

The Changing Role of Radiation in the Post-TME ERA of Rectal Cancer

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Abstract: Total mesorectal excision (TME) for rectal cancer is now considered standard in the surgical treatment of rectal cancer. The application of this technique has resulted in a pooled pelvic recurrence rate of approximately 7%. Preoperative and postoperative radiation further decreases the local regional recurrence (LRR) rate in patients with rectal cancer but the reduction in risk is counterbalanced by increased short and long term toxicity. Lower LRR rates have not uniformly translated into more favorable overall survival. In addition, advances in imaging have resulted in more accurate pretreatment staging and have improved the ability to stratify patients based on risk of recurrence. Given low pelvic recurrence rates after TME-based surgery alone, the risks and toxicities of pelvic radiation, and superior imaging to select high risk patients, radiation may not be requisite in the treatment of all rectal cancer patients. In this review, we discuss the current status of radiation and LRR rates in rectal cancer after definitive surgical resection with respect to specific subsites and stages of disease, examine the impact of imaging in the selection of patients for radiation, and raise the possibility that predictive biomarkers may help to identify patients who may not require pelvic radiation.

INTRODUCTION

Advances in practice and treatment of rectal cancer have markedly improved outcome in rectal cancer in last two decades [1]. LRR rates have dropped from greater than 25% to less than 10% directly as the result of the application of a better surgical technique. In addition, neoadjuvant chemoradiation has decreased LRR, improved postoperative function, and increased the percentage of cancers with pathologic complete response (pCR). The availability of more effective cytotoxic systemic chemotherapy agents and novel molecularly targeted biologics has further impacted the treatment of rectal cancer by increasing overall survival.

Because of the progress made in the treatment of rectal cancer, new questions arise which may impact the direction of future research on treatment. The successes of chemoradiation in downsizing and in some cases curing rectal cancer may eventually eliminate the need for surgery all together. On the other hand, the improvements in local control resulting from better surgical techniques and improved stratification of patients based on recurrence risks and response to treatment argue for a selective decrease in the routine use of pelvic radiation for resectable rectal cancer. What seems certain, regardless of the optimal rectal cancer treatment in the future, is the need to better tailor treatment for subgroups of patients with rectal cancer now [2]. In this review, we will discuss the improvements in surgical techniques and the current role of pelvic radiation. We will evaluate whether all patients require radiation based on tumor location and staging. Lastly, we will determine if evolving imaging technology and molecular biomarker science can provide non-

invasive surrogates of response, in order to identify patients who may benefit from preoperative therapy.

TOTAL MESORECTAL EXCISION DECREASES LOCAL RECURRENCE

Beginning in the 1980's, Heald and others described and advanced a surgical technique since known as the total mesorectal excision (TME) [3, 4]. Rather than blunt mobilization of the rectum from the pelvis, sharp dissection under direct vision was taught and advocated. This enabled the surgical resection to remain in the plane between the presacral fascia and the investing fascia of the rectum and the rectal mesentery (mesorectum), defined as the fibrofatty tissue containing the lymphatics and lymph nodes draining the rectum and invested by the visceral fascia. The procedure required the dissection to be carried, under direct visualization, to the end of the mesorectum, at about the level of the anorectal ring. This approach resulted in the complete resection of the rectum and mesorectum, permitted separation of the visceral from the somatic structures, and ensured adequate en-bloc removal of the cancer and cancer involved tissues such as lymph nodes.

The careful and meticulous dissection carried out by the surgeons was paralleled by the detailed evaluation of the surgical specimen by the pathologists involved. The examination of the specimen resulted in the reporting of the radial or circumferential margin (CRM), a parameter confirmed to be of great prognostic significance in determination of LRR [5]. In addition, the number of lymph nodes removed became as important as the diagnosis of disease in the lymph nodes, serving as a surrogate marker of an adequate resection as well as a marker of prognosis [6, 7]. The importance of the CRM and lymph nodes reinforced the rationale behind TME resections, leading to the widespread adoption of this technique as the gold standard in surgical treatment of rectal cancer.

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That surgery alone can affect the recurrence rate has now been confirmed in multiple population-based studies and in many centers around the world. Comparisons before and after training workshops in Norway in the early 1990's in the TME technique documented LRR rates that decreased from 16% to 8% [8]. Likewise, a systematic training program established in Stockholm from 1994 to 1995 changed the definitive surgical procedure from non-TME resection to TME resection and LRR decreased from 15% to 6% with surgery alone [9]. The LRR was 39.4% in patients with rectal cancer who did not undergo a TME resection compared with a LRR of 9.8% after TME resections were instituted in Germany [10]. Overall, the adoption of this technique has greatly impacted outcome resulting in a pooled LRR rate in patients treated with surgery alone of 7.1% with a mean follow up of 45 months [11]. If surgery alone results in LRR rates of less than 10%, what is the role for pelvic radiation in rectal cancer?

ADJUVANT PELVIC RADIATION DECREASES LOCAL RECURRENCE

In the era before TME became the gold standard, the role of radiotherapy was better defined. Without adjuvant radiotherapy, surgery alone in lesions with mural wall invasion (T3, 4 or Dukes' B) and or lymph node involvement (Dukes' C) results in LRR rates of about 18 – 30 % [12-17]. The use of radiation as adjuvant therapy in this patient population to reduce the risk of local recurrence was formally tested in a number of randomized, prospective trials in the United States and in Europe, completed in the 1980's and resulted in significantly reducing the LRR rates to 8 – 14%. While the overall survival has improved for rectal cancer patients in general, there is no direct relationship between improved local control and overall survival. Except for one notable study[12], the randomized prospective trials in rectal cancer evaluating the effectiveness of radiation with and without chemotherapy, as preoperative and postoperative treatment have shown no difference in overall survival while demonstrating improved local control with the addition of radiation [13-23].

The inability to demonstrate an overall survival advantage despite improved LRR rates continues into the contemporary trials which incorporate TME as the surgical treatment. In a landmark TME trial originally reported in 2001 and recently updated in 2007, short course preoperative radiotherapy and TME was compared to TME alone in 1,861 patients with resectable rectal cancer. While the LRR at a median follow up of 6.1 years was almost 2-fold higher in the surgery alone group at 10.9% ($p < 0.001$), the 5-year overall survival was equivalent at 64% between the treatment arms ($p = 0.90$) [18, 19]. The German Rectal Cancer Trial, which established the superiority of preoperative treatment over postoperative treatment, randomized 823 patients with resectable rectal cancer to pre- or post-operative chemoradiation. The results likewise did not demonstrate a survival benefit with decreased local recurrence in the preoperatively treated group. The LRR rates for the preoperative versus postoperatively treated groups were 6 and 13% ($p = 0.006$); the 5-year overall survival was 74 and 76% ($p = 0.80$) [20]. In the MRC CR07 trial, which has yet to be published but preliminary results are in abstract form, 1,350 pa-

tients were randomized to receive short course preoperative radiation or postoperative chemoradiation consisting of 45 Gy/25 fractions given with 5-fluorouracil. The initial findings are consistent with the German trial with the preoperative arm resulting in a lower LRR. There appears to be an overall survival advantage with preoperative therapy in this trial over post-operative chemoradiation although definitive results are still pending [21]. In summary, preoperative or postoperative adjuvant radiation with or without chemotherapy decreases local recurrence even after TME resection although overall survival benefits from improved local control remain to be determined [22].

The local recurrence advantage of preoperative chemoradiation may be exceeded by the potential induction of pCR with preoperative treatment. Preoperative treatment allows for an *in-vivo* assessment of anti-tumor activity for novel systemic agents by identifying drug-sensitive tumor populations leading to tumor downsizing and downstaging. Between 15 – 25 % of all rectal cancers treated with preoperative chemoradiation have pCR at the time of surgical resection[23-27]. The response rates may vary depending on specific cytotoxic chemotherapeutic agents and/or combination regimens, interval duration between completion of preoperative treatment and surgical resection, and newer molecularly-targeted agents. Although additional studies to better delineate the factors involved in achieving pCR are needed, currently, post-treatment staging, including non-invasive imaging as well as pathologic response assessment of the resected tissue, seems to be the best prognostic indicator for oncologic outcome. The likelihood of local relapse as well as development of systemic disease in patients with a pCR is less than 5% [25, 27, 28]. The long-term follow up of patients who are rendered disease free with preoperative chemoradiation raises the possibility that definitive surgery may no longer be required in select patients with pCR. Indeed, emerging experience with non-operative management supports such a premise [29, 30]. Whether omission of radical surgery is a tenable option in patients is currently under prospective study in the United Kingdom [31].

The use of preoperative chemoradiation, while decreasing LRR as well as increasing pCR, is associated with significant morbidity. Treatment related deaths are higher (ranging from 2 – 8%) in patients treated with adjuvant radiation and chemoradiation than with surgery alone (<1% - 2%)[13], as are acute effects including radiation enteritis, ileus, diarrhea, bowel obstruction, wound healing problems, and hematologic toxicities [17, 32, 33]. About 60 – 81% of all patients on combined modality treatment will have at least a Grade 3 toxicity during therapy [34]. In addition, anorectal outcome such as number of bowel movements per day, fecal continence as well as sexual function such as potency have been shown to be worse in patients who received radiation [35-39]. Interestingly, overall quality of life was not statistically different between the patients who received radiation and patients who did not, as addressed in follow up of the Dutch TME trial [40].

IDENTIFICATION OF FACTORS IN SELECTION OF PATIENTS WHO MAY BENEFIT FROM RADIATION

How can we reconcile radiation in the treatment of rectal cancer given low recurrence rates with surgery alone, no

additional survival benefit, and toxicities? While radiation with or without chemotherapy decreases the LRR in rectal cancer by 50% and increases the pCR rate in patients, the lack of survival benefit, as reported in multiple multi-center, prospective trials, and the acute and late toxicities of preoperative treatment argue that identification of better selection criteria such as location of cancer, stage of disease, pre-treatment imaging, and predictive biomarkers are needed to better tailor use of radiation.

RECURRENCE CORRELATES WITH LOCATION OF RECTAL CANCER

The location of the rectal cancer, defined as the distance from the anal verge, impacts on LRR. Rectal cancers which are anatomically located at greater than 10 cm from the anal verge are associated with LRR rate from < 5% in several retrospective analyses [41-44]. Rectal cancers in the mid-rectum likewise have a lower LRR than rectal cancers < 6 cm from the anal verge (5% vs. 18%, respectively) [45]. In the randomized, prospective trial evaluating the role of TME with and without preoperative radiation, distance of tumor from the anal verge is a significant variable accounting for increased LRR on multivariate analysis of clinical and pathological risk factors [19]. Taken together, patients with lower rectal cancers benefit from additional therapy. Whether patients with high rectal cancers can forego adjuvant pelvic radiation remains to be determined.

T AND N-STAGE PREDICTS OUTCOME

Stage has been shown to be predictive of LRR in rectal cancer [11, 44, 46]. For example, the series from the Mayo Clinic, with 514 patients who were treated with surgery alone, demonstrated the LRR for Stage I, II and III were 4%, 9%, 10% respectively [47]. In the TME operative series reported by Enker, patients with Dukes A had a LRR of 7%, Dukes B 0% and Dukes C 15.2% [41]. Dukes stage, however, was not statistically predictive of LRR in the series of 519 patients from Basingstoke and may have to do with the exceedingly overall low rates (4%) of local recurrence [48].

Recent analysis of the Phase III North American rectal cancer trials demonstrate independent prognostic significance of each T and N-stage category of resected rectal cancer and support the value of substaging beyond the standard stage II and III categories [49]. In these analyses, three risk groups of patients were defined: intermediate (T1-2N1, T3N0), moderately high (T1-2N2, T3N1, T4N0), and high (T3N2, T4N1, T4N2). Stage II patients with a single intermediate-risk factor (such as T3N0) had better disease-free survival and local control than patients with other categories of stage II disease. Surgery and chemotherapy, without radiation, for these patients resulted in a 5-year overall survival of approximately 85% [50].

The ability to select T3N0 remains critical. Recently, Guillem *et al.* reported that 22% of T3N0 patients who had been clinically staged with endorectal ultrasound/MRI were found to have positive mesorectal lymph nodes after preoperative chemoradiation. The group cautioned against omitting radiation and thus, undertreating patients with T3N0 disease given the current inability to accurately identify node negative disease preoperatively [23]. In addition, even within the population of patients with T3N0 lesions, other factors

associated with increased LRR as well as poorer overall survival, identified in retrospective studies, include distance of extension of tumor into the perirectal fat, differentiation, lymphovascular invasion, preoperative serum CEA, and age (over 70 years) [51, 52].

N-stage as an important predictive variable for local recurrence is underscored in the Dutch TME trial. In the TME alone arm, the LRR was 20.6% in node positive patients compared with a LRR of 7.2% in node negative patients. Preoperative radiotherapy decreased the LRR in the node positive patient to 10.6% [19]. In a retrospective analysis of rectal cancer treated with surgery only, 417 patients were evaluated for local recurrence. LRR was 4.1% in St. II disease and 24.1% in node positive patients at a follow up of 5.2 years [43]. Such high rates of local recurrence in node-positive disease strongly support the use of chemoradiation in addition to surgery.

IMPROVED IMAGING IDENTIFIES LIKELIHOOD OF NEGATIVE MARGIN RESECTION

The assessment and treatment decision regarding preoperative chemoradiation is predicated on the ability to accurately image the lesion, stage the primary and nodes, and determine the level of tumor invasion. To this end, the evolving development and use of medical imaging including computerized tomography (CT) scans, positron emission tomography (PET) scans, endorectal ultrasound (ERUS) and magnetic resonance imaging (MRI) in accurately staging rectal cancer may support selective use of radiation.

CT scans have been the work horse in the staging of rectal cancer especially in the determination of metastatic disease. However, spiral CT scans have been less useful in delineating the T and N-stage of rectal cancer with accuracy rates about 50%. Newer CT technology may improve the overall accuracy rate but use in the pelvis remains limited in preoperative staging of rectal cancer patients [53, 54]. PET scans, usually with the metabolic tracer 18-fluorodeoxyglucose (FDG), have been increasingly used in the determination of metastatic disease and response to therapy, not as a preoperative tool to improve patient selection [31]. Combination FDG-PET/CT scans has the potential to incorporate both anatomic and functional imaging for the staging and response assessment of rectal cancer.

Endorectal ultrasound (ERUS) has been compared to CT scans and shown to have greater sensitivity and specificity in staging rectal cancer. Accuracy in determining depth of tumor invasion is between 69 - 90% and involvement of lymph nodes with cancer is approximately 64 - 80% [55-59]. The limitations noted with the use of ERUS, as is the case with all ultrasound diagnostic modalities, are user reproducibility and the steep learning curve. This variability decreases with user experience [56].

MRI technology also continues to evolve with increasing ability to stage rectal cancers. Different imaging protocols have been tested with and without specialized coils to improve the images. The Magnetic Resonance Imaging and Rectal Cancer European Equivalence Study (MERCURY), a prospective multicenter study, was undertaken to demonstrate the equivalence of MRI and histopathologic assessments of extramural depth of tumor spread within the

mesorectum. Secondary endpoints of the study were to assess predicted CRM positivity rate using pre-operative MRI; develop a surgical assessment technique for excision of low rectal cancer based on pelvimetry and assessment of the mesorectal size and tumor height; evaluate the reproducibility of high-resolution pelvic phased-array body-coil MRI in multiple facilities and assess inter-/intra-observer variation in reporting; and evaluate overall utility of MRI in the staging of tumors encroaching the anal canal. Full results of the MERCURY study were reported in 2006. Preoperative MRI predicted negative CRM in 327 out of 354 patients (92% specificity) who had negative margins at time of surgical resection. 8% of the patients had imaging that were noted to be false positive, predicting for positive margins but found at pathology to have negative margins. The MERCURY study demonstrated that high quality MRI imaging is reproducible across multiple centers and that interpretation of images at different centers accurately predicts CRM status. MRI may be an effective tool in the pre-operative identification of patients at risk of positive margin resection. If so, these patients would benefit from preoperative treatment [60, 61].

A meta-analysis of 90 studies evaluating the accuracy of the different rectal cancer imaging modalities including CT scans, ERUS and MRI concluded that ERUS overall had greater sensitivity and specificity in predicting muscularis propria invasion (94 and 86%, respectively) and perirectal tissue invasion (90 and 75%). The accuracy in predicting lymph node involvement was less and similar between ERUS and MRI with sensitivity of 67 and 66% and specificity of 78 and 76% respectively. CT scan was the least accurate of the three modalities[54]. Until further advances are made in imaging, the inability to detect positive lymph nodes will limit the ability to identify patients with true node negative disease. Consequently, patients with clinical T3N0 rectal cancers will likely continue to be treated with preoperative radiation.

IDENTIFICATION OF MOLECULAR BIOMARKERS TO BETTER SELECT PATIENTS FOR THERAPY

A review of the molecular biomarkers currently being studied as prognostic of oncologic outcome and predictive of response to therapy in rectal cancer is beyond the scope of this review. Potential biomarker candidates including p53, p21, EGFR, VEGF, Cox-2, Ki-67, TS, the mismatch repair proteins, whether individually or as multi-gene panels, have been reported in rectal cancer with varying prognostic and predictive significance [62-67]. While there remains no definitive biomarker or panel of biomarkers able to identify patients with better prognosis or with responsive cancers to chemoradiation, the ability to stratify patients based on the molecular signature of their cancers is feasible, has been shown in other disease sites, and has the potential to contribute markedly to the selection of patients for preoperative treatment in rectal cancer in the future.

CONCLUSION

Significant advances have been made in the last two decades in the diagnosis and treatment of rectal cancer. Since the 1990 NCI Consensus Statement on Adjuvant Therapy for stage II-III rectal cancer and the German intergroup rectal trial, there are likely subsets of patients who do not require

pelvic radiotherapy [68]. With improving technology in both anatomic and functional imaging as well as emerging tissue and/or serum microarray signatures that are being identified, the selection of patients for tailored treatments may become a reality. In the meantime, preoperative chemoradiation remains a part of the treatment plan for Stage II and III rectal cancer patients.

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