weiser MR, Goodman KA, et al. Neoadjuvant chemotherapy without routine use of radiation therapy for patients with locally advanced rectal cancer: a pilot trial. J Clin Oncol 2014;32:513-518.

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Predicting complete response: is there a role for non-operative management of rectal cancer?

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Abstract: Pre-operative chemoradiotherapy followed by a total mesorectal excision (TME) is the standard of care for patients with locally advanced (stage II or III) rectal cancer. Approximately 20% of patients may achieve a pathologic complete response after chemoradiation therapy (CRT), which has been shown to be associated with better oncologic outcomes. Whether surgery can be avoided in this population is an area of active investigation. Recent studies demonstrated feasibility and safety of non-operative management in patients with clinical complete response (cCR) after chemoradiotherapy. In this article, we set out to review the current data on non-operative management and to identify areas requiring further investigation, including improvement in imaging for reassessment after CRT and identifying the optimal time frame for restaging. As the field moves forward with non-operative management in select patients with rectal cancer, there continues to be a need to better understand the prognostic factors and biomarkers that may more accurately characterize patients who are qualified for this "wait-and-see" approach and thereby avoid overtreatment, potentially leading to improvements in long-term quality of life.

Keywords: Rectal cancer; non-operative management; chemoradiation therapy (CRT)

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Introduction

Surgery has been the cornerstone in the management of patients with resectable rectal cancer. Selected patients with distal rectal, well-differentiated pT1 lesions can be treated with local excision alone with close follow-up. In patients with pT1 tumors with adverse pathologic features, and patients with pT2 tumors, two prospective trials by Radiation Therapy Oncology Group (RTOG) and Cancer and Leukemia Group B (CALGB) Intergroup demonstrated excellent local control rates and survival with local excision followed by adjuvant chemoradiation therapy (CRT) (1,2). Patients with early rectal cancers treated with pre-operative CRT followed by local excision also resulted in excellent local control. Borschitz *et al*. reported a long-term local recurrence rate of 7% in 237 patients with cT2-3 disease who underwent 5-fluorouracil (5-FU)-based CRT followed by local excision (3). The American College of Surgeons Oncology Group (ACOSOG) single-arm, prospective study of T2N0 rectal cancer patients who received neoadjuvant CRT and local excision demonstrated high rates of treatment response, with 34 (44%) of 77 patients experiencing a pathological complete response (pCR) (4).

In patients with more locally advanced (cT3-4) rectal cancers, pre-operative CRT has been used to downstage tumors before planned resection. The landmark German Rectal Cancer Trial randomized 823 patients with cT3-4N+ rectal cancer to either preoperative or postoperative CRT and demonstrated significantly improved local control with preoperative CRT (local recurrence rate at 5 years of 6% *vs*. 13% with adjuvant CRT). Among patients with low-lying tumors who were to require abdominoperineal resection, those received preoperative CRT were twice as likely to undergo a sphincter-sparing operation (5). Another randomized trial by the National Surgical Adjuvant Breast and Bowel Project (NSABP) investigated the same question

but was closed early due to poor accrual. Of the 267 patients enrolled, preoperative CRT demonstrated a trend toward better disease-free survival (DFS) (6).

These studies demonstrated benefits in preoperative CRT in patients with both early and more advanced rectal cancer. It is effective in inducing tumor regression; in fact, approximately 15-27% of patients who undergo preoperative CRT experience a pCR in which no residual tumor is reported on histologic examination of total mesorectal excision (TME) (7). In a meta-analysis by Maas *et al*. including 3,105 patients, of which 484 patients achieved a pCR after preoperative CRT, it was shown that patients with pCR had significantly increased DFS. The 5-year crude DFS was 83% for patients with pCR and 66% for those without (7). Whether surgery and its risk of complications in these patients could have been avoided is a topic of investigation. Until recently, the only means to detect complete response reliably is through surgical resection and microscopic evaluation of the specimen. There is growing evidence that regimented clinical assessment after CRT can reliably identify patients who achieved clinical complete response (cCR), allowing avoidance of immediate surgery. We will discuss the concept of nonoperative management in patients with rectal cancer who achieved cCR after CRT in this article.

"Wait-and-see"

In 2004, Habr-Gama *et al*. first published their experience with 265 patients with resectable cT2-4N0/N+ rectal adenocarcinoma who underwent preoperative CRT consisting of 5,040 cGy over 6 weeks, leucovorin, and bolus 5-FU administrated intravenously for 3 consecutive days on the first and last 3 days of CRT. At 8 weeks, all patients underwent repeat evaluation, including endoscopy with biopsy. In a later report, fluorodeoxyglucose positron-emission tomography (FDG-PET)/computed tomography (CT) was also reported to be used in post-CRT assessment (8). The presence of any significant residual ulcer or positive biopsies was considered incomplete clinical response and the patient went onto TME. Patients without any abnormalities were considered to have cCR and were referred to monthly physical and digital rectal examination (DRE), proctoscopy, biopsies, and serum carcinoembryonic antigen (CEA) level testing for the first year, every 2 months in the second year, and every 6 months in the third year. Abdominal and pelvic CT scans and chest radiographs were repeated every 6 months for the first year. Of the 265 patients, 71 patients had a cCR 8 weeks after CRT and were enrolled in the wait-and-see cohort. The majority of these patients had T3 disease (69%, T2 =20%, T4 =11%) and did not have radiologic evidence of nodal metastasis (77%, N+ =23%). Among the 71 patients, the 5-year overall survival (OS) was 100% and DFS was 92%, compared with 88% and 83%, respectively, among the patients who did not achieve cCR and went onto immediate TME. Only 2 patients in the wait-and-see group developed local recurrence 56 months after CRT completion; they were salvaged by local excision and brachytherapy. These promising results led the authors to conclude that surgical resection may be safely avoided in patients appropriately identified achieving cCR after CRT (9).

Subsequent to their initial publication, the authors published several updates of their experience with patients treated with preoperative 5-FU-based CRT spanning from 1991 to 2009 (10-13). The largest series was composed of 361 patients with cT2-4 tumors and 99 (27%) achieved a sustained cCR at 12 months. Only 5 patients among the 99 cCR patients developed local recurrence. The 5-year DFS was 85% and OS was 93% (11).

In 2011, Maas *et al*. from the Netherlands published a prospective series of 21 patients with a cCR who were managed nonoperatively with a wait-and-see policy (14). Between 2004 and 2010, 192 patients with cT1-3N0-2 were treated with CRT consisting of 5,040 cGy over 28 fractions with concurrent capecitabine. At 6-8 weeks after CRT, magnetic resonance imaging (MRI) was performed. In addition to standard T2-weighted imaging, diffusion-weighted MRI (DWI) was used to determine the presence of residual tumoral tissue (high signal on DWI) at the primary site, and MRI enhanced with either ultra-small superparamagnetic iron oxide or gadofosveset trisodium was used to evaluate nodal status. If no residual tumor was seen on post-CRT MRI, endoscopy with biopsy was performed. A patient was only determined to achieve a cCR when no residual tumor or nodal disease was seen on MRI, no residual tumor was seen at endoscopy, negative biopsy was achieved after CRT, and there was no palpable tumor on DRE. Among the 21 patients who met this criteria, an intensive follow-up protocol was carried out, which consisted of DRE, MRI, endoscopy with biopsies, CT scan of chest and abdomen, and CEA measurements (*Table 1*). With a mean follow-up of 25 months, only 1 patient developed endoluminal recurrence and underwent surgical salvage. The 2-year OS in this cohort was 100% and DFS was 89%. A control cohort of 20 patients who were found to have pCR had a 2-year OS of 91% and DFS of 93%, similar to patients with cCR, and enrolled in the wait-and-see protocol (14).

Table 1 Follow-up schedule of patients who achieved cCR who were enrolled on a wait-and-see policy by Maas *et al*. (14)

Year 1
Every 3 months: CEA, DRE, endoscopy, MRI
Every 6 months: CT for distant staging
Year 2-3
Every 3 months: CEA
Every 6 months: DRE, endoscopy, MRI
Every 12 months: CT for distant staging
Year 4-5
Every 6 months: CEA, DRE, endoscopy, MRI
Every 12 months: CT for distant staging

cCR, clinical complete response; CEA, carcinoembryonic antigen; DRE, digital rectal exam; MRI, magnetic resonance imaging; CT, computed tomography.

Table 2 Summary of key studies of patients who achieved cCR after CRT who did not proceed to surgery

Studies	Patients (n)	Follow-up (months)	LRR (%)	OS (%)	DFS (%)
Habr-Gama *et al*. (11)	122	60	6	5-year: 93	5-year: 85
Maas *et al*. (14)	21	25	5	2-year: 100	2-year: 89
Smith *et al*. (15)	32	28	19	2-year: 97	2-year: 88

cCR, clinical complete response; CRT, chemoradiation therapy; LRR, locoregional recurrence; OS, overall survival; DFS, disease-free survival.

At Memorial Sloan Kettering Cancer Center, a retrospective review of patients treated between January 2006 and August 2010 compared outcomes of 32 stage I-III rectal cancer patients with a cCR to CRT who were treated nonoperatively to 57 patients with a pCR after radical rectal resection. With a median follow-up time of 28 months for the nonoperative group, 6 patients developed local recurrence and all were salvaged surgically. Three of these patients also developed distant metastases. The 2-year distant DFS and OS were similar for nonoperative and rectal resection groups (15). These studies show that, with accurate identification of patients who achieved cCR and rigorous follow-up, patients could be safely monitored without undergoing immediate TME and still have excellent oncologic outcomes. *Table 2* provides a summary of the key nonoperative management studies.

Assessment of complete clinical response

Identifying accurately patients who achieved a cCR after CRT is arguably the most important aspect of a nonoperative approach in rectal cancer management. DRE, while an important clinical practice, has been shown to be a poor method for determining cCR when used alone. In 2005, Guillem *et al*. evaluated DRE immediately preceding resection and found that it only identified 21% of pCR patients, thought to be due to local inflammation and fibrosis interpreted as tumor remnant (16). Endoscopy with biopsy can provide additional information to DRE; nevertheless, a negative biopsy could represent a false negative and persistent disease could not be ruled out. In a prospective study of 46 patients who were treated with preoperative CRT for rectal cancer, 22 patients underwent presurgical endoscopic biopsies. While the biopsies were negative in the 6 patients who were found to have pCR on TME, the biopsies were also negative in 11 of 16 cases with residual cancer, yielding a concordance rate of 59% between endoscopic biopsies and surgical specimens (17). Moreover, neither DRE nor endoscopy assesses for regional nodal status after CRT.

Given the limitations of DRE or endoscopy in restaging after CRT, other modalities are needed to assess for residual disease. Endorectal ultrasound (US), while useful in initial staging, has limited benefits after CRT due to the fibrotic tissue. In a large study of 235 patients comparing post-CRT endorectal US staging and pathologic staging, it was reported that endorectal US only correctly matched the T stage in 54% and N stage in 75% of patients (18). Both FDG-PET and CT scans were evaluated prospectively in a recent study by Guillem *et al*. in the identification of complete response after preoperative CRT (19). A total of 121 patients with rectal cancer were prospectively enrolled in the study, and both FDG-PET and CT scans were obtained before and after CRT. While 26 (21%) patients had a pCR after CRT, only 54% of the pCR patients were classified as having a cCR on preoperative PET scan, and only 19% of the patients were classified as having a cCR on preoperative CT scan. Of the pathologic incomplete responders, PET and CT scans were able to identify 66% and 95% of the patients as incomplete responders, respectively. The authors concluded that neither PET nor CT scan alone has adequate predictive value to be clinically useful in identify patients with complete response after CRT.

In 2013, van der Paardt *et al*. reported a meta-analysis

including 33 studies and 1,556 patients on MRI imaging for restaging locally advanced rectal cancer after neoadjuvant treatments (20). For tumor stage, the authors reported a mean sensitivity of 50% and specificity of 91%. In the subgroup analysis, MRI demonstrated 19% sensitivity and 94% specificity for identifying pT0 disease. This is likely due to conventional MRI's inability to distinguish fibrosis and residual tumor accurately. However, after incorporating functional MRI imaging results, such as DWI or dynamic contrast enhanced MRI, significant improvement in sensitivity in detecting complete tumor response after CRT was seen (84%). The specificity was 85%. Dynamic contrast enhanced MRI provides perfusion characteristics of tumor, and some parameters, such as K(trans), differ markedly between patients with cCR and the incomplete responders (21). Serial T2-weighted MRI during CRT also showed promising results in predicting for tumor pCR. Kluza *et al*. showed that CRT induced a significant decrease in T2-weighted signal intensity distribution of 50% in complete responder. The change in T2-weighted signal intensity resulted in high diagnostic performance for identifying complete responders with an accuracy of 92% in the 39-patients study (22). For nodal stage, MRI results in a mean sensitivity of 77% and specificity of 60% (20). With a low prevalence of involved nodes after CRT, the negative predictive value of MRI was 80-90%. Gadofosveset-enhanced MRI, used in the Dutch study, demonstrated 80% sensitivity and 97% specificity in nodal staging with experienced readers (23).

From the above studies, it is appropriate to conclude that determining cCR after CRT requires utilization of multiple methods in restaging and not a single modality alone. As demonstrated by Habr-Gama *et al*. and Maas *et al*., accurate identification of cCR is achievable with a combination of physical examination, endoscopic examination, and imaging, leading to minimal local recurrence rate with nonoperative management. With the emergence of functional MRI imaging, it is hoped there will be further improvements in our accuracy in determining a cCR to therapy.

Timing of assessment

In addition to methods of assessing cCR, another area that requires further investigation is timing of examination after preoperative CRT. The reports from Habr-Gama *et al*. recommended a minimum of 6-8 weeks or longer interval after CRT for assessment of cCR (24). The Dutch series evaluated response at a mean of 6.5 weeks after CRT (14). There is lack of standardization in the timing of examination. As response continues over time, it is possible that more patients with cCR can be captured with longer wait times. A recent meta-analysis of 13 trials including 3,584 patients aimed to answer the question of whether a longer interval between the end of neoadjuvant CRT and surgery is associated with a higher pCR rate. Patients were divided into two groups: patients who underwent TME shorter than 6-8 weeks after CRT *vs*. patients who underwent TME longer than 6-8 weeks after CRT. A longer wait interval, more than the classical 6-8 weeks, from the end of CRT was found to be associated with significantly improved pCR rate (20% *vs*. 14% in patients who waited <6-8 weeks, P<0.001) (25). It has been showed that delaying surgery until after 12 weeks after CRT does not negatively impact oncologic outcomes (8).

Extended chemotherapy

Studies examining new imaging modalities, such as DWI MRI, and determining the optimal clinical assessment time frames are needed. Furthermore, additional chemotherapy after CRT could be another strategy in maximizing clinical response, leading to more patients with cCR qualifying for nonoperative management. Habr-Gamma *et al*. enrolled 70 patients with cT2-4N0-2 rectal cancer prospectively to receive concurrent CRT followed by extended chemotherapy (5-FU/leucovorin for a total of 6 cycles every 21 days). Of the 70 patients, 47 demonstrated clinical response at 10 weeks after CRT and went on to complete extended chemotherapy. Of the 47 patients, 39 demonstrated sustained cCR for 12 months after extended chemotherapy and 4 patients developed local recurrence >12 months after chemotherapy. Overall, 35 (50%) patients never underwent surgery due to sustained cCR (26). The Timing of Rectal Cancer Response to Chemoradiation consortium conducted a prospective, multicenter, Phase II study investigating extending the interval between CRT and surgery and administering additional chemotherapy during waiting period. Sixty patients underwent TME 6 weeks after completion of 5-FU-based CRT, and 67 patients with evidence of clinical response 4 weeks after CRT received 3 additional cycles of modified FOLFOX (5-FU, leucovorin, oxaliplatin) chemotherapy followed by TME 3-5 weeks later. The pCR rate was higher in patients who received additional chemotherapy (25% *vs*. 18% in those who did not receive additional chemotherapy) (27). Cercek *et al*. showed in 2014 that induction chemotherapy, followed by CRT then surgery is another possible approach to maximize cCR. In

this study, FOLFOX chemotherapy was given before CRT. Of the 49 patients who underwent TME after FOLFOX followed by CRT, 47% had tumor response >90%, including 27% of patients achieving a pCR (28).

Conclusions

Nonoperative management is an emerging trend in the treatment of rectal cancer. It has the benefits of reducing surgery-related toxicities. Modern studies with rigorous post-CRT assessments demonstrated that accurately identifying patients with cCR and avoiding/delaying surgery is feasible. Intensive follow-up regimen is needed to ensure lack of clinical progression. Despite the significant progress the field has made in moving toward nonoperative management, it continues to be an area that requires organized investigations. Developing reliable methods for repeat staging after CRT, determining the optimal time frame for maximal response assessment, and understanding the role of additional chemotherapy after CRT can all potentially allow us to capture more patients with cCR that are suitable for the wait-and-see approach, preventing overtreatment in patients with rectal cancer.

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Footnote

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References

1. Russell AH, Harris J, Rosenberg PJ, et al. Anal sphincter conservation for patients with adenocarcinoma of the distal rectum: long-term results of radiation therapy oncology group protocol 89-02. Int J Radiat Oncol Biol Phys 2000;46:313-322.
2. Steele GD Jr, Herndon JE, Bleday R, et al. Sphincter-sparing treatment for distal rectal adenocarcinoma. Ann Surg Oncol 1999;6:433-441.
3. Borschitz T, Wachtlin D, Möhler M, et al. Neoadjuvant chemoradiation and local excision for T2-3 rectal cancer. Ann Surg Oncol 2008;15:712-720.
4. Garcia-Aguilar J, Shi Q, Thomas CR Jr, et al. A phase II trial of neoadjuvant chemoradiation and local excision for T2N0 rectal cancer: preliminary results of the ACOSOG Z6041 trial. Ann Surg Oncol 2012;19:384-391.
5. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731-1740.
6. Roh MS, Colangelo LH, O'Connell MJ, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. J Clin Oncol 2009;27:5124-5130.
7. Maas M, Nelemans PJ, Valentini V, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol 2010;11:835-844.
8. Habr-Gama A, Perez RO, Proscurshim I, et al. Interval between surgery and neoadjuvant chemoradiation therapy for distal rectal cancer: does delayed surgery have an impact on outcome? Int J Radiat Oncol Biol Phys 2008;71:1181-1188.
9. Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg 2004;240:711-717; discussion 717-718.
10. Habr-Gama A, Perez RO, Nadalin W, et al. Long-term results of preoperative chemoradiation for distal rectal cancer correlation between final stage and survival. J Gastrointest Surg 2005;9:90-99; discussion 99-101.
11. Habr-Gama A, Perez RO, Proscurshim I, et al. Patterns of failure and survival for nonoperative treatment of stage c0 distal rectal cancer following neoadjuvant chemoradiation therapy. J Gastrointest Surg 2006;10:1319-1328; discussion 1328-1329.
12. Habr-Gama A. Assessment and management of the complete clinical response of rectal cancer to chemoradiotherapy. Colorectal Dis 2006;8 Suppl 3:21-24.
13. Habr-Gama A, Perez RO, São Julião GP, et al. Nonoperative approaches to rectal cancer: a critical evaluation. Semin Radiat Oncol 2011;21:234-239.
14. Maas M, Beets-Tan RG, Lambregts DM, et al. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. J Clin Oncol 2011;29:4633-4640.
15. Smith JD, Ruby JA, Goodman KA, et al. Nonoperative management of rectal cancer with complete clinical response after neoadjuvant therapy. Ann Surg 2012;256:965-972.
16. Guillem JG, Chessin DB, Shia J, et al. Clinical examination following preoperative chemoradiation for rectal cancer is not a reliable surrogate end point. J Clin

Oncol 2005;23:3475-3479.
17. Maretto I, Pomerri F, Pucciarelli S, et al. The potential of restaging in the prediction of pathologic response after preoperative chemoradiotherapy for rectal cancer. Ann Surg Oncol 2007;14:455-461.
18. Pastor C, Subtil JC, Sola J, et al. Accuracy of endoscopic ultrasound to assess tumor response after neoadjuvant treatment in rectal cancer: can we trust the findings? Dis Colon Rectum 2011;54:1141-1146.
19. Guillem JG, Ruby JA, Leibold T, et al. Neither FDG-PET Nor CT can distinguish between a pathological complete response and an incomplete response after neoadjuvant chemoradiation in locally advanced rectal cancer: a prospective study. Ann Surg 2013;258:289-295.
20. van der Paardt MP, Zagers MB, Beets-Tan RG, et al. Patients who undergo preoperative chemoradiotherapy for locally advanced rectal cancer restaged by using diagnostic MR imaging: a systematic review and meta-analysis. Radiology 2013;269:101-112.
21. Gollub MJ, Gultekin DH, Akin O, et al. Dynamic contrast enhanced-MRI for the detection of pathological complete response to neoadjuvant chemotherapy for locally advanced rectal cancer. Eur Radiol 2012;22:821-831.
22. Kluza E, Rozeboom ED, Maas M, et al. T2 weighted signal intensity evolution may predict pathological complete response after treatment for rectal cancer. Eur Radiol 2013;23:253-261.
23. Lambregts DM, Beets GL, Maas M, et al. Accuracy of gadofosveset-enhanced MRI for nodal staging and restaging in rectal cancer. Ann Surg 2011;253:539-545.
24. Habr-Gama A, Perez RO, Sabbaga J, et al. Increasing the rates of complete response to neoadjuvant chemoradiotherapy for distal rectal cancer: results of a prospective study using additional chemotherapy during the resting period. Dis Colon Rectum 2009;52:1927-1934.
25. Petrelli F, Sgroi G, Sarti E, et al. Increasing the Interval Between Neoadjuvant Chemoradiotherapy and Surgery in Rectal Cancer: A Meta-Analysis of Published Studies. Ann Surg 2013. [Epub ahead of print].
26. Habr-Gama A, Sabbaga J, Gama-Rodrigues J, et al. Watch and wait approach following extended neoadjuvant chemoradiation for distal rectal cancer: are we getting closer to anal cancer management? Dis Colon Rectum 2013;56:1109-1117.
27. Garcia-Aguilar J, Smith DD, Avila K, et al. Optimal timing of surgery after chemoradiation for advanced rectal cancer: preliminary results of a multicenter, nonrandomized phase II prospective trial. Ann Surg 2011;254:97-102.
28. Cercek A, Goodman KA, Hajj C, et al. Neoadjuvant chemotherapy first, followed by chemoradiation and then surgery, in the management of locally advanced rectal cancer. J Natl Compr Canc Netw 2014;12:513-519.

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Potential value of immunoscoring in rectal cancer patients

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Provenance: This is a Guest Editorial commissioned by Section Editor Hongcheng Zhu, MD, PhD (Department of Radiation Oncology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China).

Comment on: Glimelius B. Multidisciplinary treatment of patients with rectal cancer: Development during the past decades and plans for the future. Ups J Med Sci 2012;117:225-36.

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Rectal cancer therapy has markedly changed during the past decades with clear improvements for the patients (1). Population-based data based on registries with high validity (2,3) show that local recurrence rates can be as low as about 5% (4,5), similar to that in dedicated centers. Multidisciplinary team discussions prior to therapy initiation have likely also contributed to the improvements (5,6).

Better loco-regional staging, preferably with magnetic resonance imaging (MRI) can adequately describe whether the tumor is clear from the mesorectal fascia (MRF) and that an R0 resection thus is likely if a total mesorectal excision (TME) is done. If MRF is threatened, usually <1 mm, or cT3 mrf+, or involved, as it is in clinical stage T4 (cT4), preoperative treatment with time for down-sizing or down-staging before surgery is most often needed (1,7,8). Chemoradiotherapy is then the best documented treatment although in elderly patients, short-course radiotherapy with a delay is an attractive option (9). These tumors constitute about 10–15% of the rectal cancer patients. Many tumors less advanced than the locally advanced (cT3mrf+ or cT4s) have a risk of local recurrence even if adequate surgery is done and preoperative radiotherapy is then indicated. Since there then is no need for down-sizing/down-staging, short-course radiotherapy with immediate surgery is an attractive, convenient and well-documented treatment that reduces the risk of local recurrence by about 60% (1). These tumors, often designated locally advanced by most researchers, are best named intermediate, as for example done in the ESMO guidelines (7,8).

For early tumors, the risk of local recurrence is so small (2–5%) that radiotherapy is not indicated even if it would decrease the risk even further, since radiotherapy adds to the morbidity seen after surgery (1).

Overall survival has not improved to the same extent. The loco-regional treatments, surgery and radiotherapy have no possibilities to influence systemic disease whether already manifest at diagnosis as synchronous metastases or appearing during follow-up as metachronous metastases. Adjuvant chemotherapy is not particularly efficient and much controversy exists about whether it has any effect at all in patients pretreated with radiotherapy or chemoradiotherapy (10-13). Presently, much focus is on delivering the systemic treatment prior to the loco-regional treatment. Several trials are ongoing, among them the RAPIDO trial randomizing patients between the reference treatment chemoradiotherapy, surgery and optional adjuvant chemotherapy versus short-course radiotherapy, neo-adjuvant chemotherapy and finally surgery (14). The term "total neoadjuvant treatment, TNT" has sometimes been used to describe this most recent development.

Another trend in rectal cancer management has focused on organ preservation, i.e., to postpone surgery, potentially indefinitely in patients who respond well to chemoradiotherapy or short-course radiotherapy alone (15). If radiotherapy is indicated to loco-regionally control the disease sufficiently better than surgery alone, it is rather uncontroversial to postpone surgery if a clinical complete remission is achieved. Although some rather small distal tumors can be locally advanced since they may threaten the MRF or grow adjacent to or into the levator- or sphincter

muscles, requiring preoperative therapy with a delay to surgery, most tumors requiring preoperative therapy are quite large and the probability then to achieve a durable complete remission is much smaller. Tumor size is presently the best predictor of whether a complete clinical remission will be seen or not. In order to avoid surgery, many early tumors are thus presently treated with chemoradiotherapy. If the tumor is sensitive enough, that patient may have a clear benefit, but for most patients the additional chemoradiotherapy will only add morbidity since those patients will have both chemoradiotherapy and subsequent surgery (16).

In order to improve the outcome after rectal cancer treatments further, we need better predictors, firstly of those who will recur after adequate surgery, i.e., are at risk of having subclinical distant deposits and, secondly, of sensitivity to radiotherapy or chemoradiotherapy. The work recently published by Anitei *et al.* in *Clinical Cancer Research* (17) had the aim to determine whether tumor immune cell infiltration, as evaluated with the immunoscore methodology, could be useful as a prognostic and predictive marker in rectal cancer patients. In patients treated with surgery alone, the endpoint was risk of recurrence, either locally or systemically. In patients treated with chemoradiotherapy, the aim was to predict whether the patients will remain recurrence-free after the preoperative treatment based upon the immunoscore in the diagnostic biopsies. The results indicate that the immunoscore is both prognostic and predictive, but the strength in this is not particularly high.

In the introduction of the article, the authors refer to an assumption by many researchers that tumor progression essentially has relied upon cell autonomous processes, i.e., the genetic changes in the tumor cells. The relevance of the microenvironment has, according to the authors, been neglected. Although much knowledge how to evaluate the microenvironment, including the response of the host to the tumor has been gained during the past decade, the prognostic role of the composition of the microenvironment in colorectal cancer (CRC) has been known since at least the 1970s (18). Since then, multiple studies have revealed its prognostic impact, also in colon and rectal cancer (19-21).

In the study, a methodology named "immunoscore" was used. It was developed in a study in colon cancer (19) as a means to standardize the evaluation for routine testing and is based on the numbers of CD3+ and CD8+ lymphocytes in the center and periphery of the tumor. The use of a score that has the potential to be standardized is a strength of the study. The study with its limited number of patients, particularly in the evaluation of response after CRT, is, however, only preliminary and should be followed by a much larger validation study. The statement by the authors in the very last sentence in the discussion "an international multicenter study should now be initiated", prior to its use clinically is definitely true (22).

The need for a predictor of response to (chemo) radiotherapy is as discussed above urgently needed. This is particularly the case in early tumors where (chemo) radiation is not considered needed if major surgery is planned, but where this will be given if organ preservation is aimed at. Studies with the aim to predict outcome based upon properties of the tumor in the diagnostic biopsies are notoriously difficult, not the least depending upon the small amount of cancer cells present in the biopsies, unless "big bites" are taken. So far, no study has shown any clinically relevant predictor (23). The purpose of the diagnostic biopsy is still only to verify the cancer diagnosis. In this context, functional imaging may be methodologically easier to explore.

The performance of the immunoscore on the pretreatment biopsies in the article (17) is not possible to judge based upon limited number of patients (n=55), no prescription of what CRT was used (presumably about 50 Gy with a fluoropyrimidine) and the limited description of what constituted ypTN downstaging. An evaluation of response using either MRI pre-surgery (24) or one of the pathological tumor regression systems is likely more relevant.

While I am sceptic to that immunoscoring in the postoperative specimen will be practically valuable in the clinics to evaluate recurrence risk and in the pretreatment biopsies to predict response to CRT, I am optimistic that further studies about the interplay between the tumor cells and the environment will lead to better understanding of mechanisms of clinical value in the future. In this context, improved possibilities to measure immune reactivity in peripheral blood, beyond those that could be done using simple routinely taken tests like C-reactive protein (CRP) or the Glasgow prognostic index (25) are needed. Any new method claiming to be used clinically must be compared with what is already around, often having the advantage of being both simple and cheap.

The checkpoint PD-1 and PDL-1 inhibitors directed against the inflammatory response (26) have created greater enthusiasm for therapeutic progress than many other

targeted drugs have, also in CRC. Although the first very limited series of patients with metastatic CRC treated with pembrolizumab indicated that only MSI-H tumors, where the immune reaction is more pronounced (27), responded, the study by Anitei and co-workers (17), showing that an immune reaction in rectal cancers have prognostic information, give hope also for therapeutic attempts in rectal cancer, where MSI-H tumors virtually never are seen.

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Footnote

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References

1. Glimelius B. Multidisciplinary treatment of patients with rectal cancer: Development during the past decades and plans for the future. Ups J Med Sci 2012;117:225-236.
2. Jörgren F, Johansson R, Damber L, et al. Validity of the Swedish Rectal Cancer Registry for patients treated with major abdominal surgery between 1995 and 1997. Acta Oncol 2013;52:1707-1714.
3. Sakkestad ST, Olsen BC, Karliczek A, et al. Validity of Norwegian Rectal Cancer Registry data at a major university hospital 1997-2005. Acta Oncol 2015;54:1723-1728.
4. Guren MG, Kørner H, Pfeffer F, et al. Nationwide improvement of rectal cancer treatment outcomes in Norway, 1993-2010. Acta Oncol 2015;54:1714-1722.
5. Kodeda K, Johansson R, Zar N, et al. Time trends, improvements and national auditing of rectal cancer management over an 18-year period. Colorectal Dis 2015;17:O168-O179.
6. Brännström F, Bjerregaard JK, Winbladh A, et al. Multidisciplinary team conferences promote treatment according to guidelines in rectal cancer. Acta Oncol 2015;54:447-453.
7. Schmoll HJ, Van Cutsem E, Stein A, et al. ESMO Consensus Guidelines for management of patients with colon and rectal cancer. a personalized approach to clinical decision making. Ann Oncol 2012;23:2479-2516.
8. Glimelius B, Tiret E, Cervantes A, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24 Suppl 6:vi81-vi88.
9. Radu C, Berglund A, Påhlman L, et al. Short-course preoperative radiotherapy with delayed surgery in rectal cancer - a retrospective study. Radiother Oncol 2008;87:343-349.
10. Poulsen LØ, Qvortrup C, Pfeiffer P, et al. Review on adjuvant chemotherapy for rectal cancer - why do treatment guidelines differ so much? Acta Oncol 2015;54:437-446.
11. Glimelius B. Adjuvant chemotherapy for patients with rectal cancer - will the controversy be resolved? Acta Oncol 2015;54:433-436.
12. Bujko K, Glimelius B, Valentini V, et al. Postoperative chemotherapy in patients with rectal cancer receiving preoperative radio(chemo)therapy: A meta-analysis of randomized trials comparing surgery ± a fluoropyrimidine and surgery + a fluoropyrimidine ± oxaliplatin. Eur J Surg Oncol 2015;41:713-723.
13. Breugom AJ, Swets M, Bosset JF, et al. Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data. Lancet Oncol 2015;16:200-207.
14. Nilsson PJ, van Etten B, Hospers GA, et al. Short-course radiotherapy followed by neo-adjuvant chemotherapy in locally advanced rectal cancer--the RAPIDO trial. BMC Cancer 2013;13:279.
15. Maas M, Beets-Tan RG, Lambregts DM, et al. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. J Clin Oncol 2011;29:4633-4640.
16. Glimelius B. Optimal Time Intervals between Pre-Operative Radiotherapy or Chemoradiotherapy and Surgery in Rectal Cancer? Front Oncol 2014;4:50.
17. Anitei MG, Zeitoun G, Mlecnik B, et al. Prognostic and predictive values of the immunoscore in patients with rectal cancer. Clin Cancer Res 2014;20:1891-1899.
18. Murray D, Hreno A, Dutton J, et al. Prognosis in colon cancer: a pathologic reassessment. Arch Surg 1975;110:908-913.
19. Galon J, Costes A, Sanchez-Cabo F, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science 2006;313:1960-1964.
20. Fridman WH, Pagès F, Sautès-Fridman C, et al. The immune contexture in human tumours: impact on clinical outcome. Nat Rev Cancer 2012;12:298-306.

21. Augsten M, Hägglöf C, Peña C, et al. A digest on the role of the tumor microenvironment in gastrointestinal cancers. Cancer Microenviron 2010;3:167-176.
22. Galon J, Pagès F, Marincola FM, et al. Cancer classification using the Immunoscore: a worldwide task force. J Transl Med 2012;10:205.
23. Molinari C, Matteucci F, Caroli P, et al. Biomarkers and Molecular Imaging as Predictors of Response to Neoadjuvant Chemoradiotherapy in Patients With Locally Advanced Rectal Cancer. Clin Colorectal Cancer 2015;14:227-238.
24. Intven M, Monninkhof EM, Reerink O, et al. Combined T2w volumetry, DW-MRI and DCE-MRI for response assessment after neo-adjuvant chemoradiation in locally advanced rectal cancer. Acta Oncol 2015;54:1729-1736.
25. McMillan DC. The systemic inflammation-based Glasgow Prognostic Score: a decade of experience in patients with cancer. Cancer Treat Rev 2013;39:534-540.
26. Li X, Hu W, Zheng X, et al. Emerging immune checkpoints for cancer therapy. Acta Oncol 2015;54:1706-1713.
27. De Smedt L, Lemahieu J, Palmans S, et al. Microsatellite instable vs stable colon carcinomas: analysis of tumour heterogeneity, inflammation and angiogenesis. Br J Cancer 2015;113:500-509.

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Review of systemic therapies for locally advanced and metastatic rectal cancer

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Abstract: Rectal cancer, along with colon cancer, is the second leading cause of cancer-related deaths in the U.S. Up to a quarter of patients have metastatic disease at diagnosis and 40% will develop metastatic disease. The past 10 years have been extremely exciting in the treatment of both locally advanced and metastatic rectal cancer (mRC). With the advent of neoadjuvant chemoradiation, increased numbers of patients with locally advanced rectal cancer (LARC) are surviving longer and some are seeing their tumors shrink to sizes that allow for resection. The advent of biologics and monoclonal antibodies has propelled the treatment of mRC further than many could have hoped. Combined with regimens such as FOLFOX or FOLFIRI, median survival rates have been increased to an average of 23 months. However, the combinations of chemotherapy regimens seem endless for rectal cancer. We will review the major chemotherapies available for locally advanced and mRC as well as regimens currently under investigation such as FOLFOXIRI. We will also review vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) inhibitors as single agents and in combination with traditional chemotherapy regimens.

Keywords: Systemic therapies; locally advanced and metastatic rectal cancer (mRC); chemotherapies

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Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related death in the U.S., with an estimated 142,820 newly diagnosed cases and an estimated 50,830 deaths in 2013. An estimated 40,000 new cases of rectal cancer will be diagnosed in the U.S. in 2014 (1). A total of 20-25% of patients will have metastatic disease at diagnosis and close to 40% will develop metastatic disease (2). Despite the significant proportion of metastatic disease, the 5-year survival for all stages of rectal cancer has significantly improved over the past 4 decades (3). These advances are in large part due to the development of new systemic therapies. Rectal cancer has seen impressive treatment developments over the past 20 years, including neoadjuvant chemoradiotherapy (CRT), novel biologic therapies and second generation chemotherapeutic agents. With these advances, rectal cancer management has evolved into a multidisciplinary approach involving surgery, radiotherapy, chemotherapy, and biologics.

This review will look the current systemic therapeutic options in treating locally advanced and metastatic rectal cancer (mRC). The review will also look at therapies and novel strategies that are currently active areas of research and debate.

Neoadjuvant therapy in locally advanced rectal cancer (LARC)

The last decade has seen a shift toward neoadjuvant therapy for the treatment of LARC. Previously, adjuvant CRT involving 5-fluorouracil (5-FU) following surgical resection was the cornerstone of advanced rectal cancer treatment. The first large scale trials performed in the 1980s, NSABP R-01 and GITSG, revealed that 5-FU based treatments combined with adjuvant radiotherapy following surgery had significant improvements in disease free survival

and local recurrence compared to surgery alone (4,5). Subsequently, the North Central Cancer Treatment Group (NCCTG) performed a trial comparing radiotherapy with and without 5-FU (6). The NCCTG found significantly improved rates of local recurrence, cancer-related deaths, and overall survival (OS) with CRT compared to radiation alone (6). Based on these studies, the National Institutes of Health (NIH) recommended the treatment of LARC be a combination of postoperative chemotherapy with 5-FU and radiation (7,8).

Following the NIH recommendations, shifts in the treatment paradigm for rectal cancer began and trials began looking at the role of neoadjuvant radiotherapy. The Swedish and Dutch rectal cancer trials established the benefit of neoadjuvant radiotherapy in local disease control (9,10). These trials showed that the local recurrence rate of rectal cancer was significantly lower in those that received preoperative radiotherapy followed by surgery compared to surgery alone (9,10). In the landmark German Rectal study (CAO/ARO/AIO-94), neoadjuvant CRT was superior to post-operative therapy (11). In 825 stage II or III patients, Sauer *et al.* compared neoadjuvant CRT with 5-FU followed by surgery with the same regimen in the adjuvant setting. There was significant differences in 5-year cumulative incidence of local relapse (6% *vs.* 13%, respectively), although, there was no significant difference in 5-year survival (76% *vs.* 74%, respectively). These results have persistent at 10-year follow-up and have led to the widespread adoption neoadjuvant CRT in the treatment of LARC (11).

Other studies have looked at preoperative *vs.* postoperative CRT in the treatment of LARC and confirmed the benefit of neoadjuvant therapy. The NSABP R-03 trial was one such trial that showed no significant difference in local relapse but did show a significant difference in 5-year disease free survival with neoadjuvant CRT compared to adjuvant CRT (12). This study was only able to accrue 277 patients out of the 900 originally planned and thus the study could not reach the same power as that of the German Rectal study thus limiting analysis of local recurrence and toxicities (11,12).

Xeloda *vs.* 5-FU in LARC

Fluoropyrimidines are the backbone of both neoadjuvant and adjuvant therapy for LARC. Through inhibition of thymidylate synthetase (TS), deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis is impaired (13). 5-FU is the most commonly used drug of this class. It is administered as an infusion in conjunction with leucovorin (LV) which stabilizes the tertiary complex between 5-FU and TS thus enhancing the efficacy of 5-FU (14,15). Given the inconvenience of infusion therapies, capecitabine, the first oral fluoropyrimidine, has been developed as a promising alternative. Capecitabine is a prodrug, which is converted to 5-FU via three enzymatic steps (16). Thymidylate phosphorylase plays a key role in the conversion of capecitabine to its active metabolite and is found in higher concentrations in the malignant tissue (16). Trials looking at the toxicity profile of the drug when compared to 5-FU have suggested an improved side effect profile compared to 5-FU/LV with decreased stomatitis, diarrhea, nausea and neutropenic sepsis (17,18). However, capecitabine did have higher rates of hyperbilirubinemia and hand-foot syndrome (17,18). Considering the potential benefits of an oral pro-drug, the efficacy of capecitabine in comparison to 5-FU as neoadjuvant therapy for rectal cancer was investigated (*Table 1*).

In the first-line monotherapy setting, the two randomized, prospective phase III trials enrolled a total number of 1,207 patients, who were randomized to receive either oral capecitabine (1,250 mg/m^2 bid 2 weeks on/1 week off in 3-week cycles) or the Mayo Clinic regimen (LV 20 mg/m^2 followed by 5-FU 425 mg/m^2 iv bolus on days 1-5 in a 4-week cycle) (18). The results suggested that capecitabine was equally effective with acceptable toxicity. Further retrospective data collected from small trials without treatment protocol standardization suggested that capecitabine had a higher complete response rate in the neoadjuvant setting (24).

The role of capecitabine as neoadjuvant treatment for rectal cancer became widely accepted with Hofheinz *et al.*'s findings in 2012 (25). This phase III non-inferiority trial evaluated capecitabine *vs.* 5-FU in the neoadjuvant and adjuvant settings in LARC (25). The primary endpoint was overall 5-year survival and capecitabine was found to be non-inferior to 5-FU (76% *vs.* 67%, respectively) (25). Post-hoc analysis for superiority showed capecitabine had significantly improved 5-year survival. Capecitabine had a better 5-year survival when compared 5-FU in both the neoadjuvant cohort (66% *vs.* 61%) and adjuvant cohort (81% *vs.* 71%) (25). Local recurrence rate, a secondary endpoint, was not significantly difference between capecitabine and 5-FU (6% *vs.* 7%) (25).

Recently, the NSABP R-04 trial was completed which looked at clinical complete response (cCR), pathologic complete response (pCR) and local-regional relapse in

Table 1 Synopsis of studies comparing capecitabine containing regimens to 5-FU containing regimens. Included are the dosing regimens, PFS statistics, median OS statistics, and toxicities observed in the treatment arms

Study	German AIO group (19)	Spanish group (20)	French study (21)	Tree-1-US study (22)	GOAM-Italian study (23)
Dosing regimen CAPOX/XELOX based treatment arm	CAPOX: oxaliplatin 70 mg/m^2 2-hour infusion days 1 and 8 every 3 weeks, capecitabine 1,000 mg/m^2 bid orally days 1-14 every 3 weeks	XELOX: oral capecitabine 1,000 mg/m^2 bid for 14 days plus oxaliplatin 130 mg/m^2 on day 1 every 3 weeks	XELOX: 2-hour iv of oxaliplatin 130 mg/m^2 on day 1 plus oral capecitabine 1,000 mg/m^2 twice daily on days 1-14 every 3 weeks	CapeOx: oxaliplatin 130 mg/m^2 iv on day 1 and capecitabine 1,000 mg/m^2 orally twice daily on days 1-15 every 3 weeks	XELOX: oxaliplatin as noted below and oral capecitabine at the dose of 1,000 mg/m^2 bid from the 1st to the 14th day
Dosing regimen FU + OX based treatment arm	FUFOX: oxaliplatin 50 mg/m^2 2-hour infusion, folinic acid 500 mg/m^2 2-hour infusion, FU 2,000 mg/m^2 22-hour infusion; days 1, 8, 15, and 22 every 5 weeks	FUOX: FU 2,250 mg/m^2 diluted in saline administered by civ during 48 hours on days 1, 8, 15, 22, 29, and 36, plus oxaliplatin 85 mg/m^2 on days 1, 15, and 29 every 6 weeks	FOLFOX6: 2-hour iv of oxaliplatin 100 mg/m^2 followed by a 2-hour infusion of LV 400 mg/m^2 followed by 5-FU 400 mg/m^2 given as an intravenous bolus injection and then 5-FU 2,400-3,000 mg/m^2 as a 46-hour civ every 2 weeks	mFOLFOX6: oxaliplatin 85 mg/m^2 iv with LV 350 mg iv over 2 hours plus FU 400 mg/m^2 iv bolus and 2,400 mg/m^2 civ over 46 hours every 2 weeks bFOL: oxaliplatin 85 mg/m^2 iv on days 1 and 15 and LV 20 mg/m^2 iv over 10-20 minutes followed by FU 500 mg/m^2 iv push on days 1, 8, and 15 every 4 weeks	PVIFOX: dexamethasone 20 mg in 100 cc of saline by the intravenous (iv) route in 15 min, granisetron 3 mg in 100 cc of saline iv in 15 min, oxaliplatin at the dose of 130 mg/m^2 in 500 cc of 5% glucose solution iv in 2 hours and, at the end, 5-FU at the dose of 250 mg/m^2/daily in civ from the 1st to the 21st day
Number of patients in CAPOX treatment arm	242	171	144	48	62
Number of patients in FU + OX treatment arm	234	171	140	50 (bFOL) & 49 (mFOLFOX)	56
PFS in treatment arms CAPOX/ XELOX *vs.* FU + OX (months)	7.1 *vs.* 8.0 (P=0.117)	8.9 *vs.* 9.5 (P=0.153)	8.8 *vs.* 9.3	5.9 (CapeOx) *vs.* 6.9 (bFOL) *vs.* 8.7 (mFOLFOX)	9.0 *vs.* 7.0
OS in treatment arms CAPOX/ XELOX *vs.* FU + OX (months)	16.8 *vs.* 18.8 (P=0.26)	18.1 *vs.* 20.8 (P=0.145)	19.9 *vs.* 20.5	17.2 (CapeOx) *vs.* 17.9 (bFOL) *vs.* 17.6 (mFOLFOX)	NA
RR in treatment arms CAPOX/ XELOX *vs.* FU + OX	48% *vs.* 54%	37% *vs.* 46%	42% *vs.* 46%	27% (CapeOx) *vs.* 20% (bFOL) *vs.* 41% (mFOLFOX)	43% *vs.* 48%
Toxicity in treatment arms CAPOX/ XELOX *vs.* FU + OX	Nausea, vomiting, and diarrhea were similar in both treatment groups. Only HFS grade 2/3 was significantly higher in the CAPOX arm (P=0.028)	Lower rates of grade 3/4 diarrhea (14% *vs.* 24%, P=0.027) and grade 1/2 mucositis (28% *vs.* 43%, P=0.005), with higher rates of grade 1/2 hyperbilirubinemia (37% *vs.* 21%, P=0.001) and grade 1/2 hand-foot syndrome (14% *vs.* 5%, P=0.009) with XELOX arm *vs.* FUOX arm, respectively	XELOX arm had significantly more grade 3/4 thrombocytopenia (12% *vs.* 5%) and diarrhea (14% *vs.* 7%), but significantly less grade 3/4 neutropenia (5% *vs.* 47%), febrile neutropenia (0% *vs.* 6%) and neuropathy (11% *vs.* 26%) than FOLFOX6 patients	Grade 3/4 treatment-related adverse events during the first 12 weeks of treatment were 59%, 36%, and 67% for mFOLFOX6, bFOL, and CapeOx, respectively. CapeOx toxicity included grade 3/4 diarrhea (31%) and dehydration (27%)	Grade 3/4 diarrhea was observed in 14.0% *vs.* 8.2%, grade 3 stomatitis in 3.7% *vs.* 0%, and grade 3 neurotoxicity in 18.5% *vs.* 24.6%, when comparing *vs.* PVIFOX *vs.* XELOX

AIO, Arbeitsgemeinschaft Internistische Onkologie; iv, intravenous infusion; 5-FU, 5-fluorouracil; LV, leucovorin; civ, continuous intravenous infusion; PFS, progression free survival; OS, overall survival; NA, not available; RR, response rate; HFS, hand foot syndrome.

patients who received neoadjuvant capecitabine/radiation *vs.* 5-FU/radiation (26-28). Preliminary data suggests that neoadjuvant capecitabine/radiation compared to 5-FU/radiotherapy have comparable outcomes particularly when looking at pCR, sphincter-saving surgery, and surgical down-staging (26-28). In a preliminary report presented at the 2014 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancer Meeting, patients receiving capecitabine had comparable rates of down-staging surgery and sphincter preservation, similar pCR rates (21% *vs.* 18% for capecitabine and infusional 5-FU), similar rates of locoregional control, the primary endpoint (3-year incidence of any locoregional event 12% *vs.* 11%) and comparable OS (81% *vs.* 80%). Preliminary data has also suggested there are significant differences in overall patient reported outcomes (PROs) and quality of life (QoL) indices favoring capecitabine (26-28). Additionally, the convenience of care noted by patients in the capecitabine treatment arms was also greater (26-28). No major differences were seen in patient reported functional assessment of cancer treatment-colorectal (FACT-C), trial outcome indices (TOI), and ultimately overall PROs (26-28). These data as well as those from the NSABP R-04 and Hofheinz *et al.* strongly support capecitabine as a reasonable alternative to 5-FU in LARC (25).

Oxaliplatin in LARC

Oxaliplatin is a platinum analog which functions as an alkylator (29). Thus, oxaliplatin forms inter- and intra-strand cross-links within DNA preventing replication and transcription (29). Oxaliplatin is highly effective in combination with 5-FU in the treatment of mRC and its efficacy in the neoadjuvant setting has been extensively investigated in several randomized controlled trials (30,31).

The aforementioned NSABP R-04 had two additional treatment arms added oxaliplatin to each of the original treatment regimens (capecitabine ± oxaliplatin and 5-FU ± oxaliplatin) (26). Preliminary data analysis showed no significant differences in cCR, pCR and local-regional relapse when oxaliplatin was added to each treatment arm (26). However, the rate significant toxicity and including neuropathy and diarrhea increased in the arms containing oxaliplatin (26). In addition to the NSABP R-04, four other large trials (ACCORD 12, STAR-01, PETACC-6 and CAO/ARO/AIO-04) have failed to demonstrate a role for oxaliplatin in the neoadjuvant setting for LARC (32-35). Of all these trials, only the CAO/ARO/AIO-04 showed a statistically significant change in pCR with the addition of oxaliplatin (17% *vs.* 13%) (35). There was also a significant incidence grade 3 and 4 neuropathy and diarrhea with the addition of oxaliplatin across all trials except for the CAO/ARO/AIO-04 trial (32-35). However, although 5-FU or capecitabine were included in all trials, dosing strategies and treatment regimens varied (32-35). Additionally, the adjuvant regimens varied with only the CAO/ARO/AIO-04 trial including oxaliplatin in the adjuvant treatment arm (32-35).

An important and relevant clinical outcome after neoadjuvant treatment that was not addressed in detail in these trials was the incidence of distant metastasis after neoadjuvant therapy and prior to surgical intervention (32-35). Overall trend analysis regarding the incidence of distant metastasis indicated a decrease in the rate of distant metastasis at the time of surgery in patients treated with neoadjuvant oxaliplatin (32,33,35). Comparing the incidence of distant metastasis in the neoadjuvant treatment arms containing oxaliplatin *vs.* those without, the ACCORD trial noted 2.8% *vs.* 4.2%, the STAR-01 noted 0.5% *vs.* 2.9% and the CAO/ARO/AIO-04 showed 4% *vs.* 6%, respectively (32,33,35). Both the NSABP R-04 and the PETACC-6 did not comment on distant metastasis (26,34).

More importantly, some of the trials have provided interval analysis on disease free survival and OS. The ACCORD trial at 3 years has noted no significant difference in disease free survival (67.9% *vs.* 72.7%, respectively) between the oxaliplatin and non-oxaliplatin treatment arms (87.6% *vs.* 88.3%, respectively) (32). Preliminary data from NSABP R-04 also has supported these conclusions (26). Outcome and primary end point analysis still remains to be seen regarding the CAO/ARO/AIO-04 and PETACC-6 trials (34,35). With the current data available, consensus among the oncologic community does not support the use of neoadjuvant oxaliplatin for LARC.

Metastatic rectal cancer (mRC)

Fluoropyrimidine based therapy has been the backbone of the systemic approach to CRC over the last 30 years. In the last 2 decades, there have been new classes of chemotherapeutic agents, as well as new biologic agents such as vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) inhibitors approved for the treatment of CRC. These treatments have directly impacted the outcomes of our patients as CRC mortality in the United States has declined 3.0% from 2000 to 2009. This was among the highest rates of decline across all tumor types and likely reflects advances in detection

and the development of improved systemic treatments (1). Our current challenge lies in developing predictive and prognostic markers to enhance the activity of available agents as well as guiding the optimal sequence of treatment.

Oxaliplatin and metastatic CRC (mCRC)

Oxaliplatin is currently an important part of the systemic approach to advanced rectal cancer. It was originally studied in combination with 5-FU/LV in 1998 (36). De Gramont *et al.* subsequently randomized 420 patients to first line 5-FU/LV or FOLFOX4 (30). FOLFOX4 was found to be superior in terms of response rates (51% *vs.* 22%) and progression free survival (PFS) (9 *vs.* 6.2 months) but not in terms of OS (30). This study established FOLFOX's role as a first line therapy for mRC. FOLFOX further established its role in the treatment of mRC in 2004 when the INT 9471 trial was being conducted (31). The trial had to be unblinded early after FOLFOX4 significantly outperformed irinotecan/5-FU/LV (IFL) and irinotecan/oxaliplatin IROX (31). With 785 patients in the initial analysis, FOLFOX4 had improved objective response rates, time to tumor progression (TTP), and most importantly an improved median OS of 19.5 months (31). This is compared to IFL and IROX which had median OS times of 15 and 17.3 months, respectively (31). However, one potential flaw in the INT 9741 trial is that with the IFL regimen, 5-FU/LV are administered via bolus which had already been shown to have worse median survival compared to infusional regimens during initial investigations of 5-FU/LV in mRC (31,37). The FFCD 2000-05 trial followed in 2011 and randomized 410 patients to FOLFOX6 or infusional 5-FU/LV (38). The FOLFOX6 arm showed an improved objective response (58% *vs.* 24%) as well as TTP (7.6 *vs.* 5.3 months) (38). However, median survival was not significantly different between the two arms (38).

Following the success of oxaliplatin in combination with 5-FU, several studies have looked at the efficacy of oxaliplatin and capecitabine in combination. A meta-analysis of trials comparing capecitabine/oxaliplatin (CAPOX) to oxaliplatin/5-FU/LV regimens in the metastatic setting pooled 3,494 patients and found that although CAPOX had a lower response rate, there was no significant difference in median TTP or OS (39). Grade 3 and 4 thrombocytopenia as well as hand and foot syndrome were more common with capecitabine regimens (39). Thus, because of the toxicity profile CAPOX is an option for first line therapy in those who cannot receive or wish to avoid infusional regimens.

Oxaliplatin has also been investigated as second line therapy in advanced rectal cancer. Four multicenter trials have evaluated the efficacy of oxaliplatin after irinotecan failure. Rothenberg *et al.* randomized 463 patients who failed IFL to 5-FU/LV, or single agent oxaliplatin, or FOLFOX4 (40). FOLFOX4 was found to be superior to both 5-FU/LV and single agent oxaliplatin with a median TTP of 4.6 *vs.* 2.7 *vs.* 1.6 months, respectively (40). These findings were duplicated by Kemeny *et al.* when 214 patients were randomized to 5-FU/LV or FOLFOX4 after irinotecan failure (41). Again, FOLFOX4 was superior with a median TTP of 4.8 *vs.* 2.4 months (41). CAPOX has a role in second line therapy and has been found to have similar efficacy to FOLFOX when used as a second line agent after irinotecan failure (42). Rothenberg *et al.* randomly assigned 627 patients to FOLFOX or CAPOX and found that TTP was similar (4.8 *vs.* 4.7 months) as was median OS (12.5 *vs.* 11.9 months) (42). Toxicity profiles were also similar but there was a higher incidence of grade 3-4 diarrhea and hand/foot syndrome but fewer episodes of neutropenia in the CAPOX group (42). Given CAPOX was found to be non-inferior in the second line setting, it is an option for those who have failed irinotecan based regimens but is often deferred to FOLFOX given the side effect profile.

Neuropathy is the dose limiting toxicity of oxaliplatin (30,31,43-47). Oxaliplatin related neuropathy can present in one of two syndromes. The more common being a cumulative sensory neuropathy which begins distally and progresses proximally occurs in 10-15% of patients receiving cumulative oxaliplatin dosages of 850 mg/m^2 (48,49). The cumulative sensory neuropathy is largely reversible as 75% of patients recover roughly 13 weeks after treatment cessation (49). An acute sensory neuropathy can also occur and presents as paresthesias and dysesthesias which more commonly affect the hands, feet, and perioral region (44). This acute neuropathy can also involve jaw tightness and pharyngo-laryngo-dysesthesias (44).

Infusional reactions have been observed in up to 25% of patients receiving oxaliplatin and are characterized by fever, rash, respiratory, and ocular symptoms (50). Respiratory symptoms can be as mild as chest tightness to severe bronchospasm (50). Depending on the severity, oxaliplatin may be continued after the administration of steroids and diphenhydramine (50,51). Infusional reactions can be prevented with pre-medication with steroids and diphenhydramine as well as slowing the oxaliplatin infusion rate (50,51).

Irinotecan and mCRC

Irinotecan, a topoisomerase inhibitor, was first introduced as an active agent for mCRC in 1997 (52). Topoisomerase inhibitors function via preventing the unwinding of DNA via topoisomerase and thus prevent or halt DNA replication and thus prevent cell replication (53). The efficacy of irinotecan as a first line agent was initially defined in combination with 5-FU/LV (54-56). In three studies, irinotecan combined with 5-FU/LV had higher response rates and median TTP compared to 5-FU/LV alone (54-56). The first was performed by Douillard *et al.* where 387 patients were randomized to infusional 5-FU with or without irinotecan administered every 2 weeks (54). TTP (6.7 *vs.* 4.4 months) and median OS (17.4 *vs.* 14.1 months) were significantly improved with irinotecan (54). These results were replicated by Saltz *et al.* where IFL out performed 5-FU/LV and irinotecan as a single agent (56). Köhne *et al.* also showed improved TTP with IFL compared to 5-FU/LV (8.5 *vs.* 6.4 months) but there was only a trend towards improvement in OS in the irinotecan containing arm (20.1 *vs.* 16.9 months) (55). Toxicities were similar in all three trials and included grade 3 and 4 diarrhea and neutropenia, nausea, and mucositis (54-56).

Irinotecan in addition to capecitabine combination regimens have also been explored. A phase II study in 2007 showed promising results with a median OS of 16.8 months in the combination arm of irinotecan 250 mg/m^2 iv on day 1 + capecitabine 1,000 mg/m^2 orally twice daily on days 1 to 14, every 3 weeks (57). However, the phase III BICC-C trial in 2007 did not reflect these findings (58). This trial randomized 430 patients to capecitabine/irinotecan (CapeIRI), IFL, and FOLFIRI with the addition of bevacizumab to all arms during the trial (58). The CapeIRI arm not only had more side effects but also showed a worse PFS and trend towards worse OS compared to the other arms. Median PFS was 7.6 months for FOLFIRI, 5.9 months for irinotecan plus bolus 5-FU/LV (mIFL) (P=0.004 for the comparison with FOLFIRI), and 5.8 months for CapeIRI (58). Thus, it is currently recommended that irinotecan not be used in combination with capecitabine as first line therapy.

Irinotecan also has activity as second line therapy for mRC. Three meta-analyses pooled data on irinotecan use after failure with an oxaliplatin containing regimen (47,59,60). Within these three studies, response rates ranged 4-20% and PFS ranged 2.5-7.1 months (47,59,60). Furthermore, Grothey *et al.* pooled data and found that OS is significantly improved in patients receiving 5-FU/LV, oxaliplatin, and irinotecan at some point along their treatment course (61).

The dose limiting toxicities of irinotecan, especially in combination with 5-FU/LV, are diarrhea and neutropenia. Of important consideration, the pharmacokinetics of irinotecan can vary significantly between patients. Chemotherapies are traditionally dosed using body surface area but the pharmacokinetics of irinotecan poorly correlate with body surface based dosing (62-64). Bilirubin appears to be a better prognosticator of the incidence of neutropenia and diarrhea with irinotecan as is the presence of the UGT1A1*28 polymorphism (65-73). However, given the rarity of this polymorphism, the cost effectiveness of screening individuals for the UGT1A1*28 polymorphism is unknown (72). However, when the patients UGT1A1*28 status is known, it is recommended to dose reduce irinotecan in those that are homozygous for UGT1A1*28 (72).

FOLFOX *vs.* FOLFIRI

FOLFOX and FOLFIRI have been established as first line therapies for mRC and were compared head to head by Tournigand *et al.* in 2004 (47). Two hundred and twenty patients were randomized to FOLFIRI or FOLFOX6 and no difference between TTP (8.5 *vs.* 8.0 months, respectively) (47). At the time of progression, patients in the FOLFIRI arm were switched to FOLFOX6 and vice versa (47). As second line therapies, FOLFIRI and FOLFOX6 showed no significant difference in TTP (14.2 *vs.* 10.9 months) (47). Most importantly, there was no difference in median OS between either arm (21.5 and 20.6 months) (47). Colucci *et al.* also compared FOLFOX4 and FOLFIRI in 2005 when 360 patients were randomized (45). There was no significant difference between FOLFIRI or FOLFOX4 with median times to tumor progression of 7 months for both and a median OS of 14 and 15 months, respectively (45). The major differences between the groups were the toxicities. Gastrointestinal toxicities were more common with FOLFIRI while neuropathy and thrombocytopenia were more common with FOLFOX4 (45).

FOLFOXIRI

Given that Grothey *et al.* found that exposure to 5-FU/LV, oxaliplatin, and irinotecan at some point during the treatment course was key, the question was raised as to whether treating patients with all three agents as first line therapy would be more beneficial (61). Falcone *et al.*

conducted a trial on FOLFOXIRI *vs.* FOLFIRI as first line therapy for mRC in 244 patients (74). The results were promising with FOLFOXIRI being superior in PFS (9.8 *vs.* 6.9 months) and median OS (22.6 *vs.* 16.7 months) (74). FOLFOXIRI did have a less favorable toxicity profile with a higher rate of grade 2 and 3 neuropathy (19% *vs.* 0%) and neutropenia (50% *vs.* 28%) (74). There was no significant difference in febrile neutropenia and patients were able to tolerate the FOLFIRI with only a 9% treatment interruption rate compared to 4% in the FOLFIRI group (74). Recent data on the combination of FOLFOXIRI and bevacizumab, an antibody to the VEGF was presented at the ASCO Annual Conference in 2013. In a randomized study by Falcone *et al.*, 508 patients were randomized to FOLFIRI + bevacizumab *vs.* FOLFOXIRI + bevacizumab. In the primary analysis, FOLFOXIRI/bevacizumab had significantly greater PFS (median 12.1 months) compared with FOLFIRI/bevacizumab [9.7 months; stratified hazard ratio (HR) 0.75; 95% confidence interval (CI), 0.62-0.9; P=0.003]. Median OS for FOLFOXIRI/bevacizumab was 31.0 months compared with 25.8 months in the FOLFIRI/bevacizumab group (stratified HR 0.79; 95% CI, 0.63-1.00; P=0.054) (75). The FOLFOXFIRI/bevacizumab arm had a significantly better response rate measured by response evaluation criteria in solid tumours (RECIST) criteria (65%) compared with the FOLFIRI/bevacizumab arm (53%; P=0.006). With future studies, FOLFOXIRI combined with VEGF or EGFR inhibitors may become the first line therapy of choice in patients with mRC.

VEGF inhibitors: bevacizumab

Bevacizumab is a humanized monoclonal antibody which exerts its effect by inhibiting the effect of VEGF-A thus inhibiting its binding to the VEGF receptor and prevents angiogenesis (76). Thus, as the tumor grows, it is unable to keep up with its oxygen requirements making the tumor tissue exceedingly hypoxic, preventing further growth.

Hurwitz *et al.* demonstrated the impact of adding bevacizumab to irinotecan when they randomized 813 patients to first line IFL with or without bevacizumab (77). Those receiving bevacizumab had improved overall response, TTP, and more importantly improved median OS (20 *vs.* 16 months) (77). The BICC-C trial showed similar results with FOLFIRI combined with bevacizumab with median overall response rates of 28 months when FOLFIRI is combined with bevacizumab compared to 19.2 months with FOLFIRI alone (78). The TREE-2 trial later confirmed the benefits of adding bevacizumab to oxaliplatin containing regimens (22). With 223 patients randomized to one of three oxaliplatin/5-FU/LV regimens with or without bevacizumab, median OS with bevacizumab containing regimens was 23.7 months compared to 18.2 months in regimens without bevacizumab (22). The NO16966 trial again showed improved TTP with bevacizumab combined with XELOX or FOLFOX compared to XELOX or FOLFOX alone but no significant difference in median survival (79). More patients were noted to discontinue bevacizumab secondary to toxicities and thus lack of significant improvement in median OS could be related to patients not completing therapy (79).

Bevacizumab has also been shown to have efficacy with 5-FU/LV in patients that cannot tolerate oxaliplatin or irinotecan secondary to toxicities (80,81). Kabbinavar *et al.* found that of the 209 patients studied, those receiving bevacizumab/5-FU/LV had a median TTP of 9.2 months and OS of 16.6 months compared to 5-FU/LV in which these outcomes were 9.2 and 12.9 months, respectively (80).

Sub-analysis of the BRiTe cohort, the ARIES cohort, and a retrospective analysis of patients from community U.S. oncology practices looked at bevacizumab as a second line agent and demonstrated a survival benefit (82-84). Second line bevacizumab was directly studied in the European ML18147 study in which 820 patients who progressed on bevacizumab containing regimens were randomized to fluoropyrimidine based regimens with or without bevacizumab (85). Those receiving bevacizumab had improved median TTP (5.7 *vs.* 4.1 months) and OS (11.2 *vs.* 9.8 months) compared to those who did not receive bevacizumab (85). Thus, despite failing first line regimens that included bevacizumab, the benefit of bevacizumab was preserved when used in second line therapy. The Food and Drug Administration (FDA) approved the use of bevacizumab in this setting after these data were published.

Although generally well tolerated, side effects of bevacizumab include hypertension, proteinuria/nephrotic syndrome, bleeding, gastrointestinal (GI) tract perforation, and arterial and venous thromboembolic events (86-96). Bleeding most commonly involves epistaxis but rarely includes GI bleed, hematemesis, and intracerebral hemorrhage (89,95,96). Hypertension is the most common side effect and can be managed via regular blood pressure (BP) checks as well as antihypertensives to maintain a goal BP of <140/90 mmHg (97). Ranpura *et al.* performed a meta-analysis on bevacizumab related fatal adverse events which included 10,217 patients (98). Two point five percent

of patients experienced a fatal event related to bevacizumab with the most common being hemorrhage, neutropenia, and GI tract perforation (98).

EGFR inhibitors

Epidermal growth factor (EGF) and its receptor (EGFR) have been shown to play a role in sustaining and controlling CRCs (99,100). Messa *et al.* looked at the EGFR concentrations in 40 colorectal carcinoma specimens and found higher concentrations in tumor tissues especially those from the left side of the colon (100). EGFR has been found to play a key role in progression of cells through the G1 phase of mitosis as well as preventing apoptosis (101). This opened the door for the creation of EGFR inhibitors in the treatment of mRC.

Cetuximab is a mouse/human chimeric monoclonal Ab which is directed against the EGFR (102). Not only does cetuximab prevent binding of the EGF ligand to EGFR via binding the surface portion of the receptor, it also induces internalization of the receptor (102). In addition to direct EGFR inhibition, antibody-dependent cellular cytotoxicity (ADCC) is considered to be an important mechanism of action of cetuximab.

Cetuximab was first studied as a second line agent with one of the earliest studies in mRC in 2007 when 572 patients who failed irinotecan therapy were randomized to cetuximab or best supportive care (103). Cetuximab was found to have improved overall response, PFS, and median OS (6.1 *vs.* 4.6 months) (103). Health related QoL (HR-QoL) was also improved in those receiving cetuximab (103,104).

Cetuximab in combination with irinotecan was first investigated in the BOND trial where 329 patients who failed irinotecan were randomized to cetuximab alone or cetuximab with continued irinotecan (105). TTP was significantly improved with cetuximab/irinotecan combination compared to cetuximab as a single agent (4.1 *vs.* 1.5 months) (105). There was a trend towards improved OS with cetuximab/irinotecan combination (105). The EPIC trial followed with 1,298 patients who had failed oxaliplatin and were randomized to single agent irinotecan with or without cetuximab (106). Patients receiving cetuximab had improved PFS (4.0 *vs.* 2.6 months) and HR-QoL (106). Median OS was similar between the two arms but is likely related to a large volume of patients who were started on cetuximab after the study closed (106).

The CRYSTAL trial opened the door for cetuximab as a first line therapy (107). A total of 1,198 patients were randomized to FOLFIRI with or without cetuximab and the initial analysis showed a significantly improved overall response and PFS with cetuximab (107). Further analysis of the data which looked at wild type (WT) *KRAS* tumors showed cetuximab had improved overall response, PFS (9.9 *vs.* 8.4 months) and median OS (23.5 *vs.* 20.0 months) (108). The European phase II OPUS trial looked at FOLFOX4 with or without cetuximab as first line therapy (109). As with the CRYSTAL trial, FOLFOX4/cetuximab combination showed improved overall response and PFS with a trend towards improved OS even in the *KRAS* wild subgroup analysis (109). The CALGB trial has not published the final data yet but in the initial analysis, those receiving cetuximab with FOLFOX or FOLFIRI have shown improved response rates compared to those receiving FOLFOX or FOLFIRI alone (110). However, the United Kingdom MRC COIN and NORDIC-VII trials failed to show a difference PFS and median OS in oxaliplatin containing regimens with and without cetuximab (111,112). At this time, cetuximab is recommended in those with WT *KRAS* tumors who have failed or cannot tolerate irinotecan. It can be combined with irinotecan containing regimens but its use with oxaliplatin containing regimens has not been fully established. Currently the EXPLORE trial is underway and is comparing FOLFOX4 with and without cetuximab in those who have failed first line irinotecan (113).

Panitumumab is a fully humanized monoclonal antibody that is directed against the extracellular EGFR domain (reference). Van Cutsem *et al.* were the first to perform a phase III study with single agent panitumumab *vs.* best supportive care in 463 patients that failed 5-FU, irinotecan, and oxaliplatin (114). PFS was 13.8 weeks for those receiving cetuximab and 8.5 weeks for those receiving best supportive care (114). After the study closed, a large number of patients in the best supportive care arm were started on panitumumab which is likely why no difference in OS was observed between the two arms (114). The data was re-analyzed with those with WT *KRAS* and those that received panitumumab had improved OS (115). These mutations did predict lack of response to panitumumab.

The PRIME study looked at panitumumab in combination with FOLFOX4 as first line therapy compared to FOLFOX4 for mRC (116). In a subset of 1,183 patients with WT *KRAS*, panitumumab/FOLFOX4 had improved PFS (9.6 *vs.* 8.0 months) but no significant difference in median OS (23.9 *vs.* 19.7 months) (116). Further evaluation revealed that 108 patients that did not have *RAS* mutations at exon 2 actually did have mutations at *KRAS* exons 3 and

4 as well as *NRAS* exons 2, 3, and 4 (117). These mutations did predict a lack of tumor response to panitumumab (117).

The absence or presence of mutations in *KRAS* is extremely important when deciding whether to start EGFR inhibitors. In addition to the findings in subset analysis of the above trials involving cetuximab and panitumumab, a retrospective analysis of 394 tumors for *KRAS* mutations was performed and showed those that were WT *KRAS* had significant responses to EGFR inhibitors while those with mutated *KRAS* did not (118). KRAS is an intracellular protein downstream the EGFR pathway and mutations in the KRAS protein cause it to be turned on permanently. Thus the signal to proliferate and prevent apoptosis is propagated despite inhibition of EGFR.

To date, studies have shown the efficacy of cetuximab and panitumumab in the treatment of mRC and it can be extrapolated that they are equally efficacious. However, only one study has been designed to compare these two EGFR inhibitors head to head, the ASPECCT trial (119). The trial is still ongoing but prelim data was presented in the 4th annual ASCO GI cancer symposium in 2007 and showed that cetuximab and panitumumab are equally efficacious in terms of PFS (4.4 *vs.* 4.1 months) and OS (10.0 *vs.* 10.4 months) (119).

KRAS mutations in exon 2 (codons 12 and 13) are a successful predictive marker for cetuximab efficacy, researchers have identified additional mutations in *KRAS* and in *NRAS*, which is also mutated at a low frequency (<5%) (120,121). Retrospective analyses of tumor samples from the EGFR inhibitor studies have been expanded to include mutations in *KRAS* exon 3 codons 59 and 61 and exon 4 codons 117 and 146, as well as mutations in *NRAS* exons 2, 3, and 4 (116,117). In a retrospective analysis of the PRIME study, 17% of patients were identified too have a mutated *RAS* isoform outside of exon 2 (116,117). Use of the expanded version of *RAS*-mutation further identified a cohort of patients benefiting from EGFR inhibition (116,117). The PRIME study demonstrated improved OS for panitumumab plus FOLFOX4 *vs.* FOLFOX4 alone, specifically in first-line treatment of WT *RAS* patients (median OS, 26.0 *vs.* 20.2 months; HR 0.78; 95% CI, 0.62-0.99; P=0.04) (117).

Improved selection of *RAS* WT patients helped demonstrate a clear benefit of cetuximab in the FIRE-3 trial (122). OS was improved in patients with *RAS* WT tumors who were treated with cetuximab plus FOLFIRI, compared with the bevacizumab plus FOLFIRI arm (33.1 *vs.* 25.6 months, respectively; P=0.011) (122). Patients with *RAS*-mutant tumors showed worsened PFS when cetuximab was added to FOLFIRI (6.1 *vs.* 12.2 months in the bevacizumab arm; P=0.004), and cetuximab was not associated with an OS benefit in these patients (122). These results highlight the importance of providing EGFR inhibitors only to those patients with *RAS* WT tumors and consideration of using expanded criteria to identify *KRAS* mutations and patients not likely to benefit from this approach.

The role of EGFR inhibitors in front-line therapy and the value of expanded *RAS* testing will be validated with the release of data from the upcoming CALGB/SWOG 80405 trial. Like the retrospective analyses described above, this study will also review efficacy (bevacizumab plus FOLFOX or FOLFIRI *vs.* cetuximab plus FOLFOX or FOLFIRI) in light of the expanded mutational analysis.

Common EGFR inhibitor side effects include weakness, malaise, nausea, electrolyte abnormalities, and acneiform rashes. Infusion reactions occur in 25% of patients treated with cetuximab (123). These reactions are often severe, most common with the first infusion and within the first 3 hours of infusion (123).

Combined bevacizumab with EGFR inhibitors

Given the success of bevacizumab, EGFR inhibitors, and combination therapy in improving OS, combining the EGFR and VEGF inhibition has been studied. This question was addressed in the BOND-2, PACCE, and CAIRO2 trials (124-126). The BOND-2 trial, cetuximab and bevacizumab were combined with the addition of irinotecan to one of the arms in patients that failed oxaliplatin (124). The initial data was promising and showed significantly improved PFS (7.3 *vs.* 4.9 months, respectively) and OS (15.4 *vs.* 14.4 months, respectively) with cetuximab/bevacizumab/irinotecan compared to cetuximab/bevacizumab (124). However, the PACCE and CAIRO2 studies were larger and looked at the combination of EGFR inhibitors with bevacizumab as first line therapies (125,126). The PACCE trial compared bevacizumab with either oxaliplatin or irinotecan containing regimens with or without panitumumab (125). Hecht *et al.* had to close the study early after those receiving panitumumab with bevacizumab had worsened OS compared to those not receiving panitumumab (19.4 *vs.* 24.5 months respectively) (125). A significant increase in skin toxicities, diarrhea, infections, and pulmonary embolisms were also noted in those receiving panitumumab/bevacizumab/

oxaliplatin (125). The CAIRO2 study looked at combination XELOX and bevacizumab with and without cetuximab and had similar findings to the PACCE trial (126). PFS was significantly decreased with the cetuximab arm (9.4 *vs.* 10.7 months) and the toxicity profile was worse with cetuximab (126). Thus, given the lack of survival benefit and increased incidence of grade 3 and 4 toxicities, combination bevacizumab and EGFR inhibitors is not recommended.

Bevacizumab *vs.* EGFR inhibitors

The FIRE-3 trial presented at ASCO 2013 introduced data to challenge the use of bevacizumab over EGFR inhibitors in the first line metastatic setting (127). Five hundred and ninety-two patients with WT *KRAS* were randomized to FOLFIRI with either bevacizumab or cetuximab (127). The first analysis showed no difference in response rates or PFS between the two arms (127). However, the cetuximab arm had a significantly improved OS compared to bevacizumab (28.8 *vs.* 25.0 months, respectively) (127). Updated data were presented later in 2013 at the annual European Cancer Congress (ECC) forum and excluded patients with mutations in *KRAS* exon 2, but also those with mutations in *KRAS* exons 3 and 4 as well as *NRAS* exons 3 and 4 (122). With these exclusions, the difference in median OS was more pronounced with 33.1 months for the cetuximab arm compared to 25.9 months for bevacizumab (122). Although the trial has not published its final data, it has suggested that EGFR inhibitors may be appropriate for first line use. Both the final data from the FIRE-3 trial and the currently ongoing U.S. intergroup trial C80405 will help answer this question once the final data is published.

Summary

Since the introduction of 5-FU over 40 years ago there have been major advances in the treatment of locally advanced and mRC. The addition of neoadjuvant CRT has improved outcomes and QoL for our patients. This approach is now widely accepted and the standard of care throughout the world. Adding second-generation chemotherapeutics to the neoadjuvant setting has not improved outcomes to date, however, new approaches are under investigation in locally advanced disease.

Advances in treatment regimens for mRC have been extensive. Combination regimens with infusional 5-FU, such as FOLFOX and FOLFIRI, have significantly extended life. Currently the triplet combination FOLFOXIRI is showing additional promise but further studies are needed. The advent of EGFR and VEGF inhibitors has significantly improved outcomes in patients with advanced disease. These agents have demonstrated activity and reasonable toxicity profiles. Their addition to chemotherapy backbones has led to improved PFS and OS. Further development and expansion of our understanding of *KRAS* mutations and additional predictive and prognostic markers will continue to lead to improved outcomes. The future appears promising.

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Footnote

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

References

1. Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9-29.
2. Glynne-Jones R, Kronfli M. Locally advanced rectal cancer: a comparison of management strategies. Drugs 2011;71:1153-1177.
3. Howlader N, Noone AM, Krapcho M, et al. eds. SEER Cancer Statistics Review, 1975-2011, National Cancer Institute.
4. Prolongation of the disease-free interval in surgically treated rectal carcinoma. Gastrointestinal Tumor Study Group. N Engl J Med 1985;312:1465-1472.
5. Fisher B, Wolmark N, Rockette H, et al. Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP protocol R-01. J Natl Cancer Inst 1988;80:21-29.
6. Krook JE, Moertel CG, Gunderson LL, et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. N Engl J Med 1991;324:709-715.
7. NIH consensus conference. Adjuvant therapy for patients with colon and rectal cancer. JAMA 1990;264:1444-1450.
8. Petersen SH, Harling H, Kirkeby LT, et al. Postoperative adjuvant chemotherapy in rectal cancer operated for cure. Cochrane Database Syst Rev 2012;3:CD004078.
9. Folkesson J, Birgisson H, Pahlman L, et al. Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy

on survival and local recurrence rate. J Clin Oncol 2005;23:5644-5650.
10. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001;345:638-646.
11. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol 2012;30:1926-1933.
12. Roh MS, Colangelo LH, O'Connell MJ, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. J Clin Oncol 2009;27:5124-5130.
13. Sobrero AF, Aschele C, Bertino JR. Fluorouracil in colorectal cancer--a tale of two drugs: implications for biochemical modulation. J Clin Oncol 1997;15:368-381.
14. Mini E, Trave F, Rustum YM, et al. Enhancement of the antitumor effects of 5-fluorouracil by folinic acid. Pharmacol Ther 1990;47:1-19.
15. Thirion P, Michiels S, Pignon JP, et al. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: an updated meta-analysis. J Clin Oncol 2004;22:3766-3775.
16. Schüller J, Cassidy J, Dumont E, et al. Preferential activation of capecitabine in tumor following oral administration to colorectal cancer patients. Cancer Chemother Pharmacol 2000;45:291-297.
17. Hoff PM, Ansari R, Batist G, et al. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. J Clin Oncol 2001;19:2282-2292.
18. Cassidy J, Twelves C, Van Cutsem E, et al. First-line oral capecitabine therapy in metastatic colorectal cancer: a favorable safety profile compared with intravenous 5-fluorouracil/leucovorin. Ann Oncol 2002;13:566-575.
19. Porschen R, Arkenau HT, Kubicka S, et al. Phase III study of capecitabine plus oxaliplatin compared with fluorouracil and leucovorin plus oxaliplatin in metastatic colorectal cancer: a final report of the AIO Colorectal Study Group. J Clin Oncol 2007;25:4217-4223.
20. Díaz-Rubio E, Tabernero J, Gómez-España A, et al. Phase III study of capecitabine plus oxaliplatin compared with continuous-infusion fluorouracil plus oxaliplatin as first-line therapy in metastatic colorectal cancer: final report of the Spanish Cooperative Group for the Treatment of Digestive Tumors Trial. J Clin Oncol 2007;25:4224-4230.
21. Ducreux M, Bennouna J, Hebbar M, et al. Efficacy and safety findings from a randomized phase III study of capecitabine (X) + oxaliplatin (O) (XELOX) vs. infusional 5-FU/LV + O (FOLFOX-6) for metastatic colorectal cancer (MCRC). J Clin Oncol 2007;25:abstr 4029.
22. Hochster HS, Hart LL, Ramanathan RK, et al. Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE Study. J Clin Oncol 2008;26:3523-3529.
23. Martoni AA, Pinto C, Di Fabio F, et al. Capecitabine plus oxaliplatin (xelox) versus protracted 5-fluorouracil venous infusion plus oxaliplatin (pvifox) as first-line treatment in advanced colorectal cancer: a GOAM phase II randomised study (FOCA trial). Eur J Cancer 2006;42:3161-3168.
24. Saif MW, Hashmi S, Zelterman D, et al. Capecitabine vs continuous infusion 5-FU in neoadjuvant treatment of rectal cancer. A retrospective review. Int J Colorectal Dis 2008;23:139-145.
25. Hofheinz RD, Wenz F, Post S, et al. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial. Lancet Oncol 2012;13:579-588.
26. Allegra CJ, Yothers G, O'Connell MJ, et al. Neoadjuvant therapy for rectal cancer: Mature results from NSABP protocol R-04. J Clin Oncol 2014;32:abstr 390.
27. Roh MS, Yothers G, O'Connell M, et al. The impact of capecitabine and oxaliplatin in the preoperative multimodality treatment in patients with carcinoma of the rectum: NSABP R-04. J Clin Oncol 2011;29:abstr 3503.
28. Yothers G, Ganz PA, Lopa SH, et al. Patient-reported outcomes (PROs) comparison of 5-FU and capecitabine (cape) with concurrent radiotherapy (RT) for neoadjuvant treatment of rectal cancer: Results of NSABP R-04. J Clin Oncol 2012;30:abstr 391.
29. Graham J, Mushin M, Kirkpatrick P. Oxaliplatin. Nat Rev Drug Discov 2004;3:11-12.
30. de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 2000;18:2938-2947.
31. Goldberg RM, Sargent DJ, Morton RF, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 2004;22:23-30.
32. Gérard JP, Azria D, Gourgou-Bourgade S, et al.

Clinical outcome of the ACCORD 12/0405 PRODIGE 2 randomized trial in rectal cancer. J Clin Oncol 2012;30:4558-4565.
33. Aschele C, Cionini L, Lonardi S, et al. Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. J Clin Oncol 2011;29:2773-2780.
34. Schmoll HJ, Haustermans K, Price TJ, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin versus capecitabine alone in locally advanced rectal cancer: First results of the PETACC-6 randomized phase III trial. J Clin Oncol 2013;31:abstr 3531.
35. Rödel C, Liersch T, Becker H, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. Lancet Oncol 2012;13:679-687.
36. deBraud F, Munzone E, Nolè F, et al. Synergistic activity of oxaliplatin and 5-fluorouracil in patients with metastatic colorectal cancer with progressive disease while on or after 5-fluorouracil. Am J Clin Oncol 1998;21:279-283.
37. Delaunoit T, Goldberg RM, Sargent DJ, et al. Mortality associated with daily bolus 5-fluorouracil/leucovorin administered in combination with either irinotecan or oxaliplatin: results from Intergroup Trial N9741. Cancer 2004;101:2170-2176.
38. Ducreux M, Malka D, Mendiboure J, et al. Sequential versus combination chemotherapy for the treatment of advanced colorectal cancer (FFCD 2000-05): an open-label, randomised, phase 3 trial. Lancet Oncol 2011;12:1032-1044.
39. Arkenau HT, Arnold D, Cassidy J, et al. Efficacy of oxaliplatin plus capecitabine or infusional fluorouracil/leucovorin in patients with metastatic colorectal cancer: a pooled analysis of randomized trials. J Clin Oncol 2008;26:5910-5917.
40. Rothenberg ML, Oza AM, Bigelow RH, et al. Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: interim results of a phase III trial. J Clin Oncol 2003;21:2059-2069.
41. Kemeny N, Garay CA, Gurtler J, et al. Randomized multicenter phase II trial of bolus plus infusional fluorouracil/leucovorin compared with fluorouracil/leucovorin plus oxaliplatin as third-line treatment of patients with advanced colorectal cancer. J Clin Oncol 2004;22:4753-4761.
42. Rothenberg ML, Cox JV, Butts C, et al. Capecitabine plus oxaliplatin (XELOX) versus 5-fluorouracil/folinic acid plus oxaliplatin (FOLFOX-4) as second-line therapy in metastatic colorectal cancer: a randomized phase III noninferiority study. Ann Oncol 2008;19:1720-1726.
43. Bécouarn Y, Ychou M, Ducreux M, et al. Phase II trial of oxaliplatin as first-line chemotherapy in metastatic colorectal cancer patients. Digestive Group of French Federation of Cancer Centers. J Clin Oncol 1998;16:2739-2744.
44. Argyriou AA, Cavaletti G, Briani C, et al. Clinical pattern and associations of oxaliplatin acute neurotoxicity: a prospective study in 170 patients with colorectal cancer. Cancer 2013;119:438-444.
45. Colucci G, Gebbia V, Paoletti G, et al. Phase III randomized trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: a multicenter study of the Gruppo Oncologico Dell'Italia Meridionale. J Clin Oncol 2005;23:4866-4875.
46. Ashley AC, Sargent DJ, Alberts SR, et al. Updated efficacy and toxicity analysis of irinotecan and oxaliplatin (IROX): intergroup trial N9741 in first-line treatment of metastatic colorectal cancer. Cancer 2007;110:670-677.
47. Tournigand C, André T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 2004;22:229-237.
48. Gamelin E, Gamelin L, Bossi L, et al. Clinical aspects and molecular basis of oxaliplatin neurotoxicity: current management and development of preventive measures. Semin Oncol 2002;29:21-33.
49. Cassidy J, Misset JL. Oxaliplatin-related side effects: characteristics and management. Semin Oncol 2002;29:11-20.
50. Polyzos A, Tsavaris N, Gogas H, et al. Clinical features of hypersensitivity reactions to oxaliplatin: a 10-year experience. Oncology 2009;76:36-41.
51. Suenaga M, Mizunuma N, Shinozaki E, et al. Management of allergic reactions to oxaliplatin in colorectal cancer patients. J Support Oncol 2008;6:373-378.
52. Rougier P, Bugat R, Douillard JY, et al. Phase II study of irinotecan in the treatment of advanced colorectal cancer in chemotherapy-naive patients and patients pretreated with fluorouracil-based chemotherapy. J Clin Oncol 1997;15:251-260.
53. Pommier Y, Tanizawa A, Kohn KW. Mechanisms of topoisomerase I inhibition by anticancer drugs. Adv

Pharmacol 1994;29B:73-92.
54. Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet 2000;355:1041-1047.
55. Köhne CH, van Cutsem E, Wils J, et al. Phase III study of weekly high-dose infusional fluorouracil plus folinic acid with or without irinotecan in patients with metastatic colorectal cancer: European Organisation for Research and Treatment of Cancer Gastrointestinal Group Study 40986. J Clin Oncol 2005;23:4856-4865.
56. Saltz LB, Cox JV, Blanke C, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. N Engl J Med 2000;343:905-914.
57. Patt YZ, Lee FC, Liebmann JE, et al. Capecitabine plus 3-weekly irinotecan (XELIRI regimen) as first-line chemotherapy for metastatic colorectal cancer: phase II trial results. Am J Clin Oncol 2007;30:350-357.
58. Fuchs CS, Marshall J, Mitchell E, et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. J Clin Oncol 2007;25:4779-4786.
59. Bidard FC, Tournigand C, André T, et al. Efficacy of FOLFIRI-3 (irinotecan D1,D3 combined with LV5-FU) or other irinotecan-based regimens in oxaliplatin-pretreated metastatic colorectal cancer in the GERCOR OPTIMOX1 study. Ann Oncol 2009;20:1042-1047.
60. Recchia F, Saggio G, Nuzzo A, et al. Multicentre phase II study of bifractionated CPT-11 with bimonthly leucovorin and 5-fluorouracil in patients with metastatic colorectal cancer pretreated with FOLFOX. Br J Cancer 2004;91:1442-1446.
61. Grothey A, Sargent D, Goldberg RM, et al. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. J Clin Oncol 2004;22:1209-1214.
62. Felici A, Verweij J, Sparreboom A. Dosing strategies for anticancer drugs: the good, the bad and body-surface area. Eur J Cancer 2002;38:1677-1684.
63. Mathijssen RH, Verweij J, de Jonge MJ, et al. Impact of body-size measures on irinotecan clearance: alternative dosing recommendations. J Clin Oncol 2002;20:81-87.
64. Ratain MJ. Irinotecan dosing: does the CPT in CPT-11 stand for "Can't Predict Toxicity"? J Clin Oncol 2002;20:7-8.
65. Mathijssen RH, Marsh S, Karlsson MO, et al. Irinotecan pathway genotype analysis to predict pharmacokinetics. Clin Cancer Res 2003;9:3246-3253.
66. Michael M, Thompson M, Hicks RJ, et al. Relationship of hepatic functional imaging to irinotecan pharmacokinetics and genetic parameters of drug elimination. J Clin Oncol 2006;24:4228-4235.
67. Raymond E, Boige V, Faivre S, et al. Dosage adjustment and pharmacokinetic profile of irinotecan in cancer patients with hepatic dysfunction. J Clin Oncol 2002;20:4303-4312.
68. Innocenti F, Undevia SD, Iyer L, et al. Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. J Clin Oncol 2004;22:1382-1388.
69. Carlini LE, Meropol NJ, Bever J, et al. UGT1A7 and UGT1A9 polymorphisms predict response and toxicity in colorectal cancer patients treated with capecitabine/irinotecan. Clin Cancer Res 2005;11:1226-1236.
70. Côté JF, Kirzin S, Kramar A, et al. UGT1A1 polymorphism can predict hematologic toxicity in patients treated with irinotecan. Clin Cancer Res 2007;13:3269-3275.
71. Liu CY, Chen PM, Chiou TJ, et al. UGT1A1*28 polymorphism predicts irinotecan-induced severe toxicities without affecting treatment outcome and survival in patients with metastatic colorectal carcinoma. Cancer 2008;112:1932-1940.
72. Palomaki GE, Bradley LA, Douglas MP, et al. Can UGT1A1 genotyping reduce morbidity and mortality in patients with metastatic colorectal cancer treated with irinotecan? An evidence-based review. Genet Med 2009;11:21-34.
73. Toffoli G, Cecchin E, Corona G, et al. The role of UGT1A1*28 polymorphism in the pharmacodynamics and pharmacokinetics of irinotecan in patients with metastatic colorectal cancer. J Clin Oncol 2006;24:3061-3068.
74. Falcone A, Ricci S, Brunetti I, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. J Clin Oncol 2007;25:1670-1676.
75. Falcone A, Cremolini C, Masi G, et al. FOLFOXIRI/bevacizumab (bev) versus FOLFIRI/bev as first-line treatment in unresectable metastatic colorectal cancer (mCRC) patients (pts): Results of the phase III TRIBE trial by GONO group. J Clin Oncol 2013;31(suppl; abstr 3505).

76. Los M, Roodhart JM, Voest EE. Target practice: lessons from phase III trials with bevacizumab and vatalanib in the treatment of advanced colorectal cancer. Oncologist 2007;12:443-450.
77. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335-2342.
78. Fuchs CS, Marshall J, Barrueco J. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: updated results from the BICC-C study. J Clin Oncol 2008;26:689-690.
79. Saltz LB, Clarke S, Díaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol 2008;26:2013-2019.
80. Kabbinavar FF, Schulz J, McCleod M, et al. Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: results of a randomized phase II trial. J Clin Oncol 2005;23:3697-3705.
81. Vincenzi B, Santini D, Russo A, et al. Bevacizumab in association with de Gramont 5-fluorouracil/folinic acid in patients with oxaliplatin-, irinotecan-, and cetuximab-refractory colorectal cancer: a single-center phase 2 trial. Cancer 2009;115:4849-4856.
82. Bekaii-Saab TS, Grothey A, Bendell JC, et al. Effectiveness and safety of second-line (2L) irinotecan- and oxaliplatin-based regimens after first-line (1L) bevacizumab (BV)-containing treatment (tx) for metastatic colorectal cancer (mCRC): Results from the ARIES observational cohort study. J Clin Oncol 2012;30:abstr 535.
83. Cartwright TH, Yim YM, Yu E, et al. Survival outcomes of bevacizumab beyond progression in metastatic colorectal cancer patients treated in US community oncology. Clin Colorectal Cancer 2012;11:238-246.
84. Grothey A, Sugrue MM, Purdie DM, et al. Bevacizumab beyond first progression is associated with prolonged overall survival in metastatic colorectal cancer: results from a large observational cohort study (BRiTE). J Clin Oncol 2008;26:5326-5334.
85. Bennouna J, Sastre J, Arnold D, et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. Lancet Oncol 2013;14:29-37.
86. An MM, Zou Z, Shen H, et al. Incidence and risk of significantly raised blood pressure in cancer patients treated with bevacizumab: an updated meta-analysis. Eur J Clin Pharmacol 2010;66:813-821.
87. Scappaticci FA, Skillings JR, Holden SN, et al. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. J Natl Cancer Inst 2007;99:1232-1239.
88. Schutz FA, Je Y, Azzi GR, et al. Bevacizumab increases the risk of arterial ischemia: a large study in cancer patients with a focus on different subgroup outcomes. Ann Oncol 2011;22:1404-1412.
89. Hang XF, Xu WS, Wang JX, et al. Risk of high-grade bleeding in patients with cancer treated with bevacizumab: a meta-analysis of randomized controlled trials. Eur J Clin Pharmacol 2011;67:613-623.
90. Hurwitz HI, Saltz LB, Van Cutsem E, et al. Venous thromboembolic events with chemotherapy plus bevacizumab: a pooled analysis of patients in randomized phase II and III studies. J Clin Oncol 2011;29:1757-1764.
91. Nalluri SR, Chu D, Keresztes R, et al. Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis. JAMA 2008;300:2277-2285.
92. Ranpura V, Hapani S, Chuang J, et al. Risk of cardiac ischemia and arterial thromboembolic events with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis of randomized controlled trials. Acta Oncol 2010;49:287-297.
93. Shah SR, Gressett Ussery SM, Dowell JE, et al. Shorter bevacizumab infusions do not increase the incidence of proteinuria and hypertension. Ann Oncol 2013;24:960-965.
94. Wu S, Kim C, Baer L, et al. Bevacizumab increases risk for severe proteinuria in cancer patients. J Am Soc Nephrol 2010;21:1381-1389.
95. Hapani S, Sher A, Chu D, et al. Increased risk of serious hemorrhage with bevacizumab in cancer patients: a meta-analysis. Oncology 2010;79:27-38.
96. Kozloff M, Yood MU, Berlin J, et al. Clinical outcomes associated with bevacizumab-containing treatment of metastatic colorectal cancer: the BRiTE observational cohort study. Oncologist 2009;14:862-870.
97. Maitland ML, Bakris GL, Black HR, et al. Initial assessment, surveillance, and management of blood pressure in patients receiving vascular endothelial growth factor signaling pathway inhibitors. J Natl Cancer Inst 2010;102:596-604.
98. Ranpura V, Hapani S, Wu S. Treatment-related mortality with bevacizumab in cancer patients: a meta-analysis. JAMA 2011;305:487-494.
99. el-Hariry I, Pignatelli M, Lemoine N. Fibroblast growth

factor 1 and fibroblast growth factor 2 immunoreactivity in gastrointestinal tumours. J Pathol 1997;181:39-45.
100. Messa C, Russo F, Caruso MG, et al. EGF, TGF-alpha, and EGF-R in human colorectal adenocarcinoma. Acta Oncol 1998;37:285-289.
101. Wu X, Fan Z, Masui H, et al. Apoptosis induced by an anti-epidermal growth factor receptor monoclonal antibody in a human colorectal carcinoma cell line and its delay by insulin. J Clin Invest 1995;95:1897-1905.
102. Goldstein NI, Prewett M, Zuklys K, et al. Biological efficacy of a chimeric antibody to the epidermal growth factor receptor in a human tumor xenograft model. Clin Cancer Res 1995;1:1311-1318.
103. Jonker DJ, O'Callaghan CJ, Karapetis CS, et al. Cetuximab for the treatment of colorectal cancer. N Engl J Med 2007;357:2040-2048.
104. Au HJ, Karapetis CS, O'Callaghan CJ, et al. Health-related quality of life in patients with advanced colorectal cancer treated with cetuximab: overall and KRAS-specific results of the NCIC CTG and AGITG CO.17 Trial. J Clin Oncol 2009;27:1822-1828.
105. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 2004;351:337-345.
106. Sobrero AF, Maurel J, Fehrenbacher L, et al. EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. J Clin Oncol 2008;26:2311-2319.
107. Van Cutsem E, Köhne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 2009;360:1408-1417.
108. Van Cutsem E, Köhne CH, Láng I, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. J Clin Oncol 2011;29:2011-2019.
109. Bokemeyer C, Bondarenko I, Hartmann JT, et al. Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: the OPUS study. Ann Oncol 2011;22:1535-1546.
110. Venook A, Niedzwiecki D, Hollis D, et al. Phase III study of irinotecan/5FU/LV (FOLFIRI) or oxaliplatin/5FU/LV (FOLFOX) ± cetuximab for patients (pts) with untreated metastatic adenocarcinoma of the colon or rectum (MCRC): CALGB 80203 preliminary results. J Clin Oncol 2006;24:abstr 3509.
111. Maughan TS, Adams RA, Smith CG, et al. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. Lancet 2011;377:2103-2114.
112. Tveit KM, Guren T, Glimelius B, et al. Phase III trial of cetuximab with continuous or intermittent fluorouracil, leucovorin, and oxaliplatin (Nordic FLOX) versus FLOX alone in first-line treatment of metastatic colorectal cancer: the NORDIC-VII study. J Clin Oncol 2012;30:1755-1762.
113. Polikoff J, Mitchell E, Badarinath S, et al. Cetuximab plus FOLFOX for colorectal cancer (EXPLORE): Preliminary efficacy analysis of a randomized phase III trial. J Clin Oncol 2005;23:abstr 3574.
114. Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol 2007;25:1658-1664.
115. Amado RG, Wolf M, Peeters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 2008;26:1626-1634.
116. Douillard JY, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. J Clin Oncol 2010;28:4697-4705.
117. Douillard JY, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. N Engl J Med 2013;369:1023-1034.
118. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med 2008;359:1757-1765.
119. Price TJ, Peeters M, Kim TW, et al. ASPECCT: a randomized, multicenter, open-label, phase 3 study of panitumumab (pmab) vs cetuximab (cmab) for previously treated wild-type (WT) KRAS metastatic colorectal cancer (mCRC). European Cancer Congress. Amsterdam, the Netherlands, 2013.
120. De Roock W, Claes B, Bernasconi D, et al. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. Lancet Oncol 2010;11:753-762.
121. Vaughn CP, Zobell SD, Furtado LV, et al. Frequency of KRAS, BRAF, and NRAS mutations in colorectal cancer. Genes Chromosomes Cancer 2011;50:307-312.

122. Stintzing S, Jung A, Rossius L, et al. Analysis of KRAS/NRAS and BRAF mutations in FIRE-3: A randomized phase III study of FOLFIRI plus cetuximab or bevacizumab as first-line treatment for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC) patients. Presented at: European Cancer Congress 2013; September 27-October 1, 2013; Amsterdam, The Netherlands. Abstract LBA17.
123. O'Neil BH, Allen R, Spigel DR, et al. High incidence of cetuximab-related infusion reactions in Tennessee and North Carolina and the association with atopic history. J Clin Oncol 2007;25:3644-3648.
124. Saltz LB, Lenz HJ, Kindler HL, et al. Randomized phase II trial of cetuximab, bevacizumab, and irinotecan compared with cetuximab and bevacizumab alone in irinotecan-refractory colorectal cancer: the BOND-2 study. J Clin Oncol 2007;25:4557-4561.
125. Hecht JR, Mitchell E, Chidiac T, et al. A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. J Clin Oncol 2009;27:672-680.
126. Tol J, Koopman M, Cats A, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. N Engl J Med 2009;360:563-572.
127. Heinemann V, von Weikersthal LF, Decker T, et al. Randomized comparison of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment of KRAS wild-type metastatic colorectal cancer: German AIO study KRK-0306 (FIRE-3). J Clin Oncol 2013;31:abstr LBA3506.

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Outcome of rectal cancer after radiotherapy with a long or short waiting period before surgery, a descriptive clinical study

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Background: Radiotherapy and surgery have shown to improve local control and survival in rectal cancer. There are two applied schedules; radiotherapy with a long or short waiting period before surgery. The effect on survival and recurrence of both schedules was studied.

Methods: All consecutive patients with rectal cancer in the period 2002-2008 were included. Data were gathered on survival, tumour stage, co-morbidity score, and cause of death. The patients were divided in three groups: group 1 patients undergoing surgery without neo-adjuvant radiotherapy; group 2 patients undergoing radiotherapy followed by immediate surgery; and group 3 patients treated with (chemo) radiotherapy followed by a longer waiting period.

Results: A total of 113 patients with rectal cancer underwent surgery. Twenty two patients in group 1, 71 patients in group 2, and 20 in group 3. There was no difference in gender, time to recurrence, co-morbidity score, or causes of death. Fifty percent of patients died due to non-cancer related causes. Mean age in patients of group 3 was significantly lower than in groups 1 and 2 (P=0.02). There was a trend towards a lower tumour stage in the patients of group 3. Overall five year survival was 32% in group 1, 48% in group 2, and 35% in group 3.

Conclusions: Neo-adjuvant radiotherapy seems to be of benefit in daily practice in patients with rectal cancer. A longer waiting period results in down-staging. Clinicians have to be aware that many patients will die due to other causes than those related to the rectal cancer.

Keywords: Rectal cancer; radiotherapy; survival; recurrence; co-morbidity; Charlson score

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Introduction

Rectal cancer is one of the most prevalent cancers in the gastrointestinal tract (1). The only curative treatment option is surgery. In the past, local recurrence was a major problem. (Neo)-adjuvant radiotherapy in combination with conventional surgery, has shown to improve local control and survival. The Dutch Total Mesorectal Excision (TME) trial investigated the value of radiotherapy in combination with surgery. The local recurrence risk almost halved after six years of follow-up. However, an effect on overall survival could not be demonstrated (2-4).

There are two frequently applied schedules of neo-adjuvant (chemo)radiation. The first one is radiotherapy 5 times 5 Gy followed by immediate surgery, the second one is radiotherapy in combination with chemotherapy followed by a longer waiting period before the actual surgical resection. According to the literature there is no difference in outcome with respect to overall survival, recurrence free survival and local recurrences between both schedules (5,6).

However, patients reported in the literature are not representative of the population seen in daily practice. In trials strict inclusion and exclusion criteria are used. In the studies by Peeters and Sebag-Montefiore median ages were comparable to the one in a cohort in our clinic (7). However, 99% of patients in the study by Sebag-Montefiore had a WHO performance score of 1 or higher indicating that a group of patients with more co-morbidity has been excluded. Unfortunately functional status of patients in this cohort has not been documented (3,4).

In daily practice doctors are confronted with patients fulfilling many or all exclusion criteria applied in clinical trials. Hence, data from the literature cannot always be extrapolated to daily practice.

For this reason, a study was done in usual daily practice in a group of consecutive patients with rectal cancer in order to gather data on survival and recurrences and to correlate these to the kind of radiotherapy that was given.

Methods

All consecutive patients diagnosed with rectal cancer in the period 2002-2008 were included in the present study. This period was chosen in order to obtain adequate follow-up data of all patients. An extensive search was done of clinical records in order to evaluate the clinical course of the patients.

For all patients, treatment was determined, in addition, data were gathered on survival, stage of the tumour, co-morbidity according to the well-known Charlson score, and cause of death.

It was determined whether death was the result of the rectal cancer itself, the complication of the treatment, or not related to rectal cancer at all (death due to co-morbidity, this is non-cancer related causes).

Evaluation was done in January 2014. Hence, follow-up was longer than 5 years in all patients.

The patients were divided in three groups: group 1 patients undergoing surgery without neo-adjuvant radiotherapy; group 2 patients undergoing 5×5 Gy radiotherapy followed by immediate surgery (short course, within 4 weeks after radiation); and group 3 patients treated with (chemo) radiotherapy followed by a longer waiting period (long course) before actual surgery. The decision to choose for the short or the long course was made in a multi-disciplinary meeting and was based on clinical judgment and imaging of tumour extension, N-stage and the intention to downsize the tumour in the long course. Patients who did not undergo surgery, obviously, were excluded

Statistical analysis was done with chi-square test for contingency tables and *t*-test. A value below 0.05 was considered significant.

Results

In the period of 7 years a total of 143 patients was diagnosed and treated for rectal cancer. Of these, 113 underwent surgery. This is the group analysed in this study. Twenty two patients (12 men, 10 women) underwent surgery without neo-adjuvant radiotherapy (group 1). Ninety one patients (55 men, 36 women) were treated with neo-adjuvant radiotherapy; 71 patients in the short course (group 2), and 20 in the long course schedule (group 3).

Table 1 shows the results in the three groups of patients. There was no difference in gender. Mean age in patients of group 3 was significantly lower than in groups 1 and 2 (P=0.02). There was no significant difference in cause of death between the three groups. Recurrence of disease occurred in all three groups without any difference. *Figure 1* shows the recurrence free period graphically. There was no significant difference in time to recurrence. There was a trend towards a lower tumour stage in the patients of group 3, implying successful down-staging of the tumour. There was no difference in co-morbidity score.

Figure 2 shows the five year survival. There was no significant difference between the three groups. Overall five year survival was 32% in group 1, 48% in group 2, and 35% in group 3.

Discussion

Treatment decisions have to be made by clinicians relying on data from the literature that cannot always be strictly applied to their patients. Hence, in daily practice, sometimes decisions have to be made that contradict the guidelines from the literature. So, our study population represents daily practice and the outcome data are comparable to those of selected patients included in randomised controlled trials. All patients treated for rectal cancer, in the time period of this study, were discussed in a multi-disciplinary meeting with oncologists, gastroenterologists, radiologists, radiotherapists and surgeons. On the basis of the clinical and radiological presentation, and data from the literature, a therapeutic regimen was chosen. In the study period neo-adjuvant radiotherapy was applied in all patients with a T3 stage and judged fit enough to undergo the treatment. In the final

Table 1 Demographics, tumour stage, survival, Charlson co-morbidity score and causes of death in the three groups of patients

Characteristics	Group 1 (%)	Group 2 (%)	Group 3 (%)	P
Number	22	71	20	
Men	12	43	12	ns
Mean age (SD)	75.5 (10.5)	69.8 (9.7)	63.5 (7.8)	≤0.001
Deceased	15	37	13	ns
Cause of death				ns
Tumour related	5 (33.3)	17 (45.9)	5 (38.5)	
Therapy related	0	5 (13.5)	2 (15.3)	
Not related to cancer	10 (66.7)	15 (40.6)	6 (46.2)	
Recurrence	6 (27.0)	19 (27.0)	10 (50.0)	ns
Time to recurrence				ns
Mean (SD)	1.83 (0.89)	1.46 (1.19)	2.11 (1.73)	
Range	0.8-2.9	0-4.5	0.1-5.6	
Tumour stage (as determined in the resection specimen)				
1	6 (27.2)	10 (14.0)	0	
2	8 (36.4)	25 (35.2)	12 (60.0)	
3	6 (27.2)	29 (40.8)	3 (15.0)	
4	1 (4.6)	5 (7.0)	3 (15.0)	
Unknown	1 (4.6)	2 (3.0)	2 (10.0)	
Charlson score	5 (2.00)	4.13 (1.73)	3.95 (2.06)	ns

Group 1: no neo-adjuvant treatment; group 2: 5×5 Gy followed by surgery within four weeks; and group 3: neo-adjuvant therapy followed by long interval until surgery. ns, not significant.

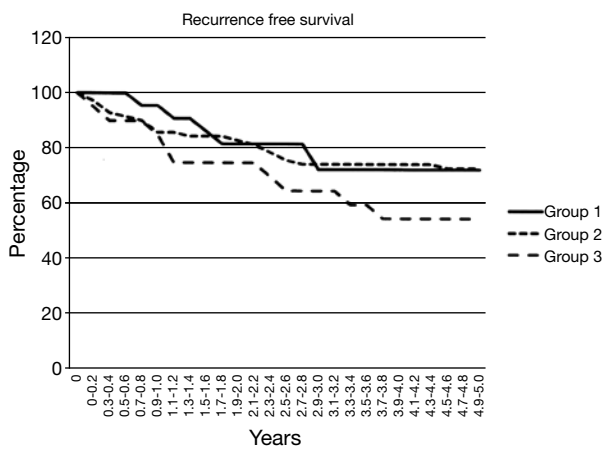

Figure 1 Recurrence free period in the three groups.

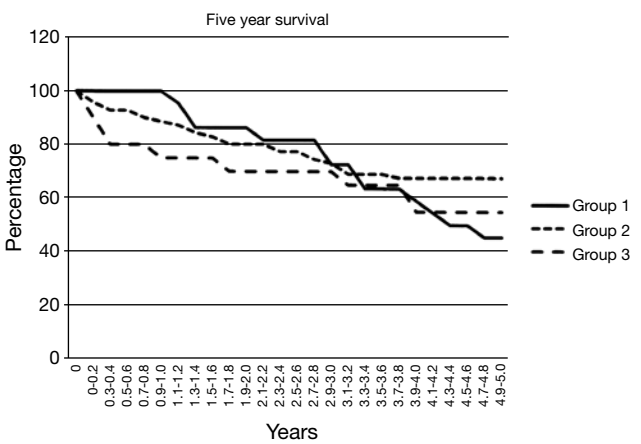

Figure 2 Overall survival in all patients.

years of the study period chemo-radiation was also applied in some patients on basis of the N-stage. In that aspect this study presents unique data, since there is also a group of patients not been treated with neo-adjuvant therapy. The five year survival was much lower than reported in the literature. Presence of co-morbidity is an important factor in mortality. These patients usually do not participate in clinical trials, simply because of their co-morbidity. There was no difference in the three groups with respect to overall survival. Also there was no difference with respect

to recurrent disease. An important observation is the fact that many patients do not die because of cancer but because of non-cancer related causes. This reduces the effect of treatment on overall survival. This is important when discussing survival after treatment of cancer. The majority of the patients in our study were older with a limited life expectancy. The patients in the three groups are comparable with respect to gender and co-morbidity score.

At a first glance, there is no benefit between surgery with or without neo-adjuvant radiotherapy. Indeed, survival and recurrence rate was the same for all three groups. However, these results can also be interpreted differently. Patients receiving neo-adjuvant radiotherapy had a higher clinical stage at presentation. Despite this the results of treatment were the same as in patients with a low stage of disease, possibly because of the effect of radiotherapy. It could be speculated that if the patients in groups 2 and 3 did not undergo neo-adjuvant therapy the survival would have been worse.

Short-term 5×5 Gy radiotherapy has become a popular preoperative treatment for patients with resectable rectal cancer in the Netherlands. An older study clearly demonstrated improved overall survival with radiotherapy. This study used radiotherapy followed by surgery within one week. The overall five-year survival rate was 58 percent in the radiotherapy-plus-surgery group and 48 percent in the surgery-alone group (P=0.004) (8,9).

The intention to down stage the tumour was the argument for a longer waiting period after radiation. According to a meta-analysis, short course radiotherapy with immediate surgery is as effective as long-course chemo-radiotherapy with delayed surgery for the treatment of rectal cancer in terms of overall survival, disease free survival, local recurrence rate, and distant metastases (5,6). Down-staging the tumour is the purpose of radiotherapy. Foster *et al*. did a literature review. They found limited evidence to support decisions regarding when to resect rectal cancer following chemo-radiotherapy. There may be benefits in prolonging the interval between chemo-radiotherapy and surgery beyond the 6 to 8 weeks that is commonly practiced (10). However, there are also data which do not show any down-staging. Sirohi *et al*. did a retrospective analysis in 110 patients and concluded that timing of surgery, a longer time interval, did not influence pathological response (11). In a study by Perez *et al*. it was shown that increased uptake of FDG during PET-scan was a sign of absence of down-staging (12). In the present study there was a trend towards successful down-staging after a longer waiting period. This did not reach statistical significance probably due to the low number of patients in this group.

The final conclusion of the present study is that neo-adjuvant radiotherapy seems to be of benefit in daily practice in selected patients with rectal cancer. Co-morbidity score is not of influence on the outcome. A longer waiting period after radiation therapy results in successful down-staging as expressed by the lower Dukes stage of the resected specimen. In addition, clinicians have to be aware that many patients will die due to other causes than those related to the rectal cancer itself, irrespective of the outcome of rectal cancer treatment.

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Footnote

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

References

1. Integraal kanker centrum Nederland. 2014. Available online: www.cijfersoverkanker.nl
2. Colorectal Cancer Collaborative Group. Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomised trials. Lancet 2001;358:1291-1304.
3. Peeters KC, Marijnen CA, Nagtegaal ID, et al. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. Ann Surg 2007;246:693-701.
4. Quirke P, Steele R, Monson J, et al. Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. Lancet 2009;373:821-828.
5. Zhou ZR, Liu SX, Zhang TS, et al. Short-course preoperative radiotherapy with immediate surgery versus long-course chemoradiation with delayed surgery in the treatment of rectal cancer: a systematic review and meta-analysis. Surg Oncol 2014;23:211-221.
6. Sajid MS, Siddiqui MR, Kianifard B, et al. Short-course versus long-course neoadjuvant radiotherapy for lower rectal cancer: a systematic review. Ir J Med Sci

2010;179:165-171.
7. van Eeghen EE, Bakker SD, van Bochove A, et al. Impact of age and comorbidity on survival in colorectal cancer. J Gastrointest Oncol 2015;6:605-612.
8. Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. N Engl J Med 1997;336:980-987.
9. Folkesson J, Birgisson H, Pahlman L, et al. Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. J Clin Oncol 2005;23:5644-5650.
10. Foster JD, Jones EL, Falk S, et al. Timing of surgery after long-course neoadjuvant chemoradiotherapy for rectal cancer: a systematic review of the literature. Dis Colon Rectum 2013;56:921-930.
11. Sirohi B, Barreto SG, Patkar S, et al. Down-staging following neoadjuvant chemo-radiotherapy for locally advanced rectal cancer: Does timing of surgery really matter? Indian J Med Paediatr Oncol 2014;35:263-266.
12. Perez RO, Habr-Gama A, São Julião GP, et al. Optimal timing for assessment of tumor response to neoadjuvant chemoradiation in patients with rectal cancer: do all patients benefit from waiting longer than 6 weeks? Int J Radiat Oncol Biol Phys 2012;84:1159-1165.

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Management of oligometastatic rectal cancer: is liver first?

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Abstract: Twenty percent of patients with rectal cancer present with synchronous liver metastases at the time of initial diagnosis. These patients can be treated with a curative intent, although the choice and sequence of treatment modalities are not well established and are commonly debated in multi-disciplinary tumor boards. In this article we review clinical evidence for various treatment approaches and attempt to formulate a pathway for clinicians to use in evaluating and managing these patients.

Keywords: Rectal cancer; oligometastatic; radiation therapy; surgery; review

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Introduction

In 2014, an estimated 40,000 new cases of rectal cancer will occur in the United States (1). Approximately 20% of patients with locally advanced rectal cancer will present with synchronous liver metastases at the time of initial diagnosis (2). A recent meta-analysis reported a median survival of 3.6 years after liver resection in metastatic colorectal cancer, and a median 5-year survival of 38% (3). Several retrospective analyses of carefully selected patients with solitary colorectal liver metastases reported 5-year survival rates as high as 70% following liver resection (4-6). This heterogeneous patient population thus presents with the daunting combination of a reasonable curative potential and a high risk of systemic disease progression. The optimal management of this subgroup of patients is not well established and includes surgical resection of primary disease, systemic therapy (including cytotoxic chemotherapy and/or targeted small molecule therapeutics), pelvic radiation therapy and liver-directed therapy. Appropriate use, sequencing and timing of these therapeutic modalities are not supported by randomized clinical trials in patients with synchronous oligometastatic liver disease with primary rectal cancer and are hence open to debate. We will attempt to synthesize a reasonable treatment paradigm based on clinical evidence, realizing that clinical experience and expertise of individual physicians as well as individual patient characteristics and preferences should guide the multidisciplinary team decision. Well-designed clinical trials and novel therapeutic modalities will be expected to either support or reverse our theoretical exercises.

Upfront surgery *vs.* systemic therapy

Upfront surgical resection of all gross disease, whether synchronous or staged, is a common practice at many institutions (7). Two primary arguments for this approach are both the concern for the known hepatic toxicity of prolonged courses of cytotoxic chemotherapy, with irinotecan-based regimens, in particular, contributing to the development of chemotherapy-associated steatohepatitis (CASH) and sinusoidal congestion, which increase the risk of complications at the time of liver resection. Another argument is a potential for liver disease progression on systemic chemotherapy and a possibility of losing a window of opportunity to administer a curative R0 resection for patients expressing a more aggressive malignant phenotype or one unresponsive to standard chemotherapy regimens.

A level 1 data set on this subject, the EORTC Intergroup trial 40983 randomized 364 patients with colorectal cancer and up to four liver metastases to either six cycles of FOLFOX4 before and six cycles after surgery or to surgery

alone. The initial publication (8) with a median follow up of 3.9 years revealed a statistically significant improvement in progression-free survival with the bi-modality approach. Reversible post-operative complications were higher in the chemotherapy group (25% *vs*. 16%, P=0.04), while post-operative death was similar in the two arms (1%), and only 1 out of 182 patients in the chemotherapy arm could not undergo resection due to liver damage. Twelve patients (7%) showed progressive disease on chemotherapy, with only 4 of these 12 becoming unresectable due to progression of liver lesions. The long-term results were published last year (9) and revealed no difference in overall survival (51% *vs*. 48% at 5 years). Two patients in the perioperative chemotherapy group and three in the surgery-only group died from complications of protocol surgery, and one patient in the perioperative chemotherapy group died possibly as a result of toxicity of protocol treatment. The retrospective analysis of EORTC 40983 data suggested a benefit of perioperative chemotherapy in patients with CEA values of >5 ng/mL, good performance score and body mass index <30 (10). While this is certainly a landmark study, it is difficult to draw definitive conclusions from the EORTC data regarding rectal cancer, as only 1/3 in each group had a rectal primary and in the entire cohort only 35% had synchronous disease. It is likely that different considerations should be weighed in those with synchronous disease at presentation. If there is concern for liver damage precluding resection with up-front chemotherapy, strong consideration should be given to proceeding with surgical resection as first-line therapy. Alternatively, in those who may be borderline for resection due to technical considerations, relationship of tumor(s) to critical structures, and size of the future liver remnant, chemotherapy should be the initial choice. Thus, careful planning in the multi-disciplinary setting prior to initiation of therapy is critical.

Response to chemotherapy is recognized as a predictor of outcome after resection (11,12), and patients who are offered metastatectomy in the setting of disease progression on chemotherapy have worse outcomes compared to those with radiographic response based on 5-year survival rates of 8% *vs*. 37%, as published by Adam *et al*. (13). Therefore systemic therapy prior to surgery appears to be safe, effective and can be used to select candidates with a more favorable tumor phenotype for liver metastases resection.

In the setting of oligometastatic rectal cancer, one should also consider the effect of the first treatment modality on the primary disease status. If a curative surgical approach is selected, obtaining local control becomes critical. Consider local recurrence rates of 22% for stage II and 46% for stage III patients treated on the Swedish Rectal Cancer Trial with surgery alone (14). Among patients with synchronous metastatic disease, the rates of advanced primary disease are high—for example, a contemporary series from Johns Hopkins University revealed 86% of patients had T3/T4 primary disease and approximately two-thirds had N+ disease at presentation (15). At the same time 50-60% of patients with stage II and III rectal cancer are down-staged following neoadjuvant therapy, with about 20% of patients showing a pathologic complete response (16-19).

For all the above mentioned reasons upfront surgery should not be considered standard in the setting of oligometastatic rectal cancer. The National Comprehensive Cancer Network (NCCN) have updated their 2014 guidelines version and removed upfront surgery from the standard treatment algorithm (20) for resectable synchronous metastatic rectal cancer.

Neoadjuvant therapy

The current version of NCCN guidelines offer two initial pathways for treating rectal cancer with resectable synchronous metastases—either an oxaliplatin-containing chemotherapy or pelvic radiotherapy with 5-FU-based concurrent chemotherapy. Clearly, the first pathway predominantly focuses on the systemic disease, whereas the second pathway is directed more at the pelvic disease control. The neoadjuvant approach that optimizes the therapeutic ratio should be effective for both local and systemic disease components, and be well tolerated by the patients, who must still have a performance status appropriate for an R0 surgical resection.

A retrospective analysis was carried out on 20 patients (with a total of 41 liver lesions) who underwent preoperative chemo-RT for rectal cancer with synchronous resectable liver metastases (21). All patients received a standard fractionated course of pelvic RT to 45 or 50 Gy over a period of 5 weeks, with operation performed 6 to 8 weeks later. Seven patients received FU-based-chemotherapy and 13 patients received oxaliplatin-based chemotherapy, concurrently with radiation. During oxaliplatin-RT 25 liver lesions showed the following response: 14 showed an objective tumor response, 10 were stable and 1 progressed. Among the 16 liver lesions during 5-FU-RT, 10 lesions were stable and 6 progressed. The absence of concomitant oxaliplatin-based chemotherapy was the sole predictive factor (P=0.002) of liver disease progression on imaging

during chemo-RT. There were no postoperative deaths after either rectal or hepatic surgeries in this series. Three years OS and DFS were 51% and 24%, and 6 out of 13 (46%) patients on oxaliplatin-RT developed disease recurrence *vs.* 6 out of 7 (86%) patients on 5-FU-RT (P=0.157).

Thus, the data suggests that pelvic RT with 5-FU or capecitabine might not be effective enough in controlling liver disease and preventing new distant disease recurrence. Therefore one might argue for either addition of oxaliplatin to pelvic RT or oxaliplatin-based systemic chemotherapy alone with pelvic RT omission. A prospective study enrolled 32 patients with stages II and III rectal cancer and treated with neoadjuvant FOLFOX/bevacizumab without RT. One hundred percent of patients achieved R0 resection, with 25% path CR rate and 100% local control rate at 4 years. The NCCTG phase II/III trial is now recruiting patients with stage II-III rectal cancer to either neoadjuvant FOLFOX or preoperative chemo-RT (clinicaltrials.gov NCT01515787). The results of this randomized trial will reveal whether patients could be spared radiotherapy-related toxicity without jeopardizing local control.

While the addition of oxaliplatin to pelvic RT would seem to be one of the reasonable solutions, prospective clinical trial data suggests otherwise when evaluated in the setting of non-metastatic rectal cancer. The STAR-01 trial randomized patients to 5-FU/oxaliplatin/RT *vs.* 5-FU/RT and revealed no difference in path response rate between the arms, whereas grade 3 and 4 toxicities were higher among patients randomized to oxaliplatin arm (24% *vs.* 8%, P<0.001) (22). Similar results were found in NSABP R-04 (23) and the ACCORD 12/0405-Prodige 2 trial (24). Therefore, addition of oxaliplatin to a 5-FU-based neoadjuvant chemo-RT platform is not justified in non-metastatic setting at this point. However, this might not apply to patients with oligometastatic disease, where systemic disease control is more critical and this approach may be worth the risk of additional treatment toxicity.

Another strategy of combining oxaliplatin with pelvic radiation is currently studied in a Polish Colorectal Study Group randomized Phase III trial. Patients with fixed T3/T4 or locally recurrent rectal cancer without distant metastases are randomized to either short-course RT (5 Gy ×5, given over 1 week) and 3 courses of FOLFOX 4 versus standard 50.4 Gy RT with concurrent 5-FU/leucovorin and oxaliplatin. Surgery in both groups is performed 12 weeks after the beginning of radiation. The interim analysis of the first 100 patients was recently published (25) and revealed a path CR of 21% in short-course RT arm (experimental) *vs.* 8% in the standard RT (control) arm. The experimental arm had 27% rate of post-operative complications and no post-operative mortality.

A small Korean prospective study (26) enrolled 6 patients with oligometastatic rectal cancer on upfront systemic chemotherapy with FOLFOX (with and without biologic agents) and a short-course RT (5 Gy ×5) sandwiched between chemotherapy cycles, prior to surgery. Five patients achieved R0 while all liver metastases had regressed. Prior to surgery, three patients had grade 3 toxicities, controlled by conservative therapy. With a median follow-up of 16 months, there was no locoregional recurrence, one patient developed distant metastases and no patient died. The long-term follow-up report of this experience will be important to confirm the early observations.

At present, it appears that either an oxaliplatin-based systemic therapy alone or with concurrent pelvic RT (either standard fractionated RT or a short-course RT) are reasonable neoadjuvant treatment strategies for patients with *de novo* oligometastatic rectal cancer. Ongoing and future studies that include well-defined cohorts of patients and pre-treatment tumor parameters will help provide clarity as to which strategy yields the optimal therapeutic ratio.

Synchronous (combined) *vs.* staged (sequential) surgical procedures

No randomized studies have ever evaluated the difference between two surgical approaches—synchronous (combined) approach, when liver metastases are resected at the time of TME of rectal tumor, versus a staged approach, when the two surgeries are temporally separated. Consequently, this issue is debated in multidisciplinary tumor boards on a routine basis. Hillingso and Wille-Jorgensen (27) set out to perform a systematic review on the surgical approach for synchronous liver metastases from colorectal cancer in 2007 and found conflicting evidence from available case series. Among the series they have identified, 11 studies showed a tendency towards a shorter hospital stay in the synchronous resection group, 14 studies revealed a lower total perioperative morbidity with this approach, while 15 studies identified a lower perioperative mortality with the staged approach. Eleven studies compared 5-year overall survival, which appeared to be similar in both strategies. Specific factors that have been shown to increase the rate of postoperative complications in the combined procedures were the presence of a diverting stoma, rectal location of

the primary tumor, duration of the surgery, intraoperative blood loss and the need for transfusion. A large multi-institutional retrospective study with over 600 patients revealed similar rates of mortality and severe morbidity after simultaneous colorectal resection and minor hepatectomy compared with isolated minor hepatectomy alone. However, major hepatectomy independently predicted for severe morbidity after simultaneous resections with a hazard ratio of 3.4 (P=0.008). Much debate exists regarding the optimal surgical approach (28). Furthermore, adequately powered studies comparing outcomes for major hepatectomy alone versus in combination with TME are lacking. Another important consideration is the move toward minimally invasive techniques for both the hepatic resection and TME for the primary. Many centers are moving toward these techniques, and the oncologic integrity of these approaches has been validated by several studies and consensus statements (29,30). Currently, laparoscopic techniques tend to yield shorter hospitalizations for major hepatectomy at the expense of increased operative times. Thus, staged operations may confer an overall benefit to the patient in terms of time in the operating room and lower complication rates. Patient and tumor characteristics, surgical experience and patient preference should guide the decision. At the same time, alternatives to these surgeries should also be discussed with patients, when appropriate.

Avoidance of primary rectal tumor resection in complete responders to neoadjuvant therapy

Following the success of neoadjuvant chemo-RT in anal cancer with a shift of treatment paradigm from resection to organ-preservation, led by Nigro over 30 years ago (31), several retrospective studies analyzed the outcomes after observation following complete clinical response to neoadjuvant therapy in patients with localized rectal cancer. One earlier study showed promising results with excellent DFS and OS rates at 5 years (32), but most clinicians remained skeptical of this approach (33). However, a more recent study (34) prospectively selected 21 patients with localized rectal cancer who achieved a clinical CR after chemoradiotherapy, as evaluated by magnetic resonance imaging (MRI) and endoscopy with biopsies, and followed these patients by observation for a mean follow-up of 25 months. Only one patient developed a local recurrence and had a successful salvage surgery, whereas the remaining 20 patients were alive without disease. Because of limited data and concern about the ability of imaging studies to accurately determine a pathologic response (35), the NCCN 2014 panel did not support the observation approach for patients with localized rectal cancer with complete response to neoadjuvant treatment. However, this treatment paradigm, although previously untested, could be considered for patients with known metastatic disease. These patients have a higher likelihood of systemic disease progression than patients with localized rectal cancer, and therefore the tradeoff of a lower primary disease local control for the improved quality of life might be reasonable and worthy of further investigation. Quality of life can be improved in this patient population with surgery reserved for patients with local recurrence in the absence of systemic disease progression or in the event of symptomatic local disease progression. This approach, if used, should incorporate pelvic radiation therapy as part of a neoadjuvant treatment recommendation, as the rate of local recurrence after pathological response to chemotherapy alone has not yet been studied.

Alternatives to liver surgery

It is rare for liver metastases to be permanently eradicated with systemic chemotherapy alone, even in the setting of complete radiographic response. One study revealed an 83% rate of local failure or disease persistence in sites that had initially shown a complete response to systemic chemotherapy by CT imaging (36). These results highlighted the potential pitfalls when interpreting the "disappearing metastasis" as complete response to chemotherapy. Surgery remains the standard of care even when there is a significant or complete radiologic response to up-front chemotherapy for isolated liver metastases, with 5-year overall survival rates up to 70% in selected patients. However, because of tumor size and location, over four-fifths of patients present with unresectable disease (37). Nonsurgical options have emerged and continue to constantly improve.

Radiofrequency ablation (RFA) has recently been shown to offer a 60% rate of local control beyond 12 months (38-40) and should be considered for patients who are technically unresectable or unable to tolerate an open resection. In general, lesions amenable to RFA should be no larger than 3 cm in size, not located near hilar structures, and be treated at centers with expertise in this field. Controversy persists as to whether RFA is equivalent to open or laparoscopic resection for those with appropriately sized lesions and prospective data are sorely needed. In

fact, lack of adequate evidence prompted the American Society of Clinical Oncology (ASCO) to publish a review on this topic, and the data regarding the equivalence or comparative utility of RFA relative to surgical resection was found insufficient to issue a practice guideline (41).

Non-conformal radiation therapy has a very limited role in treatment of hepatic metastases due to the high rates of radiation-induced liver disease (RILD), which develops after large percentage of liver is exposed to the radiation dose, necessary to control the metastatic disease. However, stereotactic body radiation therapy (SBRT) has emerged, which delivers radiation to a target in the body, with sufficient intensity to kill, or at least control, the underlying malignancy, while minimizing the radiation dose to adjacent normal tissues. Effectively and safely accomplishing these conflicting goals requires quantitative visualization and localization of the target lesion, complex radiation plans, continual management of the target position throughout treatment, and robust quality assurance. Detailed review of SBRT technique and clinical data has been expertly reviewed elsewhere (42). The largest series with a long-term follow-up on SBRT in colorectal liver metastases reported on 65 patients with 102 lesions treated at Princess Margaret Hospital, University of Colorado and Stanford University (43). The overall local control rate was 71%, while patients who received biologically equivalent dose (BED) of ≥79 Gy_{10}, 12-, 18- and 24-month local control rates were 86%, 80% and 71%, respectively. On the basis of the best-fit curve, a BED of 117 Gy_{10} would yield a 90% local control rate (which corresponds to a dose schedule of at least 48 Gy given in 3 fractions of 16 Gy, or its equivalent if a different number of fractions is used). In terms of toxicity of this treatment, 17% of patients experienced grade ≥2 acute (defined as within 3 months of SBRT) GI toxicity, 3% did grade ≥3 elevated liver enzymes, but none had symptomatic liver toxicity. Late toxicities were also limited, with 6% of patients experiencing grade ≥2 GI toxicities: two patients had grade 3 gastritis and two patients had grade 2 small bowel ulcers.

Further validation is needed before SBRT can be considered a standard of care for liver metastases from rectal cancer. Currently, phase I trials at University of Pittsburgh (NCT01360606) and the University of Texas (NCT01162278), plus a phase II study at the Massachusetts General Hospital (NCT01239381), are accruing patients. A phase III trial at University of Aarhus is randomizing patients with liver metastases to RFA or SBRT. Whenever possible, patients should be offered a chance to participate in prospective studies. Nevertheless, both RFA and SBRT should be considered for patients who cannot undergo liver resection.

Summary

The heterogeneous group of patients with oligometastatic rectal cancer involving the liver presents with a daunting combination of a reasonable curative potential, yet with a high risk of systemic disease progression. The optimal management of this subgroup of patients is not well established. The 2014 NCCN guidelines have removed upfront surgery as the treatment recommendation for most patients, realizing that systemic and pelvic control take precedence over surgical extirpation of liver and primary disease. As summarized in this review article, oxaliplatin-based chemotherapy with or without pelvic radiation therapy, followed by either resection of primary and liver disease or consideration of non-surgical modalities appear to be the most well-supported treatment approaches in the literature. Multidisciplinary evaluation of each patient is paramount to achieve best outcomes, with taking into account patients' preferences as well the expertise and experience of the multidisciplinary team. Future well-designed studies will shed light on how best manage this heterogeneous group of patients.

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Footnote

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References

1. American Cancer Society. eds. Cancer Facts & Figures 2014. Atlanta: American Cancer Society, 2014.
2. McMillan DC, McArdle CS. Epidemiology of colorectal liver metastases. Surg Oncol 2007;16:3-5.
3. Kanas GP, Taylor A, Primrose JN, et al. Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. Clin Epidemiol 2012;4:283-301.
4. Aloia TA, Vauthey JN, Loyer EM, et al. Solitary colorectal liver metastasis: resection determines outcome. Arch Surg

2006;141:460-466; discussion 466-467.
5. Hur H, Ko YT, Min BS, et al. Comparative study of resection and radiofrequency ablation in the treatment of solitary colorectal liver metastases. Am J Surg 2009;197:728-736.
6. Lee WS, Yun SH, Chun HK, et al. Clinical outcomes of hepatic resection and radiofrequency ablation in patients with solitary colorectal liver metastasis. J Clin Gastroenterol 2008;42:945-949.
7. Weiser MR, Jarnagin WR, Saltz LB. Colorectal cancer patients with oligometastatic liver disease: what is the optimal approach? Oncology (Williston Park) 2013;27:1074-1078.
8. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet 2008;371:1007-1016.
9. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. Lancet Oncol 2013;14:1208-1215.
10. Schwarz L, Michel P, Scotté M, et al. Predictive Factors for the Benefit of Perioperative FOLFOX for Resectable Liver Metastasis in Colorectal Cancer Patients (EORTC Intergroup Trial 40983). Ann Surg 2015;261:e28-e29.
11. Blazer DG 3rd, Kishi Y, Maru DM, et al. Pathologic response to preoperative chemotherapy: a new outcome end point after resection of hepatic colorectal metastases. J Clin Oncol 2008;26:5344-5351.
12. Allen PJ, Kemeny N, Jarnagin W, et al. Importance of response to neoadjuvant chemotherapy in patients undergoing resection of synchronous colorectal liver metastases. J Gastrointest Surg 2003;7:109-115; discussion 116-117.
13. Adam R, Delvart V, Pascal G, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg 2004;240:644-657; discussion 657-658.
14. Folkesson J, Birgisson H, Pahlman L, et al. Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. J Clin Oncol 2005;23:5644-5650.
15. Assumpcao L, Choti MA, Gleisner AL, et al. Patterns of recurrence following liver resection for colorectal metastases: effect of primary rectal tumor site. Arch Surg 2008;143:743-749; iscussion 749-750.
16. Collette L, Bosset JF, den Dulk M, et al. Patients with curative resection of cT3-4 rectal cancer after preoperative radiotherapy or radiochemotherapy: does anybody benefit from adjuvant fluorouracil-based chemotherapy? A trial of the European Organisation for Research and Treatment of Cancer Radiation Oncology Group. J Clin Oncol 2007;25:4379-4386.
17. Das P, Skibber JM, Rodriguez-Bigas MA, et al. Clinical and pathologic predictors of locoregional recurrence, distant metastasis, and overall survival in patients treated with chemoradiation and mesorectal excision for rectal cancer. Am J Clin Oncol 2006;29:219-224.
18. Fietkau R, Barten M, Klautke G, et al. Postoperative chemotherapy may not be necessary for patients with ypN0-category after neoadjuvant chemoradiotherapy of rectal cancer. Dis Colon Rectum 2006;49:1284-1292.
19. Park IJ, You YN, Agarwal A, et al. Neoadjuvant treatment response as an early response indicator for patients with rectal cancer. J Clin Oncol 2012;30:1770-1776.
20. NCCN Guidelines Version 3. 2014. Rectal Cancer 2014 February 7, 2014.
21. Manceau G, Brouquet A, Bachet JB, et al. Response of liver metastases to preoperative radiochemotherapy in patients with locally advanced rectal cancer and resectable synchronous liver metastases. Surgery 2013;154:528-535.
22. Aschele C, Cionini L, Lonardi S, et al. Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. J Clin Oncol 2011;29:2773-2780.
23. Roh MS, Yothers GA, O'Connell MJ, et al. The impact of capecitabine and oxaliplatin in the preoperative multimodality treatment in patients with carcinoma of the rectum: NSABP R-04. J Clin Oncol 2011;29:abstr 3503.
24. Gérard JP, Azria D, Gourgou-Bourgade S, et al. Clinical outcome of the ACCORD 12/0405 PRODIGE 2 randomized trial in rectal cancer. J Clin Oncol 2012;30:4558-4565.
25. Bujko K, Nasierowska-Guttmejer A, Wyrwicz L, et al. Neoadjuvant treatment for unresectable rectal cancer: an interim analysis of a multicentre randomized study. Radiother Oncol 2013;107:171-177.
26. Shin SJ, Yoon HI, Kim NK, et al. Upfront systemic chemotherapy and preoperative short-course radiotherapy with delayed surgery for locally advanced rectal cancer with distant metastases. Radiat Oncol 2011;6:99.
27. Hillingsø JG, Wille-Jørgensen P. Staged or simultaneous resection of synchronous liver metastases from colorectal

cancer--a systematic review. Colorectal Dis 2009;11:3-10.
28. Conrad C, You N, Vauthey JN. In patients with colorectal liver metastases, can we still rely on number to define treatment and outcome? Oncology (Williston Park) 2013;27:1078, 1083-78, 1084.
29. Buell JF, Cherqui D, Geller DA, et al. The international position on laparoscopic liver surgery: The Louisville Statement, 2008. Ann Surg 2009;250:825-830.
30. Castaing D, Vibert E, Ricca L, et al. Oncologic results of laparoscopic versus open hepatectomy for colorectal liver metastases in two specialized centers. Ann Surg 2009;250:849-855.
31. Nigro ND, Vaitkevicius VK, Buroker T, et al. Combined therapy for cancer of the anal canal. Dis Colon Rectum 1981;24:73-75.
32. Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg 2004;240:711-717; discussion 717-718.
33. Glynne-Jones R, Wallace M, Livingstone JI, et al. Complete clinical response after preoperative chemoradiation in rectal cancer: is a "wait and see" policy justified? Dis Colon Rectum 2008;51:10-19; discussion 19-20.
34. Maas M, Beets-Tan RG, Lambregts DM, et al. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. J Clin Oncol 2011;29:4633-4640.
35. Tranchart H, Lefèvre JH, Svrcek M, et al. What is the incidence of metastatic lymph node involvement after significant pathologic response of primary tumor following neoadjuvant treatment for locally advanced rectal cancer? Ann Surg Oncol 2013;20:1551-1559.
36. Benoist S, Brouquet A, Penna C, et al. Complete response of colorectal liver metastases after chemotherapy: does it mean cure? J Clin Oncol 2006;24:3939-3945.
37. Small R, Lubezky N, Ben-Haim M. Current controversies in the surgical management of colorectal cancer metastases to the liver. Isr Med Assoc J 2007;9:742-747.
38. Otto G, Düber C, Hoppe-Lotichius M, et al. Radiofrequency ablation as first-line treatment in patients with early colorectal liver metastases amenable to surgery. Ann Surg 2010;251:796-803.
39. Solbiati L, Livraghi T, Goldberg SN, et al. Percutaneous radio-frequency ablation of hepatic metastases from colorectal cancer: long-term results in 117 patients. Radiology 2001;221:159-166.
40. Livraghi T, Solbiati L, Meloni F, et al. Percutaneous radiofrequency ablation of liver metastases in potential candidates for resection: the "test-of-time approach". Cancer 2003;97:3027-3035.
41. Wong SL, Mangu PB, Choti MA, et al. American Society of Clinical Oncology 2009 clinical evidence review on radiofrequency ablation of hepatic metastases from colorectal cancer. J Clin Oncol 2010;28:493-508.
42. Kirkpatrick JP, Kelsey CR, Palta M, et al. Stereotactic body radiotherapy: a critical review for nonradiation oncologists. Cancer 2014;120:942-954.
43. Chang DT, Swaminath A, Kozak M, et al. Stereotactic body radiotherapy for colorectal liver metastases: a pooled analysis. Cancer 2011;117:4060-4069.

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Pathologic complete response and disease-free survival are not surrogate endpoints for 5-year survival in rectal cancer: an analysis of 22 randomized trials

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Background: We performed a literature-based analysis of randomized clinical trials to assess the pathologic complete response (pCR) (ypT0N0 after neoadjuvant therapy) and 3-year disease-free survival (DFS) as potential surrogate endpoints for 5-year overall survival (OS) in rectal cancer treated with neoadjuvant (chemo)radiotherapy (CT)RT.

Methods: A systematic literature search of PubMed, EMBASE, the Web of Science, SCOPUS, CINAHL, and the Cochrane Library was performed. Treatment effects on 3-year DFS and 5-year OS were expressed as rates of patients alive (%), and those on pCR as differences in pCR rates ($\Delta^{pCR\%}$). A weighted regression analysis was performed at individual- and trial-level to test the association between treatment effects on surrogate ($\Delta^{pCR\%}$ and Δ^{3yDFS}) and the main clinical outcome (Δ^{5yOS}).

Results: Twenty-two trials involving 10,050 patients, were included in the analysis. The individual level surrogacy showed that the pCR% and 3-year DFS were poorly correlated with 5-year OS (R=0.52; 95% CI, 0.31–0.91; P=0.002; and R=0.60; 95% CI, 0.36–1; P=0.002). The trial-level surrogacy analysis confirmed that the two treatment effects on surrogates ($\Delta^{pCR\%}$ and Δ^{3yDFS}) are not strong surrogates for treatment effects on 5-year OS % (R=0.2; 95% CI, –0.29–0.78; P=0.5 and R=0.64; 95% CI, 0.29–1; P=0.06). These findings were confirmed in neoadjuvant CTRT studies but not in phase III trials were 3-year DFS could still represent a valid surrogate.

Conclusions: This analysis does not support the use of pCR and 3-year DFS% as appropriate surrogate endpoints for 5-year OS% in patients with rectal cancer treated with neoadjuvant therapy.

Keywords: Rectal cancer; pathologic complete response (pCR); disease-free survival (DFS); surrogate endpoints; overall survival (OS)

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Introduction

Neoadjuvant (chemo)radiotherapy (CT)RT is the gold standard of care for locally-advanced rectal cancer. The aim of treatment is to decrease local recurrence and improve: R0 surgery with a total mesorectal excision; and disease-free survival (DFS) and overall survival (OS). Either a short course of RT with immediate surgery or a prolonged course of (5-fluorouracil-based)-CTRT with delayed surgery are acceptable options for the preoperative treatment of rectal cancer, with or without adjuvant therapy (1,2). Overall, the effect of the addition of a short course of neoadjuvant RT prior to planned surgery is similar to that of a prolonged

course of CTRT in terms of survival, local and distant recurrences, and R0 resection, with more pathologic complete responses (pCRs) with combination therapy (3). A ypT0N0 stage pCR at the histologic examination after CTRT and surgery is commonly associated with better outcomes compared to non pCR patients, with less local and distant failure (4). The addition of multidrug regimens to standard RT has conferred increased toxicity, but has not led to a better rate of pCR in phase III trials. In particular, the addition of oxaliplatin to neoadjuvant 5FU-based CTRT only modestly improved the overall pCR rate (5).

The relationship between the response to neoadjuvant (CT)RT and the prognosis of patients with rectal cancer does not imply that pathological down-staging (e.g., pCR) is also a surrogate for treatment efficacy (OS). De facto, the demonstration that the pCR is a valid surrogate marker of the efficacy of systemic therapy on survival would encourage the use of primary systemic treatment to expedite the development of new systemic therapies with randomized neoadjuvant trials in locally-advanced rectal cancer (6). Furthermore, in colon cancer, DFS at 2 and 3 years is a good surrogate for OS at 5–6 years in trials of adjuvant CT (7-10).

To assess the roles of the pCR and DFS as potential surrogates of true clinical outcomes at the trial level, we performed a systematic literature search and a trial-based meta-analysis of randomized controlled trials comparing different neoadjuvant treatments that had available data on both the observed rates of pCR and 3-year DFS% and 5-year OS% outcomes, respectively. The aim of this study was to assess whether the treatment effects on the pCR and DFS are able to predict the treatment effects on OS.

Methods

We performed a literature-based analysis of randomized controlled trials of neoadjuvant RT or CTRT for rectal cancer. The primary objective of the meta-analysis was the individual and trial-level validation of the pCR% and 3-year DFS% as surrogate endpoints of the effect on 5-year OS% of neoadjuvant therapy in rectal cancer (e.g., evaluating whether the treatment effect on the pCR%, termed $\Delta^{pCR\%}$, and difference (Δ) in 3-year DFS% allows the size of the effect on the main clinical endpoint, namely Δ5-year OS%, to be predicted).

Literature search and study selection

A systematic literature search was conducted of PubMed, the Web of Science, SCOPUS, CINAHL, the Cochrane Library, and Embase up to August 2015. The search terms included "rectal cancer" or "rectal carcinoma", "neoadjuvant" or "preoperative", "chemotherapy" or "chemoradiotherapy" or "chemoradiation" or "radiotherapy", and "randomized" or "randomised".

The search was limited to phase II–III clinical trials published in the English language involving ≥100 patients. Two researchers (FP and AC) reviewed each abstract and text against the study inclusion and exclusion criteria. Studies were included if they: evaluated RT or CTRT (plus or minus adjuvant CT) as neoadjuvant therapy for rectal cancer followed by radical surgery; and reported both 5-year OS and either 3-year DFS (or progression/relapse free survival, or time to treatment failure provided they reported similar events of DFS) or the pCR% clearly defined as the % of ypT0N0 stages after preoperative therapy. Retrospective or prospective case series and phase I studies were excluded. Trials randomizing operated patients to adjuvant *vs.* no adjuvant therapy were considered provided they were all treated with neoadjuvant RT or CTRT, and included all patients who underwent preoperative treatment. In the event that a study was published in multiple articles or abstracts, the most recent data were used.

Data extraction

For each included study, data were extracted for study design, year of publication, sample size per treatment arm, and treatment schedule. Data on the pCR%, 5-year OS%, and 3-year DFS% were also collected. Rates of 3-year DFS and 5-year OS were captured from the reported Kaplan-Meier (KM) curves (11-13). Only in the case KM estimates were not presented, they were extracted from the article.

Statistical analysis

The statistical analysis consisted of a weighted linear correlation between the primary endpoint (5-year OS) and the candidate surrogates pCR%, and 3-year DFS. Analysis was weighted to the effective sample size at the time point considered (KM estimates of 3-year DFS and 5-year OS): number of events prior to the time point plus the number of patients at risk at the time point.

In particular, two correlations were calculated between the summary statistics to determine surrogacy according to methods previously reported (14-16). The first approach, termed individual-level surrogacy, computed the association

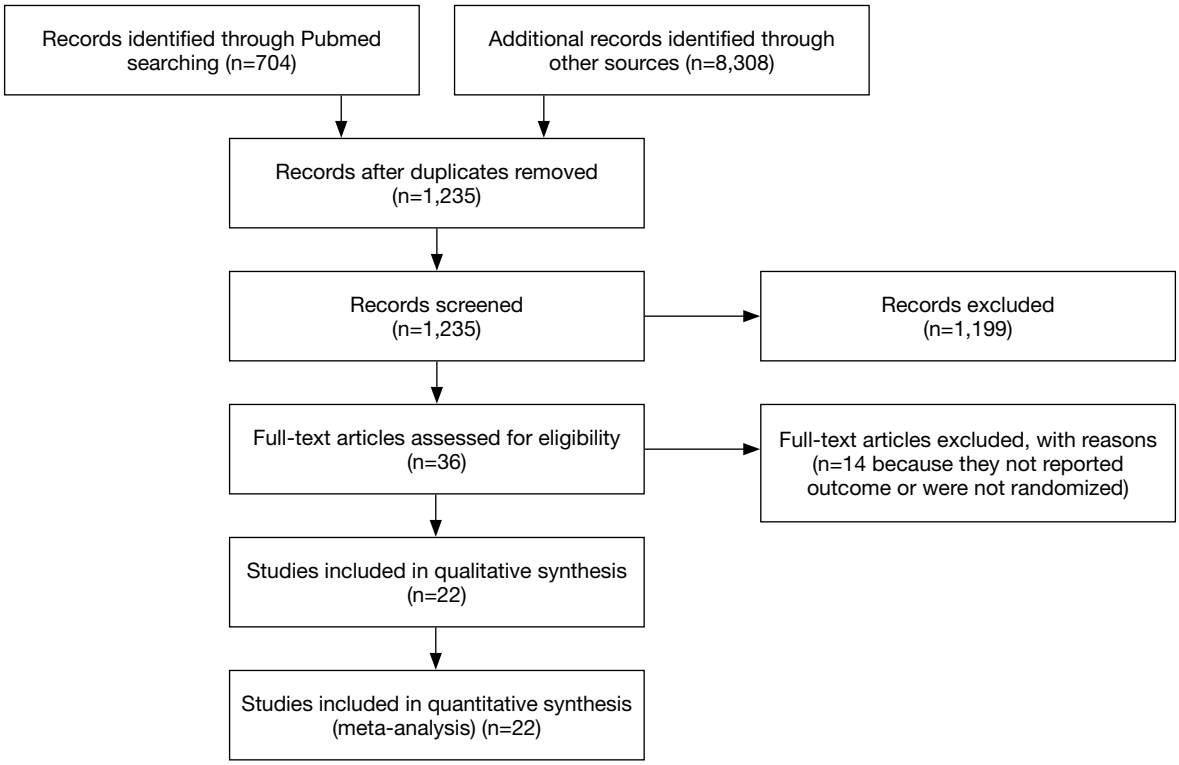

Figure 1 Flow diagram summarizing the strategy used to identify eligible studies.

between pCR% and 3-year DFS%, the potential surrogate endpoints, and 5-year OS%, for each included arm. The correlation was evaluated over all the treatment arms and is described as R (Pearson correlation coefficient). The R-squared (R^2) determination coefficient (the proportion of variability in OS explained by the variability of the surrogate endpoint) was also presented (17-19). The second approach, termed trial-level surrogacy, assessed the association between the reported treatment effects on a surrogate (Δ^{3yDFS} and $\Delta^{pCR\%}$), and those on OS (Δ^{5yOS}), which is the main endpoint. A strong correlation (R>0.8) would be consistent with surrogacy for OS (20). As a sensitivity analysis, we explored the surrogacy of the pCR and DFS in CTRT containing arms and phase III studies only. Both analyses were weighted on the sample size of each trial included.

As the number of included trials was small, we applied the non-parametric bootstrap re-sampling method (using 10,000 bootstrap samples), weighted for the sample size of each trial, to construct the 95% confidence intervals (BCI) for all weighted correlation coefficients. All the reported P values correspond to 2-sided tests, and those that were less than 0.05 were considered to be statistically significant. Analyses were performed with the NCSS 2007 software (version 07.1.21, released June 1, 2011).

Results

Following the systematic literature review, a total of 9,012 publications were analyzed (*Figure 1*), with 22 studies, published between 1999 and 2015, considered for inclusion in the final analyses (2,21-42). Most of the studies were randomized phase II (n=4) or III clinical trials (n=18).

The selected studies compared different CT backbones (n=6), different neoadjuvant treatments (RT *vs.* CTRT in n=5), and different strategies [neoadjuvant RT *vs.* surgery or neoadjuvant (CT)RT *vs.* adjuvant (CT)RT in n=5].

These studies involved 39 neoadjuvant treatment arms and 10,050 patients treated with some form of preoperative therapy (*Table 1*). There were between 50 and 924 patients with locally-advanced rectal cancer across the study treatment arms, and the reported 5-year OS rates ranged from 53% to 90% (median, 70.3%). In 4 arms, the 5-year OS% data were not available. The reported values for the 3-year DFS% ranged from 48% to 78% in n=22 arms (median, 70.5%). The pCR rates were presented in

Table 1 Characteristics of included studies

Author	Study/year	N (pts) (exp *vs.* ctr)	Neoadjuvant RT	Neoadjuvant CT (exp *vs.* ctr)	Adjuvant therapy	pCR% (exp *vs.* ctr)	$\Delta^{pCR\%}$	3Y-DFS% (exp-ctr)/Δ^{3yDFS} (%)	5Y-OS% (exp-ctr)/Δ^{5yOS} (%)	Median FU (months)/ primary endpoint
Wong RTOG 0247	Phase II RCT/2012–2015	52 *vs.* 52	50.4 Gy/28 fx	CAPIRI *vs.* CAPOX	√	10.4 *vs.* 20.8	10.4	70-62/8	59-72/–13	3.77–3.97 years/pCR
Rodel CAO/ ARO/AIO-04	Phase III/2015	613 *vs.* 623	50.4 Gy/28 fx	5-FU + OXA *vs.* 5-FU	√	17 *vs.* 13	4	76-72/4*	78-80/–2	50/DFS
Sainato I-CNR-RT	Phase III/2014	334 *vs.* 321	45 Gy/25 fx	5FU + FA bolus gg 1–5, 29–33 (all pts)	Adj *vs.* no adj CT	18.6 *vs.* 17	1.6	70-70/0	66.9-67.9/–1	63.7/OS
Appelt	Phase III/2013	111 *vs.* 110	50 Gy/28 fx + brachi RT boost *vs.* 50 Gy/28 fx + EBRT boost	Oral UFT + FA	At discretion	18 *vs.* 18	0	62-67[&]/–5	70.6-73.6/3	5.4 years/pCR
Saglam Istanbul R-01[#]	Phase II RCT/2014	76 *vs.* 77	45 Gy/25 fx	5FU 225 mg/m^2 d ic	Optional	1.3 *vs.* 1.3	0	74-74/0	76.5-74.2/2.3	56.8–59.3/local recurrences
Jeong[**]	Phase III/2014	170 *vs.* 170	45 Gy/25 fx + EBRT boost	CAP or 5FU + FA or UFT + FA or CAPIRI or CAPIRI + cetuximab	√	NR	NR	73-78/–5	83-88/–5	46–48/3Y DFS
Bosset EORTC 22921	Phase III/2006	506 *vs.* 505	45 Gy/25 fx	5FU + FA bolus gg 1–5, 29–33 (only pts in CTRT arms)	Randomization to adjuvant CT	13.7 *vs.* 5.3	8.4	NR/–	64.8-65.8/–1	5.4 years/OS
Gerard ACCORD 12	Phase III/2012	299 *vs.* 299	45 Gy/25 fx (arm 1) *vs.* 50 Gy/25 fx (arm 2)	CAP (arm 1) *vs.* CAPOX (arm 2)	At discretion	19.2 *vs.* 13.9	5.3	72-67.9/4.1	NR/–	36.8/pCR
Ngan Trans Tansman RTOG 01-04	Phase III/2012	163 *vs.* 163	50.4 Gy/28 fx (arm 1) *vs.* 25 Gy/5 fx (arm 2)	5FU 225 mg/m^2 d ic (arm 1)	√	NR	NR	68-74[&&]/–6	70-74/–4	5.9 years/local recurrences
Sauer CAO-ARO-AIO-94	Phase III/2004	415[^]	50.5 Gy/28 fx (arm 1)	5FU 1,000 mg/m^2 gg 1–5 week 1 & 5 (arm 1)	√	8	NA	75/–	76/–	45.8/OS
Hofheinz	Phase III/2012	81 *vs.* 80[^^]	50.4 Gy/5–6 weeks	CAP *vs.* 5FU 1,000 mg/m^2 gg 1–5 week 1 & 5	√	14 *vs.* 5	9	71-63/8	66-61/5	52/OS
Park	Phase III/2011	107[^^]	50.4 Gy/25 fx	CAP	√ (+ randomization to adjuvant CTRT)	17	NA	77/NA	90/NA	52/3Y DFS

Table 1 (*continued*)

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Author	Study/year	N (pts) (exp *vs.* ctr)	Neoadjuvant RT	Neoadjuvant CT (exp *vs.* ctr)	Adjuvant therapy	pCR% (exp *vs.* ctr)	$\Delta^{pCR\%}$	3Y-DFS% (exp-ctr)/Δ^{3yDFS} (%)	5Y-OS% (exp-ctr)/Δ^{5yOS} (%)	Median FU (months)/ primary endpoint
Roh NSABP R-03	Phase III/2009	123^^	45 Gy/25 fx (+ randomization to adjuvant CTRT)	5FU + FA bolus x6 weeks → 5FU + FA bolus weeks 1 & 5	√	15	NA	70/NA	67/NA	NA/DFS & OS
Braendengen	Phase III/2008	98 *vs.* 109	50 Gy	± 5FU bolus gg 1,2,11,12,21,22	5FU + FA in CTRT arm (permitted in RT arm)	16 *vs.* 7	9	65-48[§]/13	66-53/13	61/5Y OS
Bujko	Phase III/2006	157 *vs.* 155	50 Gy/28 fx (arm 1) *vs.* 25 Gy/5 fx (arm 2)	5FU + FA bolus weeks 1 & 5 (arm 1)	Optional	16.1 *vs.* 0.7	15.4	60-63/–3	NA/–	48/sphincter preservation
Mohiuddin RTOG-0012	Phase II RCT/2013	50 *vs.* 53	45.6 Gy/1.2 Gy fx bid + boost (arm 1) *vs.* 45 Gy/1.8 Gy fx + boost (arm 2)	5FU 225 mg/m^2 d ic (arm 1) + 5FU 225 mg/m^2 d ic + weekly CPT11 (arm 2)	–	30 *vs.* 26	4	NA/NA	61-75/–14	6.4–7 years/pCR & toxicity
Pach	Phase II RCT/2012	77 *vs.* 77	25 Gy/5 fx (random to immediate *vs.* delayed surgery)	–	–	10.4 *vs.* 0	10.4	NA/–	73-63/10	86/recurrences and OS
Sebag Montefiore MRC CR07	Phase III/2009	674^^	25 Gy/5 fx (+ randomization to adjuvant CTRT)	–	At discretion	NR	–	70.3/–	77.5/–	48/local recurrence
Gerard FFCD 9203	Phase III/2006	367 *vs.* 375	45 Gy/25 fx	5FU + FA bolus weeks 1 & 5 *vs.* no CT	√	11.4 *vs.* 3.6	7.8	NA[&]/–	67.9-67.4/0.5	81/OS
Glehen Lyons R90-01	Phase III/2003	99 *vs.* 101	39 Gy/13 fx (random to immediate *vs.* delayed surgery)	–	–	7 *vs.* 14	7	NA/–	69–66/3	6.3 years/sphincter preservation & local control
Peeters/ Kapiteijn TME trial	Phase III/2001–2007	924^^	RT *vs.* TME surgery alone	–	–	1	1	NA/–	64.2/–	6 years/local control
Allegra NSABP R-04	Phase III/2015	1608	RT 45 Gy/25 fx	5FU ic or CAP ± OXA	Not known	19.5 *vs.* 17.8	1.7	NA/–	81.3-79/2.3	NA/locoregional control at 3 y
Wong RTOG 0247	Phase II RCT/2012–2015	52 *vs.* 52	50.4 Gy/28 fx	CAPIRI *vs.* CAPOX	√	10.4 *vs.* 20.8	10.4	70-62/8	66-46/20	3.77–3.97 years/pCR

*, statistically significant; **, randomized to open *vs.* laparoscopic surgery; [#], the study investigated different timing of surgery (4 *vs.* 8 weeks after neoadjuvant therapy); ^, randomization to neoadjuvant *vs.* adjuvant therapy but only neoadjuvant arm considered for the purpose of the study; ^^, only neoadjuvant arm; [§], time to treatment failure; [&&], relapse-free survival; [&], progression-free survival. pCR, pathologic complete response; N, number; CT, chemotherapy; RT, radiotherapy; exp, experimental; ctr, control; Δ3yDSF, difference in 3-year disease-free survival rate; Δ5yOS, difference in 5-year overall survival rate; ref, reference; √, offered to all patients ; pts, patients; NA, not applicable for neoadjuvant comparisons; UFT, uracil + tegafur; FA, folinic acid; ic, continuous infusion; 5FU, 5-fluorouracil; CAPOX, capecitabine + oxaliplatin; CAPIRI, capecitabine + irinotecan; OXA, oxaliplatin; d, daily; NR, not reported; 3Y DFS, 3-year disease free survival; 5Y OS, 5-year overall survival; fx, fractions.

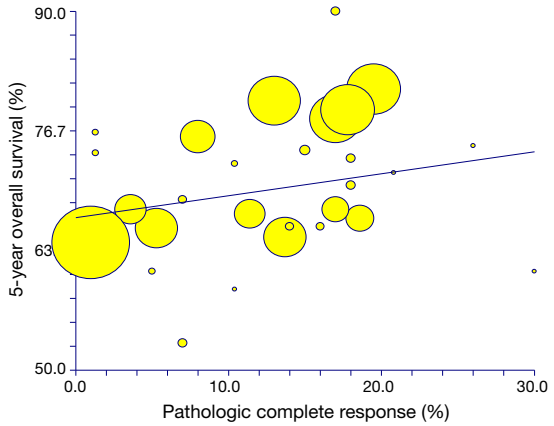

Figure 2 Correlation of pCR% with 5-year OS. pCR, pathologic complete response; OS, overall survival.

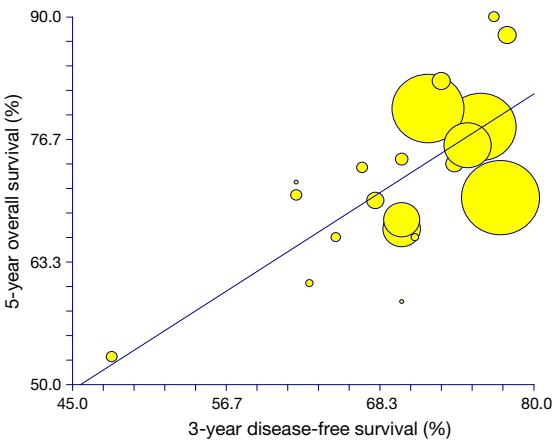

Figure 3 Correlation of 3-year DFS with 5-year OS. DFS, disease-free survival; OS, overall survival.

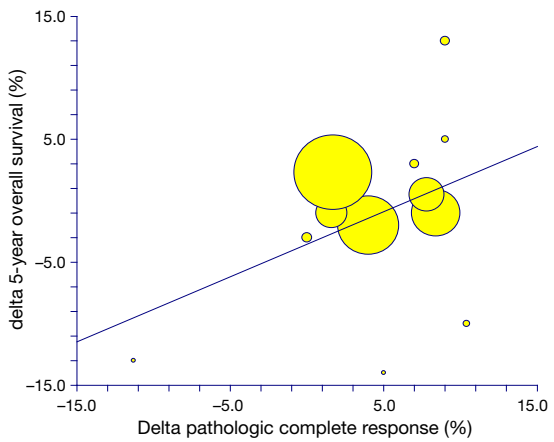

Figure 4 Correlation of treatment effect on pCR% (delta pCR) with delta 5-year OS (%). pCR, pathologic complete response; OS, overall survival.

n=36 arms (range, 0–30%; median, 13.95%). In n=1, n=1, and n=2 studies, respectively, relapse-free survival (RFS), time-to-treatment failure, and PFS were presented instead of DFS. All these endpoints, however, included in their definition both recurrences and death as their first events.

For the individual surrogacy, n=22 and n=30 arms were used for the correlation of 3-year DFS% and the pCR% with 5-year OS%. Conversely, only trials with a randomization and direct comparison of different neoadjuvant treatments were considered for trial level surrogacy (n=9 and 12 trials with data available, including a total of n=18 and n=24 arms for the Δ^{3yDFS} and $\Delta^{pCR\%}$ correlation with Δ^{5yos}).

Outcome surrogacy

Among a total of 39 treatment arms available, the values for the pCR%/5-year OS correlation were reported in n=30 of them. In the analysis of all the treatment regimens, the pCR% correlated weakly with OS (R=0.52; BCI 95% CI, 0.31–0.91; P=0.002; *Figure 2*). The R^2 values were 0.28 (P=0.002). The correlation between 3-year DFS/OS was available for n=22 arms and was similarly poor (R=0.6; BCI 95% CI, 0.36–1; P=0.002; *Figure 3*). R^2 was 0.37 (P=0.002).

Restricting the analysis to the phase III trials only (n=22 arms), the correlation of the pCR% with 5-year OS was moderate (R=0.60; P=0.002); the correlation of the 3-year DFS with 5-year OS was similar (R=0.61; P=0.01). In the studies that adopted CTRT treatment in all comparisons (n=17 arms and 19 arms for the DFS and pCR% analysis), the correlation of 3-year DFS/5-year OS was similar (R=0.66; P=0.0037). The correlation of the pCR% with 5-year OS was negligible (R=0.05; P=0.81).

Trial-level surrogacy

A total of 9 pairs of Δ^{3yDFS} and Δ^{5yOS} between the treatment arms were available in the randomized trials. The correlation between Δ^{3yDFS} and Δ^{5yOS} was 0.64 (BCI 95% CI, 0.29–1), and P=0.06. The correlations $\Delta^{pCR\%}/\Delta^{5yOS}$ were available for 13 pairs of comparisons and R was 0.2 (BCI 95% CI, 0.29–0.78), and P=0.5 (*Figure 4*). The R^2 values were 0.41 and 0.04.

The slope of the regression equation, namely the estimated change in the Δ^{5yOS} per unit change in the rate of $\Delta^{pCR\%}$, was 0.22, with a standard error of 0.33 [$\Delta^{5yOS} = (-1.08) + 0.22*\Delta^{pCR\%}$]. This means that a treatment associated with a 10% increase in $\Delta^{pCR\%}$ translated into an approximately (not

significant) 2% increase in 5-year OS probability. Similarly, the slope of the regression equation, and the estimated change in the Δ^{5yOS} per unit change in the Δ^{3yDFS}, was 0.51, with a standard error of 0.23 [$\Delta^{5yOS} = (-2.16) + (0.51)*\Delta^{3yDFS}$]. This means that a treatment associated with a 10% increase in 3-year DFS % translated into a non-significant 5% increase in the risk of 3-year chance of being progression-free or alive.

For the phase III and CTRT-only trials, the correlations of $\Delta^{pCR\%}$ and Δ^{3yDFS} with Δ^{5yOS} were poor (R=0.78, P=0.11, and R=0.8, P=0.02 for the phase III trials; and R=–0.21, P=0.68, and R=0.17, P=0.71 for the CTRT trials, respectively).

Discussion

Rectal cancer patients with a pCR defined as no residual cancer found upon the histological examination of surgical specimens (ypT0N0) after CTRT have better long-term outcomes, less risk of developing local or distal recurrences, and improved survival. In particular, after neoadjuvant CTRT and delayed surgery, a pCR is obtained in 15–27% of patients (43). Patients obtaining a pCR have a 50% reduced of risk of death and relapse, but they still portend a residual risk of local (2.8%) and distant (9%) metastases. In rectal cancer, which is a disease with a different biology and treatment approach compared to colon carcinoma, a formal validation of the surrogacy of the pCR and DFS is still lacking, and a demonstration of a correlation with OS would be required.

In the present analysis, with data extracted from a total of 22 trials, we estimated the correlation equation of the effect on the pCR and 3-year DFS% on the effect on the main outcome (5-year OS%). We observed that both the pCR and 3-year DFS are not candidates for surrogates of OS in rectal cancer studies. In particular, the R^2 results (0.02 and 0.48 for the 2 trial-level correlation analysis) suggest that the neoadjuvant effect on the pCR and 3-year DFS% are able to explain no more than 2% and 48%, respectively, of the effects detected on 5-year OS% in patients with rectal cancer.

Recently, Valentini *et al.* identified 2-year DFS more than pCR to be a good predictor of survival in a pooled analysis of five randomized European trials (44). They did not provide a formal surrogacy analysis, but did identify three risk classes of patient for whom reduced intensity treatment (in excellent and good prognosis subgroups) may be hypothesizable, as well as those with a poor prognosis (20% of total population) for whom more intensive/effective therapies do not lead to a definitive cure, with more efficacious therapies urgently awaited.

The question of the surrogacy of the pCR has arisen for other solid tumors with similar negative results (45,46). In our series, more intensive neoadjuvant schedules were offered in only three trials, and so a formal subgroup analysis was not performed. However, the results were similar in both larger phase III studies and those with concurrent CTRT in both comparison arms.

There could be several reasons for our findings, and this represents the main limitations of this analysis. First, this is a literature-based analysis, and more appropriate validation with individual patient data is necessary. Second, the relatively short follow-up for most trials did not potentially capture late recurrences, as shown in Valentini *et al.*'s analysis (5% more distant metastases were found at 10, compared to 5, years in patients who obtained a pCR). Third, some older trials with RT and surgery-alone arms, and with intrinsic technical issues related to radiation and surgical pathology accuracy, could have led to surprising results. Fourth, the randomized or non-choice of adjuvant CT in many trials could have diluted the final result. However, this is the first analysis that systematically evaluated the surrogacy of pCR and DFS with 5-year OS in rectal cancer through a systematic evaluation of 22 randomized trials of neoadjuvant therapy involving more than 10,000 patients. The analysis confirmed the negative findings of surrogacy for both intermediate endpoints in CTRT studies, but significant results for surrogacy were found in 5 large phase III trials for 3-year DFS endpoint.

With the possible influence of adjuvant and salvage therapies at relapse, the results of this trial-based meta-analysis indicated only a poor correlation between neoadjuvant treatment effects on the pCR and a moderate correlation of 3-year DFS% on 5-year OS%. The findings do not therefore support the use of these intermediate endpoints as surrogate endpoints of treatment efficacy in patients with locally-advanced rectal cancer treated with neoadjuvant-based therapy. New clinico-pathological and molecular biomarkers are potentially useful for predicting final outcomes. Among them, the NAR score has been developed based on cT, pT and pN pathological results (47,48). The score has been validated in the NSABP-R04 trial, and is emerging as a useful short-term surrogate clinical trial endpoint in rectal cancer study designs. This approach is undergoing trial level validation, and has already been adopted as a secondary and, possibly, primary endpoint in several ongoing phase I and II studies testing novel preoperative interventions in rectal cancer.

Further studies are needed to assess the surrogacy of the pCR in a small subgroup of patients with an excellent prognosis and for whom conservative surgery or the wait-and-see strategy can be options. In the meantime, due to the occurrence of late relapses and deaths identified in long-term follow-up observations in major phase III trials, 5-year OS should still remain the surrogate of a definitive cure for most patients.

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None.

Footnote

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

References

1. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol 2012;30:1926-1933.
2. Peeters KC, Marijnen CA, Nagtegaal ID, et al. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. Ann Surg 2007;246:693-701.
3. Zhou ZR, Liu SX, Zhang TS, et al. Short-course preoperative radiotherapy with immediate surgery versus long-course chemoradiation with delayed surgery in the treatment of rectal cancer: a systematic review and meta-analysis. Surg Oncol 2014;23:211-221.
4. Martin ST, Heneghan HM, Winter DC. Systematic review and meta-analysis of outcomes following pathological complete response to neoadjuvant chemoradiotherapy for rectal cancer. Br J Surg 2012;99:918-928.
5. An X, Lin X, Wang FH, et al. Short term results of neoadjuvant chemoradiotherapy with fluoropyrimidine alone or in combination with oxaliplatin in locally advanced rectal cancer: a meta analysis. Eur J Cancer 2013;49:843-851.
6. Bonnetain F, Bosset JF, Gerard JP, et al. What is the clinical benefit of preoperative chemoradiotherapy with 5FU/leucovorin for T3-4 rectal cancer in a pooled analysis of EORTC 22921 and FFCD 9203 trials: surrogacy in question? Eur J Cancer 2012;48:1781-1790.
7. Sargent D, Sobrero A, Grothey A, et al. Evidence for cure by adjuvant therapy in colon cancer: observations based on individual patient data from 20,898 patients on 18 randomized trials. J Clin Oncol 2009;27:872-877.
8. Sargent D, Shi Q, Yothers G, et al. Two or three year disease-free survival (DFS) as a primary end-point in stage III adjuvant colon cancer trials with fluoropyrimidines with or without oxaliplatin or irinotecan: data from 12,676 patients from MOSAIC, X-ACT, PETACC-3, C-06, C-07 and C89803. Eur J Cancer 2011;47:990-996.
9. Sargent DJ, Patiyil S, Yothers G, et al. End points for colon cancer adjuvant trials: observations and recommendations based on individual patient data from 20,898 patients enrolled onto 18 randomized trials from the ACCENT Group. J Clin Oncol 2007;25:4569-4574.
10. de Gramont A, Hubbard J, Shi Q, et al. Association between disease-free survival and overall survival when survival is prolonged after recurrence in patients receiving cytotoxic adjuvant therapy for colon cancer: simulations based on the 20,800 patient ACCENT data set. J Clin Oncol 2010;28:460-465.
11. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 1998;17:2815-2834.
12. Tierney JF, Stewart LA, Ghersi D, et al. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8:16.
13. Williamson PR, Smith CT, Hutton JL, et al. Aggregate data meta-analysis with time-to-event outcomes. Stat Med 2002;21:3337-3351.
14. Tang PA, Bentzen SM, Chen EX, et al. Surrogate end points for median overall survival in metastatic colorectal cancer: literature-based analysis from 39 randomized controlled trials of first-line chemotherapy. J Clin Oncol 2007;25:4562-4568.
15. Buyse M, Molenberghs G, Burzykowski T, et al. The validation of surrogate endpoints in meta-analyses of randomized experiments. Biostatistics 2000;1:49-67.
16. Alonso A, Van der Elst W, Molenberghs G, et al. On the relationship between the causal-inference and meta-analytic paradigms for the validation of surrogate endpoints. Biometrics 2015;71:15-24.
17. Bland JM, Altman DG. Calculating correlation coefficients with repeated observations: Part 2--Correlation between subjects. BMJ 1995;310:633.
18. Burzykowski T, Molenberghs G, Buyse M. editors. Evaluation of Surrogate Endpoints. New York, NY:

Springer, 2005.
19. Gail MH, Pfeiffer R, Van Houwelingen HC, et al. On meta-analytic assessment of surrogate outcomes. Biostatistics 2000;1:231-246.
20. Chambers JM. Linear models. In: Chambers JM, Hastie TJ. editors. Statistical Models in S. Pacific Grove. CA: Wadsworth & Brooks/Cole, 1992.
21. Allegra CJ, Yothers G, O'Connell MJ, et al. Neoadjuvant 5-FU or Capecitabine Plus Radiation With or Without Oxaliplatin in Rectal Cancer Patients: A Phase III Randomized Clinical Trial. J Natl Cancer Inst 2015;107:djv248.
22. Rödel C, Graeven U, Fietkau R, et al. Oxaliplatin added to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy of locally advanced rectal cancer (the German CAO/ARO/AIO-04 study): final results of the multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2015;16:979-989.
23. Wong SJ, Moughan J, Meropol NJ, et al. Efficacy endpoints of radiation therapy group protocol 0247: a randomized, phase 2 study of neoadjuvant radiation therapy plus concurrent capecitabine and irinotecan or capecitabine and oxaliplatin for patients with locally advanced rectal cancer. Int J Radiat Oncol Biol Phys 2015;91:116-123.
24. Sainato A, Cernusco Luna Nunzia V, Valentini V, et al. No benefit of adjuvant Fluorouracil Leucovorin chemotherapy after neoadjuvant chemoradiotherapy in locally advanced cancer of the rectum (LARC): Long term results of a randomized trial (I-CNR-RT). Radiother Oncol 2014;113:223-229.
25. Appelt AL, Vogelius IR, Pløen J, et al. Long-term results of a randomized trial in locally advanced rectal cancer: no benefit from adding a brachytherapy boost. Int J Radiat Oncol Biol Phys 2014;90:110-118.
26. Jeong SY, Park JW, Nam BH, et al. Open versus laparoscopic surgery for mid-rectal or low-rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): survival outcomes of an open-label, non-inferiority, randomised controlled trial. Lancet Oncol 2014;15:767-774.
27. Saglam S, Bugra D, Saglam EK, et al. Fourth versus eighth week surgery after neoadjuvant radiochemotherapy in T3-4/N0+ rectal cancer: Istanbul R-01 study. J Gastrointest Oncol 2014;5:9-17.
28. Mohiuddin M, Paulus R, Mitchell E, et al. Neoadjuvant chemoradiation for distal rectal cancer: 5-year updated results of a randomized phase 2 study of neoadjuvant combined modality chemoradiation for distal rectal cancer. Int J Radiat Oncol Biol Phys 2013;86:523-528.
29. Gérard JP, Azria D, Gourgou-Bourgade S, et al. Clinical outcome of the ACCORD 12/0405 PRODIGE 2 randomized trial in rectal cancer. J Clin Oncol 2012;30:4558-4565.
30. Ngan SY, Burmeister B, Fisher RJ, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. J Clin Oncol 2012;30:3827-3833.
31. Hofheinz RD, Wenz F, Post S, et al. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial. Lancet Oncol 2012;13:579-588.
32. Pach R, Kulig J, Richter P, et al. Randomized clinical trial on preoperative radiotherapy 25 Gy in rectal cancer--treatment results at 5-year follow-up. Langenbecks Arch Surg 2012;397:801-807.
33. Park JH, Yoon SM, Yu CS, et al. Randomized phase 3 trial comparing preoperative and postoperative chemoradiotherapy with capecitabine for locally advanced rectal cancer. Cancer 2011;117:3703-3712.
34. Roh MS, Colangelo LH, O'Connell MJ, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. J Clin Oncol 2009;27:5124-5130.
35. Sebag-Montefiore D, Stephens RJ, Steele R, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet 2009;373:811-820.
36. Braendengen M, Tveit KM, Berglund A, et al. Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. J Clin Oncol 2008;26:3687-3694.
37. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg 2006;93:1215-1223.
38. Gérard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. J Clin Oncol 2006;24:4620-4625.
39. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006;355:1114-1123.

40. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731-1740.
41. Glehen O, Chapet O, Adham M, et al. Long-term results of the Lyons R90-01 randomized trial of preoperative radiotherapy with delayed surgery and its effect on sphincter-saving surgery in rectal cancer. Br J Surg 2003;90:996-998.
42. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001;345:638-646.
43. Maas M, Nelemans PJ, Valentini V, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol 2010;11:835-844.
44. Valentini V, van Stiphout RG, Lammering G, et al. Selection of appropriate end-points (pCR vs 2yDFS) for tailoring treatments with prediction models in locally advanced rectal cancer. Radiother Oncol 2015;114:302-309.
45. Berruti A, Amoroso V, Gallo F, et al. Pathologic complete response as a potential surrogate for the clinical outcome in patients with breast cancer after neoadjuvant therapy: a meta-regression of 29 randomized prospective studies. J Clin Oncol 2014;32:3883-3891.
46. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014;384:164-172.
47. George TJ Jr, Allegra CJ, Yothers G. Neoadjuvant Rectal (NAR) Score: a New Surrogate Endpoint in Rectal Cancer Clinical Trials. Curr Colorectal Cancer Rep 2015;11:275-280.
48. Yothers G, George TJ, Petrelli NJ, et al. Neoadjuvant rectal cancer (RC) score predicts survival: potential surrogate endpoint for early phase trials. J Clin Oncol 2014;32:abstr 3533.

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