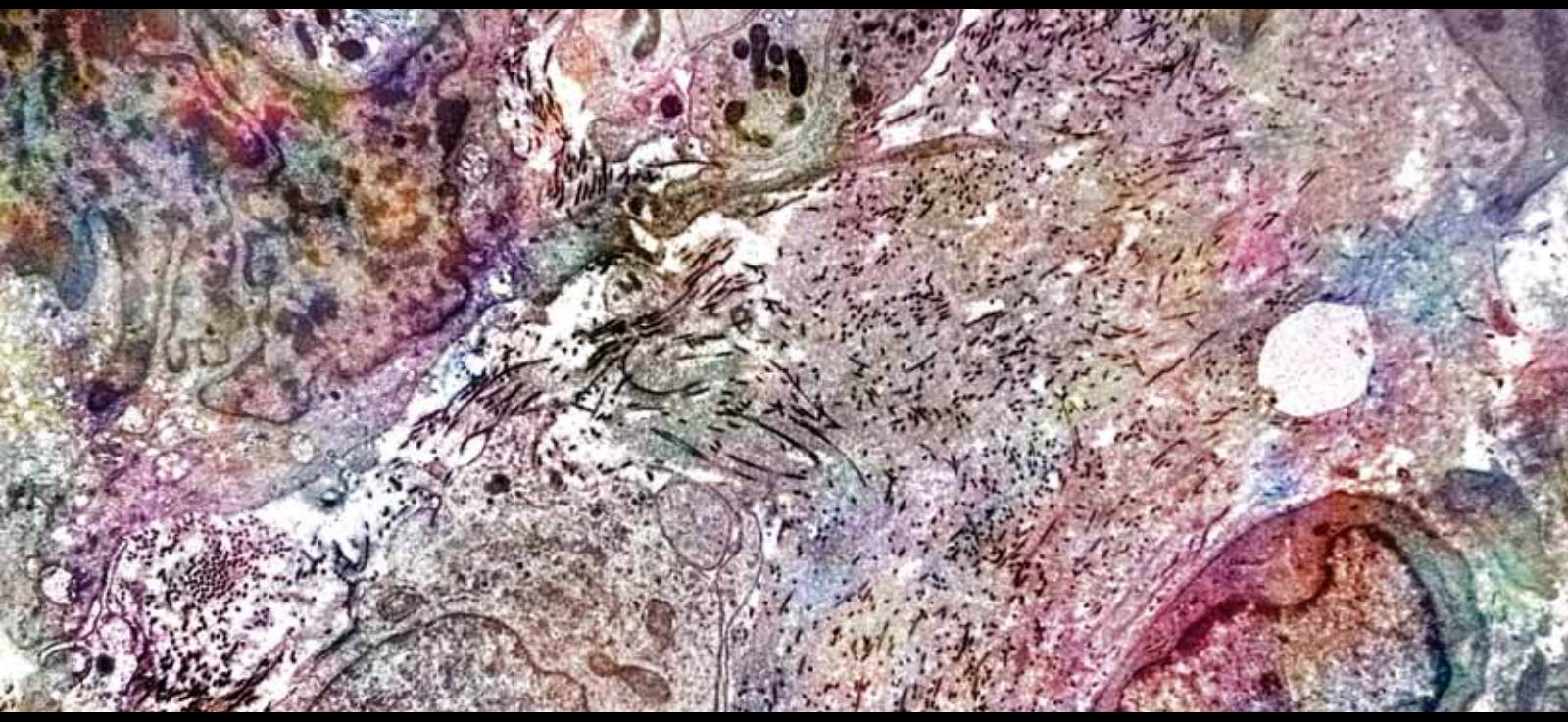
International Journal of Surgical Oncology

Rectal Cancer: Multimodal Treatment Approach

Guest Editors: Manousos-Georgios Pramateftakis, Dimitrios Kanellos, Paris P. Tekkis, Nikolaos Touroutoglou, and Ioannis Kanellos



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Editorial Board

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Editorial

Rectal Cancer: Multimodal Treatment Approach

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Colorectal cancer is a major health problem. More than 1 million patients worldwide are diagnosed annually. It is the 3rd most common cancer type and about half a million people die of the disease each year. Incidence suggests that eating habits, lifestyle, and environmental parameters, beyond genetic background, are responsible for the disease progression. The treatment of rectal cancer has changed over the last two decades as far as surgical techniques, chemotherapy, and radiotherapy are concerned. From carcinogenesis and screening to the improvement of diagnosis and from tumor staging to the multimodal treatment approach, several fields of the management of rectal cancer as an entity have been significantly developed over the last years. Effective surgery, neoadjuvant radiotherapy, and modern cytotoxic chemotherapy have improved survival rates [1, 2].

The improvement of conventional diagnosis and the introduction of molecular screening have improved the chances of early cancer diagnosis. Computed tomography (CT), magnetic resonance imaging (MRI), virtual colonoscopy, endorectal ultrasound and positron emission tomography (PET) constitute significant means for the diagnosis and staging of colorectal cancer. Endorectal ultrasound demonstrates high accuracy in identifying penetration of the rectal wall, but is poor in assessing the N stage of the disease. CT is particularly useful in identifying other organs involvement but weak in distinguishing between T stages of the tumor, whereas MRI is accurate in identifying the presence or absence of the circumferential margin involvement. In the last five years preoperative staging has become more refined by advances in MRI imaging. Detailed assessment of MRI images is a very important parameter of the multidisciplinary rectal cancer meetings, due to its potential to predict the presence of tumor in the circumferential resection margin [3, 4].

One of the main milestones in the treatment of rectal cancer, which has overall resulted in the five-year survival improvement, is the multimodal therapy approach. The multimodal therapy of the rectal disease imposes the close interdisciplinary cooperation between colorectal surgeons, oncologists, radiologists, and radiotherapists. Locally advanced cancer is treated with combined modality therapy that includes surgery, radiation therapy and chemotherapy. It is possible to identify two patient groups, which have significantly different prognostic outcomes in terms of local recurrence. These include tumors with good prognosis that is, T1, T2, and those with poor prognosis such as T3 and T4 stage tumors. In the case of some correctly identified Tis or T1 tumors, one can find candidates for treatment with local excision alone. In the case of T2 tumors, major radical surgery should suffice, depending on the N stage of the disease. In the case of the group with poor outcome, the T3 and T4 tumors require preoperative treatment by chemoradiotherapy followed by major surgery. Neoadjuvant therapy is widely accepted as the current standard of care in the treatment of advanced rectal cancer. However, there is considerable debate regarding the best approach to neoadjuvant therapy. Studies from the United States have largely focused on a "long course" of preoperative radiation using conventional doses of 1.8–2 Gy per fraction over 5-6 weeks, for a total dose of 45 to 50.4 Gy. The Swedish Rectal Cancer

Trial was the first randomized study to show that a "short course" of preoperative radiation, 5 Gy × 5 alone, without chemotherapy, followed by immediate surgery, resulted in significant improvement in 5-year survival and a reduction in the local recurrence rate for all stages of cancer [5, 6].

Following diagnosis and staging of a rectal tumor, a decision needs to be made with regards to the optimal method of surgical treatment. A few dilemmas rise up during that decision stage: To save or not to save the sphincter complex is a common question. Is there a level below which an anastomosis should not be attempted, in fear of anastomotic failure? The ideal surgical technique for low rectal tumors remains controversial in the absence of randomized trials. Unfortunately, in a passionate effort to avoid a colostomy and to re-establish intestinal continuity, surgeons often compromise on the margins of resection, with tragic consequences for the patient (local recurrence, anastomotic failure, gastrointestinal tract dysfunction and/or pelvic pain).

The introduction of total mesorectal excision (TME) by Heald in 1981, today seen as the "gold standard" of rectal cancer surgery, reduces considerably the frequency of local recurrence and increases disease-free survival rates [7]. The type of operation that can be offered to a patient with rectal cancer depends on tumour stage and on the location of the tumour in relation to the surgical anatomy. The rectal cancer NCI consensus recommended localizing the tumour relation to the anal verge, which is defined as starting at the intersphincteric groove. Another important landmark defining the upper limit of the anal canal is the anorectal ring. From the surgeon's perspective, the top of the anorectal ring is the lower limit of a distal resection margin. A large, full-thickness cancer needs to be located high enough above the top of the anorectal ring to allow for an adequate distal margin if sphincter preservation is contemplated.

Several procedures are available to the surgeon, depending on disease stage and tumor location. A low anterior resection is performed in order to remove tumors of the middle and lower rectum. For a resection to be radical, a "5 cm rule" distal free margin below the tumor is important. In case of a very low anterior resection, the anastomosis is performed at the level of the dentate line either transanally, or by the use of a circular stapler.

The sphincter-saving procedures have significantly reduced the frequency of abdominoperineal resections of the rectum. The principle of the intersphincteric resection is based on an anatomic dissection plane between the internal and external anal sphincter. It can be performed for tumors less than 3 cm from the dentate line. Due to its complexity, strict inclusion criteria have to be followed, such as absence of distant metastases, local spread restricted to the rectal wall or the internal anal sphincter and adequate distal margin potentials. The local transanal excision of tumors also seems as an attractive therapeutic option because of the minor morbidity and the short recovery time. There are, however, significant issues with regards to long-term disease control, because of the inability of the technique to control regional disease. Nevertheless, ideal candidates for this approach can be identified in patients with low-risk tumors, smaller than 4 cm, and involving less than 40% of the lumen circumference. Furthermore, significant comorbidities not allowing a more radical resection can also be a decision parameter towards local resection [8–10].

Preoperative radiotherapy or chemoradiation has been used to downstage rectal tumors and to facilitate sphincter-saving surgery. In addition to the increased resectability of bulky rectal cancers, another benefit of neoadjuvant therapy seems to be the reduction of locoregional recurrence and the improved survival. But, when the options of sphincter-saving procedures fail, the surgeon still has the option of the abdominoperineal resection (APR). Described by Miles in 1908, the APR describes the removal of the rectum with the anal mechanism, followed by the creation of an end colostomy. Many factors influence the decision to perform an APR, such as tumor level and invasion, organ involvement, anal sphincter dysfunction, systemic diseases, body habitus, and many more. Therefore, the surgeon should make the final decision of operative technique upon completion of total mesorectal excision, being certain of the absence of macroscopic and microscopic evidence of cancer invasion in the circular and distal margin of expected resection. An inadequacy of providing uninvaded margins (inability to achieve clear margins of resection) can serve as an indication to perform APR [11].

The current special issue overviews rectal cancer as a surgical oncological problem, and looks at issues surgeons are faced with when dealing with that disease. T. C. Chua et al. review the modern approach to rectal cancer surgery at all disease time points with an emphasis on some of the controversies and the accepted standards of treatment. The multimodal approach to the surgical management of locally recurrent rectal cancer is presented in the paper by N. M. Hogan and M. R. Joyce, including details on presentation, risk factors, preoperative preparation, contraindications and resectability, and also palliation. Furthermore, the review by I. Zlobec et al. outlines three situations in which the assessment of tumor budding may have direct implications on the treatment of rectal cancer within the multimodal approach.

A very informative current state-of-the-science on neoadjuvant and adjuvant therapy for patients with locally advanced rectal adenocarcinomas is written by J. T. Yorio et al., describing in detail the benefits of chemotherapy, radiotherapy and combined modality therapy regimens. A review by D. D. Kim and C. Eng explores the effects and outcome of the use of targeted agents in locally advanced and metastatic colorectal cancer, and patient benefits particularly in rectal cancer. Jabbour et al. retrospectively compared two groups of patients following neoadjuvant intensity-modulated radiation therapy or 3D-conformal radiation therapy for rectal cancer, and concluded that IMRT can reduce treatment breaks, hospitalization, and higher-grade toxicities compared to 3D CRT. Furthermore, the paper by J. A. Smith et al. assesses the differences in clinical, radiologic, and pathologic outcomes between neoadjuvant treatment of stage II-III rectal adenocarcinoma with conventional external beam radiotherapy or intensity-modulated radiotherapy versus high-dose-rate endorectal brachytherapy.

Technical details have also been issued by authors. A. Carrara et al. address the issue of local excision as appropriate treatment for early stage rectal cancer analyzing the risk factors for lymph nodal involvement. M. G. Prametaftakis et al. look at one of the operative parameters during abdominoperineal resection for low rectal cancer, namely, the localization of the pelvic drain. One of the technically demanding options for treating low rectal cancer by keeping part of the sphincter mechanism is the intersphincteric resection technique, which is analyzed in the paper by C. P. Spanos. Furthermore, a novel technique offering multiple advantages compared to the original TEM for rectal adenomas or early carcinomas is described by A. Carrara et al., namely, the glove port technique. Finally, G. Tsoulfas et al. address the issue of hepatic metastatic disease and the dilemma of which treatment step should come first, rectal resection or liver metastatic resection.

In order to be successful in treating rectal cancer, good oncologic outcome is the first priority. Equally important is the achievement of an acceptable quality of life for the patient. Despite advances in surgical technique along with improvements in neoadjuvant and adjuvant therapy, the surgical treatment of rectal cancer involving the pelvic floor and sphincter complex remains complicated. Patients with low rectal cancer pose difficulties with regards to optimal management and targeted strategies are needed to improve outcome in this complex cancer. Careful patient selection, high quality preoperative imaging, and functional assessment, with emphasis on sound operative technique and coordinated involvement of medical and radiation oncology should lead to superior results.

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Clinical Study

Intensity-Modulated Radiation Therapy for Rectal Carcinoma Can Reduce Treatment Breaks and Emergency Department Visits

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Purpose. To compare the acute toxicities of IMRT to 3D-conformal radiation therapy (3DCRT) in the treatment of rectal cancer. *Methods and Materials*. Eighty-six patients with rectal cancer preoperatively treated with IMRT ($n = 30$) and 3DCRT ($n = 56$) were retrospectively reviewed. Rates of acute toxicity between IMRT and 3DCRT were compared for anorexia, dehydration, diarrhea, nausea, vomiting, weight loss, radiation dermatitis, fatigue, pain, urinary frequency, and blood counts. Fisher's exact test and chi-square analysis were applied to detect statistical differences in incidences of toxicity between these two groups of patients. *Results*. There were fewer hospitalizations and emergency department visits in the group treated with IMRT compared with 3DCRT ($P = 0.005$) and no treatment breaks with IMRT compared to 20% with 3DCRT ($P = 0.0002$). Patients treated with IMRT had a significant reduction in grade ≥ 3 toxicities versus grade ≤ 2 toxicities ($P = 0.016$) when compared to 3DCRT. The incidence of grade ≥ 3 diarrhea was 9% among 3DCRT patients compared to 3% among IMRT patients ($P = 0.31$). *Conclusions*. IMRT for rectal cancer can reduce treatment breaks, emergency department visits, hospitalizations, and all grade ≥ 3 toxicities compared to 3DCRT. Further evaluation and followup is warranted to determine late toxicities and long-term results of IMRT.

1. Introduction

The standard management of locally advanced rectal cancer consists of preoperative 5-fluorouracil (5-FU)-based chemoradiation (CRT), which has been established over the past several decades with multiple pivotal clinical trials. A large randomized trial compared preoperative to postoperative CRT for locally advanced rectal cancer and demonstrated that neoadjuvant treatment improved local control and reduced toxicity [1]. Although both short- and long-term

Table 1: Patient characteristics.

Characteristic	3DCRT ($n = 56$)	IMRT ($n = 30$)	P value
Mean age (years)	56.3	52.7	0.23
Male/female (n) (%)	40/16 (71/29)	15/15 (50/50)	0.06
Total elapsed days (mean)	40.5	38.7	0.081
Treatment suspended (n) (%)	11 (20%)	0 (0)	0.0002
Median total dose (cGy)	5040	5040	0.23
Chemotherapy types (n) (%)			0.71
Capecitabine or 5-FU	45 (80)	27 (90)	
Capecitabine/oxaliplatin	7(12)	3 (10)	
Capecitabine/CPT-11	1 (2)	0	
5-FU/leucovorin/oxaliplatin	3 (5)	0	
Preoperative T stage (n) (%)			0.85
T2	0	1 (3)	
T3	51 (91)	27 (90)	
T4	5 (9)	2 (7)	
Preoperative N stage (n) (%)			0.21
N0/x	26 (46)	10 (33)	
N1/N2	30 (54)	20 (67)	
Preoperative M stage (n)%			0.91
M0	52 (93)	27 (90)	
M1	4 (7)	3 (10)	
Pathological complete response (%)	21%	20%	0.555
Downstaging T stage (%)	50	60	0.26
Downstaging N stage (%)	34	40	0.37

side effects decreased with a preoperative approach, absolute rates of toxicity were still noteworthy. Rates of grade 3-4 diarrhea were 12% with preoperative CRT and 18% in the postoperative setting. All acute grade 3-4 toxicities (diarrhea, hematologic, and dermatologic) were 27% with preoperative chemoradiation versus 40% with postoperative therapy.

Since intensity-modulated radiation therapy (IMRT) has the potential to improve dose distributions to nearby dose-limiting structures, it is of potential benefit in the management of rectal cancer with a recent study showing a reduction in gastrointestinal toxicity [2]. It may help reduce dose to bowel, bone marrow, and bladder and therefore reduces the associated organ-specific side effects for cervical, prostate, and anal cancers. For carcinoma of the cervix, pelvic IMRT permitted sparing of pelvic bone marrow [3] and was associated with lower toxicity rates and favorable outcomes compared to standard radiation therapy [4]. Additionally, for prostate cancer patients treated with androgen deprivation therapy, IMRT significantly reduced acute and late GI toxicities compared to 3DCRT [5]. For anal canal carcinoma, IMRT appeared comparable to 3DCRT with regard to local control and survival while decreasing dermatologic, GI, and hematological toxicities and associated treatment breaks [6, 7].

For the management of rectal cancer, dosimetric studies have shown that IMRT reduces doses of irradiated small bowel [8]. This study seeks to evaluate the toxicity profiles and clinical data with IMRT versus 3DCRT for rectal cancer, with the hypothesis that IMRT would lessen the severity of acute toxicities during the preoperative management of rectal cancer.

2. Materials and Methods

Under a protocol approved by the institutional review boards (IRB) of three institutions, patients with rectal cancer treated with concurrent CRT were identified. The procedures followed were in accordance with the IRB ethical standards and with the Helsinki Declaration of 1975, as revised in 2000. Preoperative CRT was the preferred paradigm among patients with locally advanced rectal cancer. Postoperative radiation therapy cases were omitted, and patients treated preoperatively with IMRT and 3DCRT were analyzed. All patients provided informed consent for treatment. Concurrent chemotherapy consisted of continuous infusion 5-fluorouracil at doses of 225 mg/m^2 or capecitabine 825 mg/m^2 twice a day. Other chemotherapy regimens included capecitabine 825 mg/m^2 twice a day, concurrently with irinotecan or oxaliplatin 50 mg/m^2 weekly and radiation therapy. Also, a regimen of oxaliplatin 130 mg/m^2 on day 1, followed by 5-day continuous infusion 5-FU 350 mg/m^2 and leucovorin 100 mg/m^2 during weeks 1 and 5, was used with radiation therapy (Table 1). Patient weight, performance status, total treatment time, need for treatment breaks, and toxicity assessments were performed prior to, weekly during treatment, and 6–8 weeks after chemoradiation. The use of antidiarrheal and antiemetic medications was documented on weekly medication flow sheets. Any use of intravenous fluids

was documented in the chart on separate physician order sheets. Toxicities were graded according to the Common Terminology Criteria for Adverse Events Version 3.0. Acute toxicities assessed included anorexia, dehydration, diarrhea, nausea, vomiting, weight loss, radiation dermatitis, fatigue, pain, and urinary frequency. Blood counts were also assessed. Hospital admissions and emergency department visits were available via the electronic medical record for all institutions. The data on treatment breaks was extracted from the record and verify system of each institution. The rates of toxicities among patients receiving IMRT were then compared to those treated with 3DCRT. Fischer's exact test was applied to test for statistically significant side effects related to treatment with IMRT and 3DCRT. A value of $P \leq 0.05$ was considered significant.

2.1. Radiation Therapy Planning. Computed tomography (CT)-based simulation with 2.5 mm slice thickness was performed. Patients were simulated either supine or prone (IMRT, 97% supine) (3DCRT, 91% prone) with arms up and a full bladder. Oral contrast was given to patients for small bowel delineation. A custom immobilization was designed for supine patients, and a belly board was used for those placed in the prone position.

Gross tumor volume (GTV) and enlarged regional lymph nodes were determined by a combination of findings on physical exam, transrectal ultrasound, CT, PET-CT, and/or MRI. The clinical target volume (CTV) was defined as the GTV plus internal iliac (T3) and external iliac (T4) and perirectal, mesorectal, and presacral lymph nodes. The rectal CTV included the rectal GTV with a 1.5–2 cm radial expansion and 2.5–3 cm craniocaudal expansion, while the nodal GTV was given a 1.5–2 cm uniform expansion. Uninvolved iliac nodal regions had a 1.0–1.5 cm expansion. The presacral lymph nodes began at the sacral promontory and ended at the bottom of S5. CTV and mesorectum were generated according to the RTOG anorectal contouring atlas when available [9]. PTV expansions were 0.5–1.0 cm.

2.2. IMRT Technique. A total of 4500 cGy in 180 cGy daily frac-tions was delivered to the pelvis (rectum and draining lymph nodes at risk) using inverse-planned IMRT. This was followed by a cone-down phase consisting of either a 3-dimensional conformal boost designed with a 3-field technique to GTV and a minimum 2 cm uniform margin including all of the presacral space for an additional 540 cGy in 180 cGy daily fractions or an IMRT plan with the same volumes. Every effort was made to limit the dose to the small and large bowel doses. Figures 1 and 2 demonstrate a representative IMRT plan. Three radiation oncologists, who specialize in the management of gastrointestinal malignancies, prepared the field design of these cases. Prior to incorporation of these IMRT cases in this series, each submitting radiation oncologist reviewed their cases to ensure that they met the abovementioned planning constraints.

Small bowel, femoral head, and bladder IMRT constraints were followed as per RTOG 0822. For patients treated prior to release of RTOG 0822 ($n = 1$), patients whose plans met the RTOG 0822 constraints were included in this analysis. Inverse planning with seven-to-nine equally spaced, coplanar IMRT fields was constructed. Image guidance with either cone-beam CT or orthogonal films was utilized daily. Acute toxicities were defined as those which occurred during or up to 8 weeks following the completion of CRT.

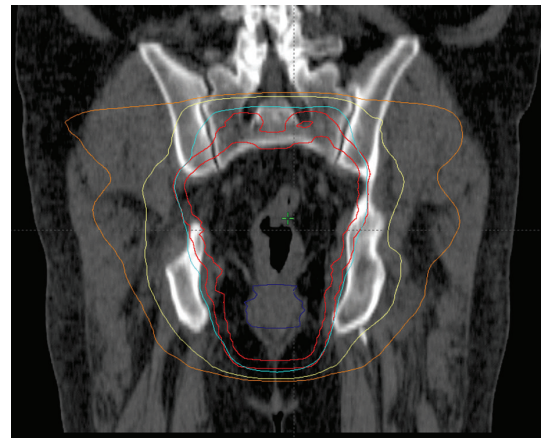

Figure 1: Coronal images of an IMRT plan.

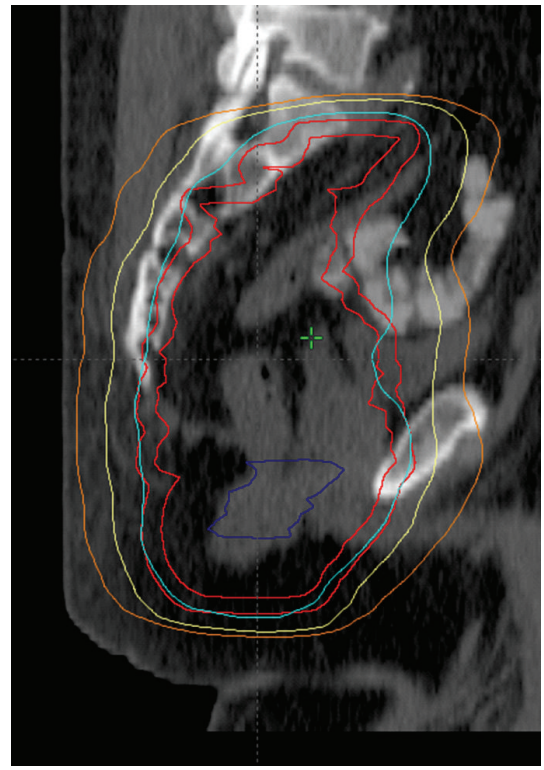

Figure 2: Sagittal images of an IMRT plan. This 56-year-old man was found to have an uT3N0 rectal adenocarcinoma and managed with preoperative CRT consisting of capecitabine with a seven-field coplanar IMRT plan to a total dose of 4500 cGy followed by a boost to the GTV to a total of 5040 cGy. The 95%, 70%, and 50% isodose curves are displayed along with the PTV.

Table 2: Rates of toxicity by CTCAE grade.

Toxicity	3DCRT *n* (%)	IMRT *n* (%)	*P*
Diarrhea			0.31
Grade 0–2	51 (91)	29 (97)	
Grade 3-4	5 (9)	1 (3)	
Dehydration			0.17
Grade 0–2	52 (93)	30 (100)	
Grade 3-4	4 (7)	0	
Nausea/vomiting			
Grade 0–2	56 (100)	30 (100)	
Grade 3-4	0	0	
Fatigue			
Grade 0–2	56 (100)	30 (100)	
Grade 3-4	0	0	
Pain			0.72
Grade 0–2	54 (96)	29 (97)	
Grade 3-4	2 (4)	1 (3)	
Urinary frequency			
Grade 0–2	55 (98)	30 (100)	0.65
Grade 3-4	1 (2)	0	
Nadir white blood cell count			0.27
Grade 0–2	53 (95)	30 (100)	
Grade 3-4	3 (5)	0	
Nadir Hemoglobin			0.42
Grade 0–2	54 (96)	30 (100)	
Grade 3-4	2 (4)	0	

3. Results

All study patients with rectal cancer were treated from 2005 to 2011, while IMRT was utilized after 2007. Thirty patients (35%) received IMRT, and 56 patients (65%) received 3DCRT to a median total dose of 5040 cGy (IMRT range 5000–5040 cGy and 3DCRT range 4500 cGy–5140 cGy). There were no significant differences in median age, gender, type or duration of chemotherapy, or stage between groups (Table 1). Median followup time was 23 months in the 3DCRT group compared to 11 months in the IMRT group ($P = 0.00005$).

Patients who received IMRT had a significant reduction in all grade ≥3 toxicities versus grade ≤2 toxicities ($P = 0.016$) with respect to hematological, urinary, pain, fatigue and GI (anorexia, dehydration, diarrhea, nausea, vomiting, and weight loss) symptoms, as compared to those treated with 3DCRT (Table 2). The rate of GI grade ≥3 ($n = 9$ with 3DCRT versus $n = 1$ with IMRT) toxicities versus grade ≤2 toxicities was not significantly different ($P = 0.085$). The incidence of grade ≥3 diarrhea was 9% among 3DCRT patients compared to 3% among IMRT patients ($P = 0.31$).

Overall, patients who received two or more chemotherapy agents concurrently with radiation therapy demonstrated higher rates of grade ≥3 toxicity (43%) compared to those receiving single-agent chemotherapy (11%; $P = 0.009$). On multivariate analysis, there was a significant relationship between GI toxicity and chemotherapy type when adjusting for age and stage with the two or more chemotherapy group having higher toxicity than the one chemotherapy type group when treated with either 3DCRT or IMRT ($P = 0.022$). On multivariate analyses, there were no significant relationships found among the use of infusional 5-FU or capecitabine and the outcomes of pathological complete response, GI toxicity, or all toxicity.

There were fewer hospitalizations and emergency department visits in the group treated with IMRT (2%) compared with 3DCRT (14%; $P = 0.005$). There were no treatment breaks with IMRT compared to 20% with 3DCRT ($P = 0.0002$). Likewise, the median total time to treatment completion was shorter with IMRT (38.7 days) versus 3DCRT (40.5 days) but did not reach statistical significance ($P = 0.081$). From the start to end of radiation therapy, performance status showed less decline in the IMRT group with 33% of patients showing a decline in performance status and 51% in the 3DCRT group ($P = 0.091$).

3.1. Pathologic Response Rates. The rates of pathological complete response were similar in the 3DCRT group at 21% versus 20% with IMRT ($P = 0.55$). Preoperative tumor T-stage downstaging was similar with 50% of 3DCRT patients and 60% of IMRT patients ($P = 0.25$). Nodal downstaging occurred in 34% of 3DCRT patients and 40% of IMRT patients ($P = 0.37$). Also, rates of local recurrence were similar between the groups with 6.7% local failure in the IMRT

group and 7% in the 3DCRT group ($P = 0.65$). Of the local failures in the IMRT group, none were marginal failures. Rates of distant metastases after completion of therapy were not significantly different at 12.5% of 3DCRT patients and 6.7% of IMRT patients ($P = 0.33$).

4. Discussion

By implementing inverse planning and improving conformality of targets, IMRT allows limitation of radiation dose to nearby normal organs at risk, while allowing delivery of high doses to the tumor and regional lymph nodes. In so doing, it can reduce side effects by conforming dose to avoid normal, uninvolved tissues, which may correlate with an improvement in the toxicity profile. The use of IMRT for rectal cancer may also potentially prevent delays in time to surgery, facilitate improved postoperative healing, and allow improved tolerability of adjuvant chemotherapy [2]. This is the first study to show that IMRT not only results in a more timely administration of chemoradiation, but also results in fewer hospitalizations and emergency room visits.

IMRT for rectal cancer can reduce treatment-related toxicities, as compared to standard 3DCRT. In our study, IMRT significantly reduced all toxicities including GI, hematological, urinary, pain, and fatigue, compared to 3DCRT. Toxicity management is well enumerated in patient charts at these tertiary care hospitals, with significant documentation of prescribed medications according to JCAHO regulations, which are accounted in the CTCAE grading. In this study, grades of diarrhea were lessened but overall GI toxicities (independent of hematological, urinary, pain, and fatigue) were not significantly reduced with IMRT compared to 3DCRT.

Patients tolerated IMRT with fewer treatment breaks relative to 3D-CRT. Despite the omission of the postoperative patients, treatment breaks still remained at a level of 20% in the 3D-CRT cohort. Although the possibility of hospitalizations/ED visits and treatment breaks could be due to chance, the use of the electronic record to determine elapsed treatment days and hospitalization/ED visits increases the objectivity of this measure.

Patient characteristics were quite similar between the groups with regard to age, stage, and chemotherapies used. Although there was no prospective quality assurance of the plans, all IMRT planning was conducted by only three radiation oncologists (SKJ, JMH, SNN) with expertise and primary focus in the management gastrointestinal malignancies. The RTOG guidelines and anorectal contouring atlas were employed. Although the median followup was not long, assessment of short-term toxicity was the main endpoint.

Understanding the limitations of a retrospective comparison, the rates of toxicity seen with IMRT in this series appear encouraging when evaluated in relation to prior studies. The 3DCRT toxicity rates were comparable to the German rectal trial in terms of diarrhea, with a rate of grade ≥3 diarrhea of 12–18% compared to 9% in our 3DCRT group and 3% in the IMRT group [1]. The NSABP R-03 trial which randomized rectal cancer patients to preoperative (with one cycle of induction 5-FU and leucovorin before chemoradiation) or postoperative RT (3DCRT) with concurrent 5-FU and leucovorin showed a rate of 36% of grade ≥3 diarrhea for the preoperative arm and 29% for the postoperative group [10].

A prior dosimetric comparison of 3DCRT to IMRT for rectal cancer showed that the bowel volume irradiated was significantly reduced with IMRT [11]. Specifically, the planning techniques most successful at bowel sparing were a 3-field forward planned IMRT technique and a 9-field equally spaced IMRT technique [11]. In addition, IMRT can reduce median doses to small bowel by 5.1 Gy for rectal cancer [8]. Other studies have demonstrated improvements in target coverage, homogeneity, and conformality, while reducing doses to the small bowel, bladder, and pelvic bones for preoperatively planned cases in the prone position [12]. Likewise, implementation of IMRT and CT-based image-guidance can decrease irradiated small bowel and the normal tissue complication probability [13]. Therefore, the data suggest that the volume of small bowel irradiated can be reduced with IMRT.

Patients who received IMRT in our series were usually treated in the supine position to improve the setup reproducibility and tolerability, whereas most of the patients who received 3DCRT were treated in the prone position. One study evaluating the optimal method for reducing irradiated small bowel volumes in preoperative rectal cancer patients showed that a combination of prone positioning with bladder distention was most effective [14], but this was in an Asian population with presumably smaller body habitudes than Americans. In contrast, another study showed no difference in toxicity outcomes with the use of IMRT in prone versus supine positioning for endometrial cancer [15]. Drzymala et al. compared supine versus prone position in 19 rectal cancer patients and showed that at the low dose levels, a significantly higher volume of bowel was irradiated in the supine position, but from 20 to 45 Gy, there was no significant difference in the volume of bowel irradiated with each 5 Gy increment. Therefore, the volume of bowel irradiated at doses associated with bowel toxicity with concurrent CRT was not significantly higher in the supine position [16]. The data as to the optimal positioning of patients for pelvic RT is conflicting, and the benefit of bowel sparing with each of these techniques (bladder distention, positioning, IMRT) may be incremental or patient dependent and requires further study.

Another important consideration with the use of IMRT is the potential for compromising outcomes by missing or potentially underdosing tumor and target volumes. In our study, the efficacy of IMRT downstaging appeared to be similar to 3DCRT. Of the small cohort of patients treated with IMRT, only two experienced local recurrence, neither of which were marginal failures. However, further followup is needed to adequately assess outcome, and this rate was not significantly different compared to patients treated with 3D-CRT. Given the potential for marginal failures with the use of IMRT for rectal cancer, care must be taken to contour according to available data and atlases. Prior studies in other GI malignancies have shown the importance of adherence to protocol in order to achieve the expected benefit of radiation therapy [17].

Certainly, daily changes in organ positioning can potentially impact outcomes, including side effects. However, with the available information from anal cancer IMRT and cervical cancer IMRT, we recognize that the benefit of these treatments was realized even in the setting of daily changes in positioning. In this study, interfraction motion was corrected by the use of on-board imaging. In our study, patients were instructed and counseled on appropriate bladder filling and rectal emptying procedures. In addition, expansions for GTV to CTV and PTV were quite reasonably sized to achieve PTV's in IMRT planning that resembled those of 3DCRT fields. In fact, with the expansions used in our study, the PTV received full dose, whereas using standard field arrangements, the IMRT PTV often would have been in the penumbra. This situation occurs because standard 3DCRT blocks are usually placed 2 cm from the iliac vessels therefore, full dose is delivered approximately 1–1.2 cm from the iliac vessels due to normal dose falloff. However, in our IMRT expansions, these normal iliac vessels would have been expanded 1.0–1.5 cm, with an additional margin of 0.5–1.0 cm for PTV, which would then receive full dose with IMRT to the PTV.

It should be noted that two of the four grade-3 leukopenia cases in the 3DCRT arm occurred in patients who were treated with concurrent oxaliplatin, leucovorin, and 5-FU. Nevertheless, the other two patients who experienced grade-3 leukopenia received capecitabine alone with radiation therapy. There was no change in toxicity with the administration of 5-day versus 7-day 5-FU or capecitabine, and no differences were detected between 5-FU and capecitabine in terms of outcomes. Due to the self-administration of capecitabine, patient adherence to medication administration could be a factor in determining patient outcomes.

In this cohort, chemotherapy was primarily 5-FU or capecitabine concurrently with radiation. The available literature about this topic has been quite clear that the standard of care is 5-day continuous infusion 5 fluorouracil or 5 days of capecitabine concurrent with radiation therapy. The NSABP R-04 trial demonstrated no differences in outcomes including pathological complete response rates, surgical downstaging, or sphincter sparing surgery with either of these regimens [18]. Given that the majority of our patients were treated with concurrent 5-FU or capecitabine, the cohorts appear relatively homogeneous and comparable.

Our study demonstrates that IMRT may help reduce treatment interruptions, emergency department visits, and hospitalizations compared to 3DCRT. In addition, grade ≥ 3 toxicities were rare in this IMRT cohort. Grade ≥ 3 diarrhea was also reduced with the use of IMRT compared to 3DCRT. This series adds to the available literature favoring the use of IMRT in gastrointestinal malignancies. However, additional studies are needed to assess the impact of IMRT on long-term clinical outcomes and late toxicities in the treatment of rectal adenocarcinoma.

Conflict of Interests

The authors have declared that they have no conflict of interests.

Acknowledgments

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Review Article

Role of Intra- and Peritumoral Budding in the Interdisciplinary Management of Rectal Cancer Patients

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The presence of tumor budding (TuB) at the invasive front of rectal cancers is a valuable indicator of tumor aggressiveness. Tumor buds, typically identified as single cells or small tumor cell clusters detached from the main tumor body, are characterized by loss of cell adhesion, increased migratory, and invasion potential and have been referred to as malignant stem cells. The adverse clinical outcome of patients with a high-grade TuB phenotype has consistently been demonstrated. TuB is a category IIB prognostic factor; it has yet to be investigated in the prospective setting. The value of TuB in oncological and pathological practice goes beyond its use as a simple histomorphological marker of tumor aggressiveness. In this paper, we outline three situations in which the assessment of TuB may have direct implications on treatment within the multidisciplinary management of patients with rectal cancer: (a) patients with TNM stage II (i.e., T3/T4, N0) disease potentially benefitting from adjuvant therapy, (b) patients with early submucosally invasive (T1, sm1-sm3) carcinomas at a high risk of nodal positivity and (c) the role of intratumoral budding assessed in preoperative biopsies as a marker for lymph node and distant metastasis thus potentially aiding the identification of patients suitable for neoadjuvant therapy.

1. Introduction

Tumor budding (TuB) refers to the presence of detached single tumor cells or clusters of up to 5 cells scattered within the stroma at the invasive tumor front of many different solid cancers [1]. TuB as a histomorphological feature is best described in gastrointestinal tumors and was first comprehensively investigated by Jass in the mid 1980s in patients with rectal cancer [2]. TuB can be evaluated at high magnification using regular H&E staining but its visualization is markedly facilitated with the use of pan-cytokeratin stains (Figure 1).

It is hypothesized that tumor buds, or at least a subpopulation of these cells, have undergone a process similar to epithelial mesenchymal transition (EMT) and have acquired the ability to act as malignant stem cells [3]. Immunohistochemical staining of tumor buds in colorectal cancers shows a clear overexpression of markers involved in extracellular matrix degradation, angiogenesis, migration, and invasion and decreased Ki67 staining indicative of a low proliferation rate [4]. An overexpression of nuclear beta-catenin and simultaneous loss of cell adhesion markers, in particular, E-cadherin is classically observed in tumor-budding cells [5].

With such an aggressive phenotypic constellation, it is not surprising that TuB has consistently been linked to lymph node positivity, the presence of lymphatic and venous invasion, as well as with the presence of distant metastatic disease [6–12]. The frequency of high-grade TuB in colon and rectal cancer varies; it has generally been reported to occur in 25–60% of all cases but is correlated with disease progression [7, 9, 13–15]. For example, high-grade TuB is reported in 15–17% of patients with early pT1 tumors [8, 15, 16], 26% of pT2 cases [17], 36–51% of pT3 tumors [12, 17, 18], and up to 73% of pT4 cancers [18]. In addition, it occurs significantly more frequently in patients with node-positive tumors (51–75%) in comparison to patients with TNM (6th ed.) stage II

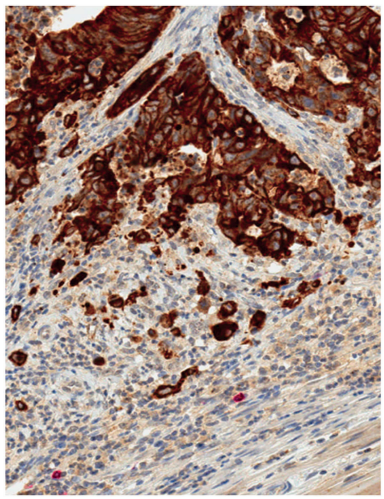

Figure 1: Immunohistochemical analysis highlighting the presence of peritumoral buds at the invasion front of rectal cancer (pancytokeratin stain: CK22, 40x magnification).

(T3/T4, N0) (15–29%) cancers [8, 15, 17]. Currently, TuB is listed as a category IIB prognostic factor and many studies have confirmed that the presence of TuB is associated with poorer overall and disease-specific and disease-free survival, in most cases independently of the TNM stage [19].

The value of TuB in oncological and pathological practice goes beyond its use as a simple histomorphological marker of tumor aggressiveness. In this paper, we outline three situations in which the assessment of TuB may have direct implications on treatment within the multidisciplinary management of patients with rectal cancer. These include (a) the identification of patients with TNM stage II disease potentially benefitting from adjuvant therapy, (b) the identification of patients with early submucosally invasive (T1) carcinomas at a high risk of nodal positivity, and (c) the use of tumor budding as a marker of prognosis and predictor of local and distant relapse assessable in preoperative biopsies.

1.1. Stage II Rectal Cancer Patients. Stage II colorectal cancer patients represent a clinically heterogeneous group. Data from the SEER (1975–2005) Public Use File show 5-year survival trends for patients with colon and rectal cancer [35]. In particular for the latter, 5-year overall survival rates decrease dramatically from 64.5% for IIA (T3N0), to 51.6% for IIB (T4aN0) and 32.3% for IIC (T4bN0). Generally, patients with stage II colorectal cancer are not typically considered for additional adjuvant therapy without the presence of additional high-risk features such as perforation or venous and lymphatic invasion [36]. It is suggested, however, that a subgroup of patients with stage II disease who would otherwise have unfavorable clinical outcome and high-risk for metastasis may in fact benefit from adjuvant therapy but the identification of such patients using histomorphological or molecular markers is unclear [37].

Although the prognostic effect of high-grade TuB has been well described, studies focusing on the subgroup of stage II cancers are few. Kevans and colleagues evaluated 258 patients with stage II disease and the correlation of TuB with survival and with expression of EMT-related protein markers [38]. They showed that TuB was the only independent marker of poor outcome and had a major effect on the relative risk (RR) of death; patients with high-grade TuB were nearly 8 times more likely to die of disease compared to patients with low-grade TuB. Wang et al. performed a study using 128 patients and evaluated 5-year cancer-specific survival [12]. They show a significant reduction in survival from 91% to 63% in patients with low- versus high-grade TuB and a RR of death of 4.76. Nakamura and colleagues studied 5- and 10-year survival rates for 200 stage II patients as well as the association of TuB on the presence of distant metastasis [9]. Again a substantial reduction in 5-year (93.9% and 73.9%) and 10-year (90.6% and 67.8%) survival time was observed in patients with low-grade versus high-grade TuB tumors. Tanaka and colleagues confirm this finding, reporting disease-specific survival rates of 98% versus 74% in patients with and without TuB, respectively, [10]. Moreover, TuB in stage II patients has been shown to be independent of other prognostic features [13, 39]. An increased frequency of liver and peritoneal metastasis was noted in the high-grade TuB group [9]. Earlier studies show that the sensitivity and specificity of high-grade TuB for distant metastatic disease in patients with stage II tumors are 0.76 and 0.739, respectively, [14]. Frequencies of local recurrence are significantly higher in patients with high- versus low-grade TuB (48% versus 4.5%, resp.) [10]. Finally, the presence of TuB has been significantly associated with isolated tumor cells in lymph nodes of patients with stage II disease in both univariate and multivariate analysis [40].

Taken together, these results strongly suggest that TuB in patients with stage II colorectal cancers has the potential to contribute independent prognostic information. It is linked to more aggressive tumor behavior and is associated with local and distant metastasis. These findings indicate that TuB should be considered as an important histomorphological parameter and may be worthy of investigation and inclusion in prospective clinical trials of patients with stage II disease.

1.2. Tumor Budding in Early Rectal Cancers. An important issue in the management of patients with submucosally invasive (T1) colorectal carcinomas is the identification of patients after endoscopic resection that may be at "high risk" for lymph node positivity and thus likely to benefit from surgical resection. The rate of lymph node positivity in this setting is low, approximately 10–15% [23, 24, 27, 29]. Nonetheless histomorphological features capable of predicting lymph node involvement are highly sought after.

TuB has been shown in several studies to have predictive power for lymph node involvement in either univariate or multivariate analyses (Table 1). In addition to other features such as histological type, lymphatic and venous invasion, TuB is significantly more frequent in cases with lymph node positivity [22, 24–26, 28, 29]. One study evaluated the impact of TuB in T1 cancers and the potential for the development of distant metastasis. In one subgroup of T1 patients eventually developing metastatic disease and a control group of

Table 1: Summary of studies evaluating tumor budding in submucosally invasive (T1) colorectal carcinomas.

Ref.	Number of patients	Endpoint	Summary of relevant findings
[20]	499	LN+	8.2% of T1 were LN+. Several features were independent predictors of LN+: tumor differentiation/mucinous histology, depth of submucosal invasion, venous invasion, and TuB.
[6]	111	LN+	TuB was associated with LN+ in univariate but not multivariate analysis when analysed with protein markers.
[21]	32	DM	In comparison to a control group, TuB was more frequent in patients who eventually had a distant metastasis in univariate but not multivariate analysis.
[22]	111	LN+	Several features were evaluated including lymphatic and venous invasion, submucosal depth, histologic type, and TuB. In multivariate analysis, only histologic type and TuB predicted LN+.
[23]	65	LN+	T1-T2 rectal cancers. 6.9% of T1 were LN+. TuB predicted lateral LN+.
[24]	322	LN+	14.3% of T1 were LN+. Several features predicted LN+: invasion depth, lymphatic and venous invasion, tumor differentiation, growth pattern, and TuB. Only lymphatic invasion, differentiation, and TuB were independent predictors in multivariate analysis.
[25]	124	LN+ and DM	Elastica von Gieson, D2-40, and CAM5 were used to enhance visualization of venous invasion, lymphatic invasion, and TuB, respectively. TuB was an independent predictor of LN+ and DM+ in multivariate analysis.
[26]	87	LN+ and LR	Prospective study evaluating two groups of patients after endoscopic resection: a surgical group and a follow-up group without surgery. TuB was the only independent predictor of LN+ in multivariate analysis.
[27]	164	LN+	9.8% of T1 were LN+. TuB was significantly associated with LN+ in univariate and multivariate analysis.
[28]	71	LN+	Tumor size, depth of invasion, histologic type, TuB, and lymphatic invasion were predictors in univariate analysis but only TuB and lymphatic invasion were significant in multivariate analysis.
[29]	86	LN+	13% of T1 were LN+. Vascular invasion, tumor budding, and degree of submucosal invasion could be combined to strongly predict LN+.
[30]	214	LN+	Several histopathological and protein markers were evaluated. TuB was a significant predictor in univariate and multivariate analysis.
[31]	76	LN+	TuB can be used in a predictive equation for LN+.
[32]	56	LN+	TuB evaluated using CAM5 was significantly more frequent in LN+ (16/42) than LN negative (0/14) cases.
[16]	159	LN+, OS	10.1% of T1 were LN+ and were associated with several features including TuB. TuB did not influence overall survival.
[33]	51	LN+, LR	TuB was associated to lymphatic invasion, LN+, and local relapse.
[34]	79	LN+	13.9% were LN+. TuB was one of five risk factors for LN+.

TuB: tumor budding; LN: lymph node; DM: distant metastasis; LR: local recurrence; OS: overall survival.

T1 patients with favorable long-term outcome, TuB was significantly more frequent in the metastatic cohort [21]. A different study on 145 patients with T1 cancers used immunohistochemistry and special stains to identify venous invasion, lymphatic invasion, and the presence of TuB by Elastica van Gieson, D2-40 and CAM5 staining, respectively, [25]. In multivariate analysis of lymph node positivity, only venous invasion and TuB were independently predictive of involvement. TuB could predict the presence of distant metastases but only in univariate analysis.

The examples listed in Table 1 underline the potential importance of the additional assessment of TuB in the pathological diagnosis of early pT1 cancers. TuB assessed in these submucosally invasive carcinomas during daily routine may have a promising role as a histomorphological marker for the prediction of lymph node positivity in this setting.

1.3. Is There a Role for Tumor Budding in the Preoperative Setting? Traditionally, the preoperative rectal biopsy can supply three different types of information. The first is the histopathological diagnosis and confirmation of carcinoma, the second is the histological subtype, and the third is the degree of differentiation (tumor grade). However, recently, studies have not only noted the presence of tumor buds within the preoperative biopsy specimen but have also linked this feature to unfavorable prognostic parameters. We have described the presence of tumor budding within the biopsy specimen as "intratumoral" budding (ITB) in order to distinguish it from the classical "peritumoral" budding (PTB) that is located at the invasive front and thus not normally evaluable in biopsy specimens [41] (Figure 2).

The first assessment of tumor budding in rectal cancer biopsies dates to 1989 [42]. Morodomi and colleagues observed that nearly half of all rectal cancer biopsies contained ITB and its presence was a strong indicator of lymph node positivity. Specifically, lymph node involvement was observed in 78.8% of ITB-positive cases and in only 28.1% of ITB-negative rectal cancers. Despite these promising results,

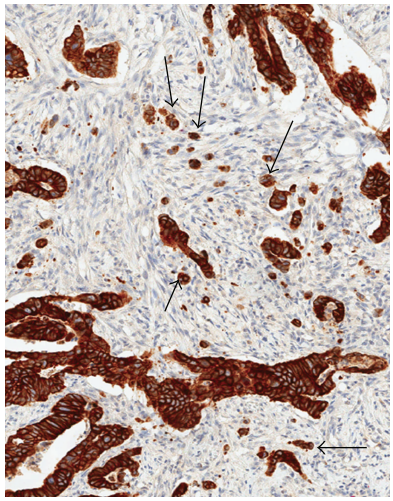

Figure 2: Presence of intratumoral buds (arrows) in the main tumor body of a rectal cancer (pan-cytokeratin stain: CK22, 40x magnification).

the issue of budding within biopsy specimens was only addressed once again in 2011. Using two cohorts of colorectal cancer patients from all stages totaling more than 500 cases, we could confirm the value of ITB as a predictor of lymph node positivity with similar sensitivity (72.7%) and specificity (72.1%) [41]. The presence of ITB not only correlated with vascular invasion but also showed an independent and unfavorable prognostic effect in multivariable analysis. A recent study by Giger et al. evaluated ITB in preoperative biopsies and the predictive values for both lymph node and distant metastasis in a series of 72 colorectal cancers of all TNM stages [43]. Seventeen percent of all cases were found to have high-grade ITB. Of the ITB positive cases, 83.3% had lymph node metastasis and 82% had distant metastasis. This is in contrast to only 51% and 35% of ITB-negative cases, respectively.

A strong linear correlation between the presence of ITB in biopsies and corresponding PTB in resection specimens has been made [41, 43]. This is relevant since the identification of "invasion front" can in some postoperative specimens be challenging. A recent meta-analysis of 42 different histomorphological and immunohistochemical markers in colon and rectal cancers aimed to identify predictors of lymph node metastasis. Focusing on the subset of rectal cancers, Glasgow and colleagues found only two predictive factors, one of which was tumor budding at the invasion front. Again, the sensitivity and specificity of tumor budding for node-positivity across 7 studies with more than 1500 patients were 70% and 69.4% [44].

Taken together, the current body of evidence indicates that regardless of its localization, that is, within the main tumor body or invasion front, tumor budding may be a reliable histomorphological predictor of lymph node metastasis and a factor of poor prognosis which can be applied to both postoperative specimen and, most importantly, preoperative biopsy.

2. Conclusion

At least two avenues of investigation should still be clarified before implementing TuB as a criterion for patient management. First, no prospective studies have been conducted to definitely validate the potential of TuB in the clinical decision-making process. Secondly, TuB remains severely underreported in daily diagnostic routine due largely to the absence of a standardized or internationally accepted method for its assessment. Nonetheless, efforts are currently on-going to compare and validate the prognostic effects of TuB using various methods of assessment and in particular their inter- and intraobserver agreement. The evidence supporting an important role of TuB in the clinical and multidisciplinary management of patients with rectal cancer, for example in the setting of stage II and submucosally invasive tumors continues to grow. Although less than a handful of studies have evaluated the presence of intratumoral budding from the preoperative rectal biopsy, the ability to predict, with high accuracy, the presence of lymph node metastases in the pretreatment setting would be of considerable clinical value.

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Research Article

Clinicopathologic Comparison of High-Dose-Rate Endorectal Brachytherapy versus Conventional Chemoradiotherapy in the Neoadjuvant Setting for Resectable Stages II and III Low Rectal Cancer

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Purpose. To assess for differences in clinical, radiologic, and pathologic outcomes between patients with stage II-III rectal adenocarcinoma treated neoadjuvantly with conventional external beam radiotherapy (3D conformal radiotherapy (3DRT) or intensity-modulated radiotherapy (IMRT)) versus high-dose-rate endorectal brachytherapy (EBT). *Methods*. Patients undergoing neoadjuvant EBT received 4 consecutive daily 6.5 Gy fractions without chemotherapy, while those undergoing 3DRT or IMRT received 28 daily 1.8 Gy fractions with concurrent 5-fluorouracil. Data was collected prospectively for 7 EBT patients and retrospectively for 25 historical 3DRT/IMRT controls. *Results*. Time to surgery was less for EBT compared to 3DRT and IMRT ($P < 0.001$). There was a trend towards higher rate of pathologic CR for EBT ($P = 0.06$). Rates of margin and lymph node positivity at resection were similar for all groups. Acute toxicity was less for EBT compared to 3DRT and IMRT ($P = 0.025$). Overall and progression-free survival were noninferior for EBT. On MRI, EBT achieved similar complete response rate and reduction in tumor volume as 3DRT and IMRT. Histopathologic comparison showed that EBT resulted in more localized treatment effects and fewer serosal adhesions. *Conclusions*. EBT offers several practical benefits over conventional radiotherapy techniques and appears to be at least as effective against low rectal cancer as measured by short-term outcomes.

1. Introduction

Colorectal cancer is the 3rd most common malignancy among both men and women in the United States [1]. Approximately thirty percent of colorectal adenocarcinomas occur in the rectum, totaling approximately 40,290 newly diagnosed cases per year [2]. There are two main goals of treatment for rectal adenocarcinoma, with the first being

complete resection to minimize the risk of recurrence and the second being sphincter preservation in order to maintain normal evacuative function. The current standard of care for patients with stage II-III resectable adenocarcinoma of the rectum is neoadjuvant chemoradiation consisting of 5-fluorouracil- (5-FU-) based chemotherapy and external beam radiation using intensity modulated (IMRT) or 3D conformal (3DRT) radiotherapy techniques. Chemoradiation is followed by total mesorectal excision (TME) with either a lower anterior resection (LAR; sphincter preserving) or an abdominoperineal resection (APR; nonsphincter preserving) and adjuvant FOLFOX chemotherapy [3]. The time frame of conventional neoadjuvant therapy is 5-6 weeks of concurrent chemoradiation followed by a 6–8 week recovery window, then surgical resection. 3DRT or IMRT techniques are considered the standard of care, with a total dose of 50.4 Gy given over 28 fractions.

Preoperative external beam radiation has been shown to increase pathological response rates and reduce the risk of local recurrence [3], but it is also associated with an increased risk of therapy-induced side effects and increased morbidity [4]. These acute toxicity events may lead to treatment breaks, compromising the efficacy of treatment and delaying surgery [3]. In an attempt to reduce treatment-related toxicity, high-dose-rate endorectal brachytherapy (EBT) was developed as an alternative neoadjuvant option for locally advanced low rectal cancer. This technique has been previously described as monotherapy for the treatment of prostate, cervical, esophageal, and buccal mucosal tumors [5–7]. EBT is a radiotherapy technique that allows for delivery of a focused high dose of ionizing radiation at the mucosal surface directly overlying the tumor while avoiding injury to surrounding normal tissues. Rapid dose fall off from the iridium-192 point source and the lack of external radiation beams that must pass through the normal pelvic tissues to reach the tumor combine to minimize dose to normal surrounding structures such as the femoral heads, bowel, bladder, and reproductive organs compared to conventional radiotherapy techniques (Figure 1). In high-dose-rate brachytherapy, the radioisotope is inserted for a brief period of time (approximately 15 minutes for EBT) to deliver the required dose and then withdrawn from the body, as opposed to low-dose-rate brachytherapy where a radioactive source is left implanted in the patient. EBT is given in 4 fractions of 6.5 Gy, for a total dose of 26 Gy. The treatment consists of 4 days of radiation treatment alone followed by a 6–8 week recovery window, then surgical resection and adjuvant chemotherapy. Investigators at McGill University have achieved excellent tumor regression with over 29% of patients having a complete pathologic response at surgery [4, 6, 8]. The response rates of EBT are similar if not superior to those achieved with conventional neoadjuvant chemoradiation, for which the associated pathologic CR rate ranges from 8% to 19% [9–14]. The potential benefits of EBT for patients include the short duration of therapy, the seemingly high response rate reported thus far, and the avoidance of concurrent neoadjuvant systemic chemotherapy and its associated toxicity.

At this point, only one group has published data on patients with resectable rectal adenocarcinoma who were treated with EBT. Herein, we analyze the preliminary outcomes obtained with EBT and compare them to patients receiving conventional neoadjuvant chemoradiation (3DRT/IMRT) at our institution. The primary goal of this study, therefore, is to compare radiologic, pathologic, and short-term clinical outcomes between EBT and conventional radiation techniques in the neoadjuvant setting.

2. Materials and Methods

2.1. Patient Selection. From 2010–2012, 7 patients with locally advanced low rectal adenocarcinoma (within 12 cm of the anal verge) were enrolled in a prospective study of neoadjuvant EBT (NCT01226979) at Johns Hopkins Hospital. Patients were required to meet the following inclusion criteria: greater than 18 years of age, histologically confirmed adenocarcinoma of the rectum, able to undergo local staging by MRI and/or EUS demonstrating a T2N1 or T3N0-1 tumor, and ECOG performance status of 0 or 1. Patients were excluded if they had tumors greater than 12 cm from the anal verge, metastatic disease at time of enrollment, positive inguinal or iliac lymph nodes on MRI, PET, or EUS, concurrent malignancy, bulky tumors that would not allow application of the endorectal probe, or previous pelvic irradiation. For comparison, historical controls were obtained by identifying all patients with stage II-III rectal adenocarcinoma who received conventional neoadjuvant chemoradiation with IMRT or 3DRT at our institution from 2008–2012 and went on to surgical resection.

2.2. Clinical Outcomes. Clinical data for patients treated with EBT was gathered prospectively as part of the trial protocol. To gather data for historical controls, retrospective chart review was performed using the electronic patient record (EPR) system after approval by the Institutional Review Board. For all patients, toxicity was evaluated using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

2.3. Neoadjuvant Therapy. Patients in the EBT group were treated with 4 consecutive daily fractions of 6.5 Gy targeted to the tumor and mesorectal lymph nodes without concurrent chemotherapy. Each fraction was delivered over approximately 15 minutes using a flexible silicone intracavitary applicator (OncoSmart, Nucletron, Veenendaal, The Netherlands) positioned in the rectum using fluoroscopic guidance and a microSelectron high-dose-rate iridium-192 remote afterloading system (Nucletron) as described by Vuong et al. [4]. Treatment planning was performed using the Oncentra brachytherapy planning system (Nucletron). Patients in the 3DRT and IMRT groups received 28 daily (Monday through Friday) fractions of 1.8 Gy over a period of 5 to 6 weeks (total dose of 50.4 Gy) with concurrent oral 5-FU.

2.4. Surgical Resection. At the initial assessment for all patients, surgery was preplanned according to the standard of care to take place from 6 to 8 weeks following completion

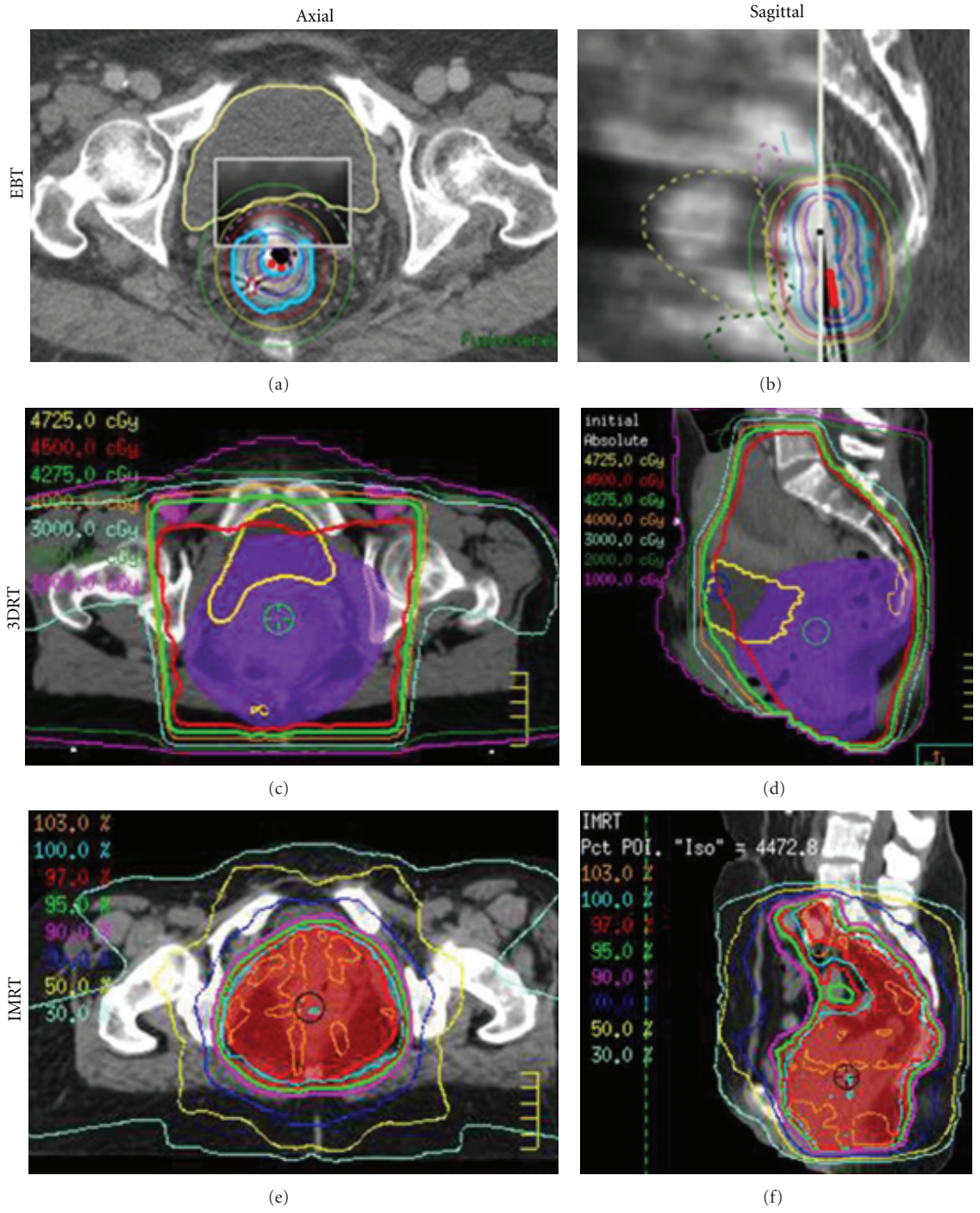

Figure 1: Representative slices from each of the three radiation plan types taken from a similar level in the pelvis. EBT can be seen to achieve a high dose to the tumor while exposing markedly less normal tissue volume to ionizing radiation as a result of rapid dose fall off from the point source. Top row: in axial (a) and sagittal (b), slices from an EBT plan, the 100% (light blue), 95% (red), 50% (yellow), and 30% (green) isodose lines are shown and the tumor perimeter is contoured (thick light blue line) as well as the bladder perimeter (thick yellow line in axial image, dotted yellow line in sagittal image). Middle row: in axial (c) and sagittal (d) slices from a 3DRT plan, the 100% (red), 95% (bright green), 89% (orange), 67% (gray), 44% (dark green), and 22% (fuchsia) isodose lines are shown, and the planning target volume receiving the full radiation dose around the tumor is indicated (purple shading) as well as the bladder perimeter (yellow). Bottom row: in axial (e) and sagittal (f) slices from an IMRT plan, the 100% (light blue), 97% (red), 95% (green), 90% (fuchsia), 70% (royal blue), 50% (yellow), and 30% (gray) isodose lines are shown, and the planning target volume receiving the full radiation dose around the tumor is indicated (red shading).

Table 1: Demographic and baseline disease characteristics for patients broken down by EBT, 3DRT, and IMRT groups with statistical comparison. EBT: endorectal brachytherapy; 3DRT: 3D conformal radiotherapy; IMRT: intensity-modulated radiotherapy; ECOG: eastern cooperative oncology group performance status; RT: radiotherapy; CEA: carcinoembryonic antigen.

Characteristic	EBT ($n = 7$)	3DRT ($n = 14$)	IMRT ($n = 11$)	P
Age (mean ± SD)	60.4 ± 17.4	58.2 ± 12.0	52.3 ± 7.6	0.32
Sex (female%)	100	29	64	0.007
Race (Caucasian%)	85.7	64.2	63.6	0.55
ECOG (mean ± SD)	0.21 ± 0.41	0.17 ± 0.39	0.20 ± 0.42	0.84
Pre-RT CEA (median (range) ng/mL)	4.5 (1.5–15.5)	7.4 (1.5–168.1)	3.7 (1.5–11.9)	0.35*
Pre-RT tumor volume (median (range) cm^3)	13.1 (0.9–26.4)	25.2 (6.3–119.0)	6.1 (1.9–76.6)	0.11*
Time between pre-RT MRI and RT start (mean ± SD days)	20 ± 11	22 ± 10	34 ± 31	0.30
Number. T3 (%)	5 (71)	12 (86)	8 (73)	0.66
Number T4 (%)	0 (0)	2 (14)	0 (0)	0.25
Number N0 (%)	4 (57)	4 (29)	3 (27)	0.36
Number N1 (%)	3 (43)	8 (57)	6 (55)	0.82
Number N2 (%)	0 (0)	2 (14)	0 (0)	0.25
Distance of tumor from anal verge (mean ± SD cm)	6.2 ± 1.9	8.4 ± 5.0	5.4 ± 2.5	0.80

* Medians and ranges are given to better represent the data, but statistical comparison was performed among means.

of neoadjuvant therapy. All patients were able to undergo surgical resection after neoadjuvant therapy consisting of total mesorectal excision (TME) accomplished as part of a lower anterior resection (LAR) or abdominoperineal resection (APR) procedure. When possible, LAR was performed in preference to APR so that the anal sphincter and normal evacuative function could be preserved.

2.5. Radiologic Assessment. MRI images of the pelvis, including high resolution T2 weighted images of the rectum, were acquired in 3 planes both prior to and following neoadjuvant therapy (see Tables 1 and 3 for specific timing of MRI imaging in relation to radiotherapy). Each study was evaluated by a blinded gastrointestinal radiologist. At each time point, the tumor was measured in 3 dimensions (maximum length and width on axial cross-section as well as maximum craniocaudal extent in the coronal or sagittal plane). These measurements were used to generate volume estimates for each tumor using the formula for volume of an ellipsoid ($V = \pi/6 \times A \times B \times C$, where A, B, and C are the maximum tumor diameters along the x-, y-, and z-axes). Changes in tumor volume after neoadjuvant therapy were calculated and tumor response rates were assessed using the sum of the maximum tumor diameters according to RECIST. Contrast enhanced T1 weighted MRI images obtained pre- and postneoadjuvant therapy were used to delineate and measure any abnormal mesorectal lymph nodes as well as any suspicious appearing lymph nodes in the inguinal or iliac chains measuring greater than 1 cm in diameter.

2.6. Pathologic Assessment. Pathologic tumor response was assessed by postoperative evaluation of TME specimens. After macroscopic examination of the surgical specimens, the entire tumor was submitted along with representative sections of the surgical margins, surrounding bowel, and dissected lymph nodes for formalin fixation. After fixation, the tissue was paraffin embedded and serially cut into 5-micrometer sections. Hematoxylin and eosin (H&E) stained sections were examined microscopically. Final pathologic stage, tumor size, nodal status, metastatic disease, and documentation of treatment effect were recorded. If present, lymphovascular invasion and positive surgical margins were also noted. Tumors considered to be completely responsive to preoperative therapy had no histologic evidence of residual carcinoma. Tumors with microscopic disease or large areas of residual carcinoma were considered partially responsive or nonresponsive to treatment, respectively. Slides from 5 randomly selected patients from each treatment group were rereviewed by a blinded pathologist to evaluate for any differences in radiation-induced treatment effects between the EBT, 3DRT, and IMRT groups.

2.7. Statistical Analysis. Statistical analyses were performed with IBM SPSS Statistics software, version 19 (International Business Machines Corporation, Armonk, NY). Patient characteristics consisting of continuous and dichotomous variables were summarized using descriptive statistics. Comparison of proportions between two or more groups was performed using the Pearson chi-squared test. Comparison of means between two groups (usually the EBT group versus the 3DRT and IMRT patients combined) was performed using the nonparametric Mann-Whitney U test. Comparison of means among three or more groups (usually EBT versus 3DRT versus IMRT) was performed using a one-way analysis of variance (ANOVA). An alpha level of less than or equal to 0.05 was considered significant in all cases.

3. Results

3.1. Patient Characteristics. All patient characteristics are summarized in Table 1. The EBT, 3DRT, and IMRT groups

Table 2: Clinical outcomes broken down by EBT, 3DRT, and IMRT groups with statistical comparison. EBT: endorectal brachytherapy; 3DRT: 3D conformal radiotherapy; IMRT: intensity-modulated radiotherapy; RT: radiotherapy; CEA: carcinoembryonic antigen.

Clinical outcome	EBT ($n = 7$)	3DRT ($n = 14$)	IMRT ($n = 14$)	P
Time to surgery from RT start (mean ± SD days)	53 ± 8	104 ± 21	119 ± 51	<0.001
Time to surgery from RT end (mean ± SD days)	50 ± 8	65 ± 20	79 ± 51	0.038
Post-RT CEA (median (range) ng/mL)	3.2 (1.1–18.3)	3.9 (1.4–67.8)	1.9 (0.5–12.3)	0.41*
Change in CEA pre-RT → post-RT (median (range) %)	−20 (−45 to +18)	−40 (−83 to +300)	−12 (−91 to +20)	0.36*
No. with grade 1 toxicity (%)	4 (57)	14 (100)	9 (82)	0.025
No. with grade 2 toxicity (%)	1 (14)	8 (57)	2 (18)	0.056
No. with grade 3 toxicity (%)	1 (14)	1 (7)	1 (9)	0.87
No. who underwent sphincter-preserving surgery (%)	6 (86)	13 (93)	10 (91)	0.87
No. with postoperative complications (%)	4 (29)	4 (36)	2/7 (29)	0.90
No. alive at 6 months post-RT/total (%)	7 (100)	14 (100)	11 (100)	1.0
No. with local recurrence at 6 months post-RT (%)	0 (0)	0 (0)	0 (0)	1.0
No. with distant metastasis at 6 months post-RT (%)	0 (0/7)	1 (7)	1 (9)	0.73

* Medians and ranges are given to better represent the data, but statistical comparison was performed among means.

Table 3: Radiologic outcomes broken down by EBT, 3DRT, and IMRT groups with statistical comparison. EBT: endorectal brachytherapy; 3DRT: 3D conformal radiotherapy; IMRT: intensity-modulated radiotherapy; RT: radiotherapy; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; LN: lymph nodes.

Radiologic outcome	EBT ($n = 7$)	3DRT ($n = 10$)	IMRT ($n = 7$)	P
Post-RT tumor volume (median (range) cm^3)	1.0 (0.0–3.6)	3.8 (0.7–26.3)	0.4 (0.0–5.5)	0.16*
Time between RT end and post-RT MRI (mean ± SD days)	35 ± 3	35 ± 7	36 ± 9	0.98
% decrease in tumor volume pre-RT → post-RT (median (range))	89 (38–100)	87 (16–96)	93 (66–100)	0.78
No. CR (%)	1 (14)	0 (0)	1 (14)	0.46
No. PR (%)	4 (57)	9 (90)	6 (86)	0.23
No. SD (%)	2 (29)	1 (10)	0 (0)	0.26
No. PD (%)	0 (0)	0 (0)	0 (0)	1.0
No. with clinically significant mesorectal LN before treatment (%) → no. after treatment (%)	1 (14) → 0 (0)	6 (43) → 3 (21)	1 (14) → 1 (14)	—
No. with clinically significant pelvic LN before treatment (%) → no. after treatment (%)	0 (0) → 0 (0)	4 (29) → 4 (29)	1 (14) → 0 (0)	—

* Medians and ranges are given to better represent the data, but statistical comparison was performed among means.

consisted of 7, 14, and 11 patients, respectively. Median lengths of followup were 7 months for EBT, 15 months for 3DRT, and 12 months for IMRT. Demographic and baseline disease characteristics, including age, race, ECOG performance status, pre-RT carcinoembryonic antigen (CEA) level, pre-RT tumor volume, T stage, N stage, and tumor distance from the anal verge, were similar among the 3 groups (all $P > 0.05$; Table 1). There was, however, a difference in gender distribution between the 3 groups, with 100% of EBT patients being female compared to only 29% and 64% of the 3DRT and IMRT groups, respectively ($P = 0.007$).

3.2. Clinical Outcomes. Clinical outcomes of interest included time to surgical resection, change in CEA level after neoadjuvant therapy, acute toxicity, sphincter preservation, and postoperative complications; these outcomes are summarized in Table 2. Time elapsed from the start of neoadjuvant therapy to surgical resection was reduced by nearly half in patients who underwent EBT as opposed to 3DRT or IMRT ($P < 0.001$). This reduction is not unexpected given the shorter time course of EBT (4 days) compared to 3DRT or IMRT (5-6 weeks). More interestingly, however, the time elapsed from conclusion of neoadjuvant therapy to surgical resection was also reduced for patients who underwent EBT ($P = 0.038$), despite the fact that all surgeries were similarly planned to take place 6–8 weeks following completion of neoadjuvant therapy. All 3 groups demonstrated similar median reductions in CEA levels after neoadjuvant therapy ($P = 0.36$). Fewer patients experienced grade 1 or 2 acute toxicity in the EBT group than in the external beam group ($P = 0.025$). Grade 3 toxicity was rare, occurring in one patient from each of the 3 groups with all 3 incidents taking the form of proctitis. No grade 4 toxicity was reported. Rates of sphincter preservation and postoperative complications were similar among the 3 groups. Given the natural history of rectal adenocarcinoma, length of followup was not sufficient to perform informative analyses of survival and disease progression; however, preliminary results are given here to allow

Table 4: Pathologic outcomes broken down by EBT, 3DRT, and IMRT groups with statistical comparison. EBT: endorectal brachytherapy; 3DRT: 3D conformal radiotherapy; IMRT: intensity-modulated radiotherapy; RT: radiotherapy; CR: complete response; LN: lymph nodes.

Pathologic outcome	ERBT ($n = 7$)	3DRT ($n = 14$)	IMRT ($n = 11$)	P
No. with pathologic CR of primary tumor at surgery (%)	3 (43)	1 (7)	2 (18)	0.06
No. with positive margins at surgery (%)	0 (0)	1 (7)	0 (0)	0.47
No. with LN involvement at surgery (%)	3 (43)	8 (57)	4 (36)	0.57
No. with lymphovascular invasion (%)	1 (14)	1 (7)	2 (18)	0.60

for comparison of EBT to conventional neoadjuvant therapy at the current length of followup. The rates of overall survival and local recurrence free survival at 6 months were 100% in all 3 groups. The rate of distant metastasis at 6 months was 0% for EBT, 7% for 3DRT, and 9% for IMRT. Thus, at a 6-month time point, EBT appears noninferior to conventional neoadjuvant chemoradiation using 3DRT or IMRT.

3.3. Radiologic Outcomes. Radiologic outcomes of interest included change in tumor volume, tumor response rates analyzed according to RECIST, and change in mesorectal and pelvic nodal disease status over the course of neoadjuvant therapy. These outcomes are summarized in Table 3 for all patients in each group who had pre- and posttreatment MRI studies available ($n = 7$ for EBT, $n = 10$ for 3DRT, $n = 7$ for IMRT). All 3 groups showed a striking response to neoadjuvant therapy, with similarly marked reductions in tumor volume. Thus, EBT achieved a comparable degree of reduction in tumor volume as measured on MRI after only 4 days of treatment without chemotherapy as 3DRT and IMRT achieved over 5 to 6 weeks with concurrent 5-FU. Tumor response rates according to RECIST were also similar to the 3 treatment techniques ($P > 0.05$ for rates of CR, PR, SD, and PD, as summarized in Table 3). Identification of clinically significant (≥ 1.0 cm in longest dimension) lymph nodes on pre- and posttreatment MRI showed that the proportion of patients with radiologic mesorectal nodal involvement decreased over the course of neoadjuvant therapy in the EBT and 3DRT groups, but remained stable in the IMRT group. Clinically significant pelvic lymph nodes were identified on pretreatment MRI in 4 patients in the 3DRT group; in all 4 patients, these nodes remained clinically significant following treatment. One patient in the IMRT group was observed to have a pelvic lymph node prior to treatment, which subsequently resolved after chemoradiation. No patient in any group developed new pelvic nodal involvement over the course of neoadjuvant therapy. The degree of radiologic tumor response, however, did not appear to correlate with pathologic complete response (pCR), with more patients manifesting a pCR at surgery than were observed to have a complete radiologic response on post-EBT MRI (Figure 2).

3.4. Pathologic Outcomes. Pathologic outcomes of interest included tumor complete response rate, surgical margin status, lymph node involvement, and lymphovascular invasion; these outcomes are summarized in Table 4. There was a trend towards higher rate of complete pathologic response in patients who underwent EBT (43%) compared to the external beam group consisting of 3DRT and IMRT patients combined (12%) ($P = 0.06$). Rates of margin positivity, lymph node involvement, and lymphovascular invasion were similar among the three treatment groups.

Surgical pathology slides from 5 cases in each of the 3 treatment groups (15 cases total) were randomly selected for rereview by a blinded pathologist to assess for qualitative differences in microscopic treatment effects. The surgical resection specimens showed disruption of tumor architecture (regions of necrosis and the presence of mucinous pools with sparse floating tumor cells) and radiation treatment effects for all 3 radiotherapy techniques. However, the distribution and degree of radiation-induced changes throughout the layers of the rectal wall were different for EBT versus conventional 3DRT/IMRT (since radiation treatment effects were found to be virtually identical between specimens from the 3DRT and IMRT groups, these groups will be collectively referred to as the conventional external beam group from this point forward). Compared to the conventional external beam group, specimens from EBT patients demonstrated more pronounced radiation-induced changes to the superficial layers of the rectal wall (mucosa, lamina propria, submucosa, and muscularis interna) in the region where the tumor was located (Figure 3). The mucosa overlying the tumor was observed to be ulcerated and the underlying lamina propria manifested extensive fibrosis and hyalinization (Figure 3(a)). The vessels in the submucosa were seen to have a thickened and sclerosed vascular smooth muscle layer (Figure 3(b)), but deeper vessels located in the subserosa were largely spared (Figure 3(d)). Atrophy, disorganization, and degeneration were evident in the muscularis propria interna, but to a lesser degree in the deeper muscularis propria externa (Figure 3(c)). Few serosal adhesions were observed.

In specimens from patients treated with conventional external beam radiation, pathologic findings were similar in nature, but opposite in distribution with deeper layers of the rectal wall being more prominently affected than more superficial layers (Figure 3). Ulceration of the mucosal surface overlying the tumor was milder (Figure 3(f)); the muscularis propria externa rather than interna exhibited more extensive degeneration (Figure 3(h)); deeper vessels near the serosa (Figure 3(d)) were more affected than submucosal vessels (Figure 3(g)); more numerous serosal adhesions were present (Figure 3(j)). These contrasting distributions of treatment effect suggest that EBT imparts a more intense ablative effect to the tumor and rectal tissue immediately surrounding it, while conventional external beam treatment generates more diffuse ablative effects throughout all layers

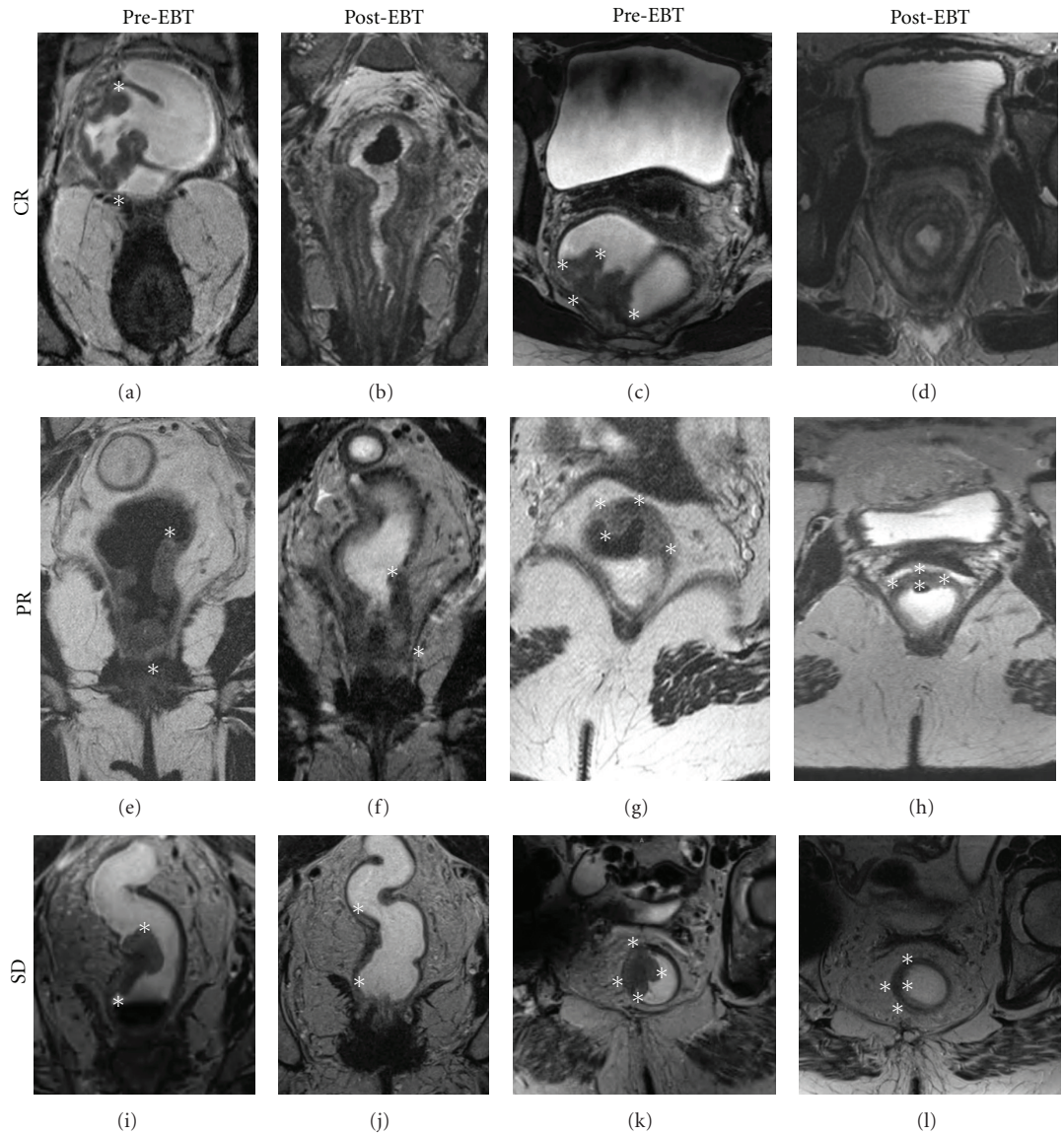

Figure 2: Representative pre- and posttreatment MRI slices from patients who underwent EBT and were found to have a complete pathologic response (pCR: defined as no residual tumor on histopathologic examination) at surgery. Although all 3 patients achieved a complete pathologic response, they demonstrated differing degrees of radiologic response on MRI according to RECIST, suggesting that degree of radiologic response does not necessarily predict for degree of pathologic tumor response. The longest tumor dimensions in 3 planes used for RECIST assessment are indicated by white asterisks. Scans represented in the top, middle, and bottom rows were obtained 39, 34, and 32 days following the completion of radiotherapy, respectively. Top row: coronal (a), (b) and axial (c), (d) MRI slices from a patient with a pCR who also demonstrated a radiologic complete response (CR); no residual tumor is visualized on post-EBT MRI (b), (d). Middle row: coronal (e), (f) and axial (g), (h) MRI slices from a patient with a pCR who demonstrated a radiologic partial response (PR) on post-EBT MRI (f), (h). Bottom row: coronal (i), (j) and axial (k), (l) MRI slices from a patient with pCR who demonstrated stable disease (SD) on post-EBT MRI (j), (l).

of the rectal wall. These patterns are consistent with the different modes of radiation delivery represented by EBT and conventional external beam radiotherapy.

4. Discussion

The current standard of care for locally advanced resectable adenocarcinoma of the rectum (AJCC stage II-III) is neo-adjuvant chemoradiation with a 5-FU-based regimen, followed by total mesorectal excision and adjuvant FOLFOX chemotherapy [9]. Conventional neoadjuvant chemoradiation has shown improved local control but not survival compared to surgery alone [3]. Neoadjuvant chemoradiation results in downstaging of tumors with 8–16% of patients achieving a pathologic complete response (pCR) [9, 10, 14–16]. Patients that achieve pCR due to neoadjuvant chemoradiation have improved disease-free and overall survival [10, 17–22]. However, acute grade 3 and 4 toxicities associated

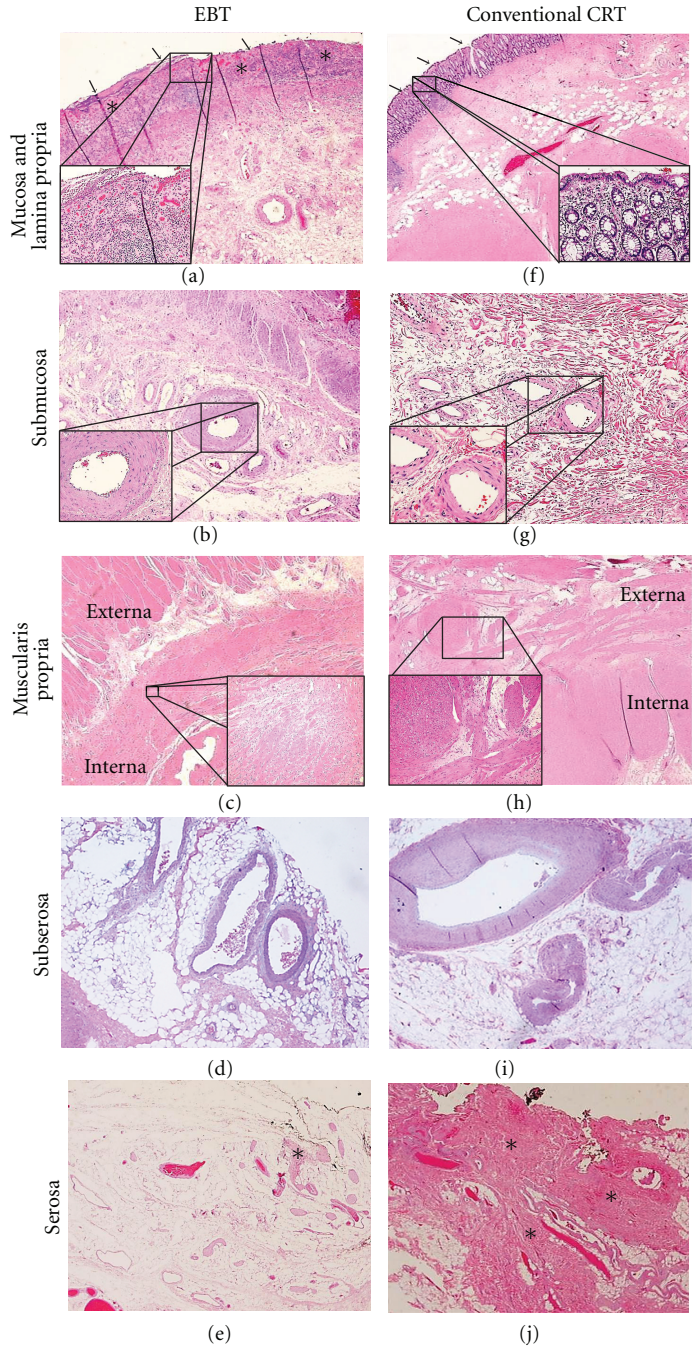

Figure 3: Representative H&E stained histopathologic sections at 4x magnification from patients who exhibited a complete pathologic response to EBT (a)–(e) and conventional external beam radiation (f)–(j). All images are taken from the region of the rectal wall where the tumor was located prior to neoadjuvant therapy. All insets are shown at 20x magnification. First row: at the mucosa, extensive ulceration (solid arrows) is apparent after EBT (a), while the mucosa remains intact (solid arrows) after conventional CRT (f). Hyalinization of the lamina propria (asterisks) is also evident after EBT (a). Second row: in the submucosa, marked hypertrophy and sclerosis of vessel walls can be seen following EBT (b), while only slight hypertrophy of vessel walls is seen after conventional CRT (g). Third row: within the muscularis propria, the more superficial interna layer can be seen to exhibit degeneration and atrophy after EBT while the externa layer remains largely intact (c); in a contrary fashion, following conventional CRT, it is the externa layer that exhibits more prominent degeneration compared to the interna (h). fourth row: at the level of the subserosa, vessel walls appear normal in patients treated with EBT (d), but distinctly hypertrophied in patients treated with conventional CRT (i). Fifth row: the serosa demonstrates few adhesions (asterisk) after treatment with EBT (e), in contrast to the extensive adhesions (asterisks) present after treatment with conventional CRT (j).

with this treatment are seen in up to 30% of patients [9, 10, 15, 16]. To further improve pathological response rates and systemic disease control, additional chemotherapy agents, including oxaliplatin or irinotecan, were given with 5-FU based chemotherapy and concurrent radiation. This resulted in minimal improvement in pCR (15–20%) and often increased grade 3 and 4 acute toxicity [9, 10, 15, 16]. With the advent of total mesorectal excision (TME), local recurrence rates have decreased from 25–30% to 6–12% [23, 24]. As a result, some have questioned whether it is still necessary to treat all locally advanced rectal cancer patients with pelvic radiation.

One of the main goals of rectal cancer treatment is sphincter preservation to maintain normal bowel function. Sauer et al. found that neoadjuvant conformal chemoradiation results in increased rates of sphincter preservation; however, long-term studies have demonstrated an overall decline in anorectal function [9]. For this reason, efforts have been made to limit the radiation dose to normal rectum and surrounding organs at risk (OARs) including the bladder and reproductive organs. Three-dimensional conformal radiation therapy (3DRT) seeks to accomplish this through the use of multileaf collimators and 3 to 5 beams in order to shape the radiation delivered to fit the profile of the target tumor. Intensity modulated radiation therapy (IMRT) utilizes a greater number of radiation beams (typically 5 to 9) to spare organs through a wider distribution of dose and more precise targeting of the rectal tumor plus a margin. While both 3DRT and IMRT attempt to decrease radiation dose to normal structures, they require an additional 2-3 cm margin in order to cover microscopic extension (clinical target volume; CTV) and account for set up error as well as rectal motion (planning target volume; PTV) [4, 6, 8]. Similar to 3DRT, IMRT requires 5-6 weeks of radiation with concurrent chemotherapy and is substantially more expensive than conformal radiation. It still remains to be determined whether IMRT confers a significant improvement in toxicity rates and quality of life relative to 3DRT.

High-dose-rate (HDR) endorectal brachytherapy (EBT) is a possible alternative to conventional external beam radiation. It has been used in various malignancies (prostate, head and neck, uterine, cervical, vaginal) to deliver high doses of radiation to the tumor over a short period of time. HDR EBT delivers endoluminal radiation to the mucosal surface overlying the rectal tumor in four fractions of 6.5 Gy (26 Gy total) over one week. Its rapid dose fall off limits the exposure of the normal surrounding tissues to radiation (Figure 1), thereby reducing treatment-related toxicities [4, 6, 8]. The advantages of HDR brachytherapy relative to low-dose-rate permanent implants include decreased geometric uncertainties arising from edema resolution and seed migration as well as the ability to tailor dose delivery by use of specific dwell times [4, 6, 8]. Compared to 3DRT and IMRT, HDR brachytherapy requires smaller margins (CTV/PTV expansion = approximately 1 cm for EBT) around the tumor, which allows greater sparing of organs at risk [8, 25]. The benefits of EBT include high tumor response rates and reduced cost relative to 3DRT and IMRT without the need for concurrent systemic chemotherapy and its associated toxicities [4, 6, 8, 25]. Other benefits of EBT are the short duration of treatment and decreased time to surgery. EBT planning takes less than a day while 3DRT and IMRT typically require 1-2 weeks for treatment planning. On average, patients receiving EBT will undergo surgical resection and receive adjuvant chemotherapy 5 weeks earlier than with conventional treatment [4]. Our study showed an even greater decrease in time to surgery, with patients who underwent EBT undergoing surgery approximately 7 weeks sooner than their 3DRT and IMRT counterparts.

There is limited data on the clinical outcomes and therapeutic benefits of EBT. Data on high-dose-rate brachytherapy for rectal cancer has only been published from one institution (McGill University in Montreal) by Vuong et al., who has treated over 300 patients with 29% achieving a pCR and 37% with only microscopic disease at the time of resection, while less than 1% experience acute grade 3 to 4 toxicities [4]. Estimated local recurrence rate is 5%, which is comparable to the standard of care [9]. Importantly, nodal recurrence was observed to be low with EBT and disease-free survival and overall survival were similar to historical controls. While encouraging, these results have not been externally validated. Preliminary results of the first 7 patients enrolled on a prospective EBT pilot study at Johns Hopkins Hospital documented here show similar results to the Montreal study. All patients had tumors less than 12 cm from the anal verge, no clinical/radiographic suspicious lymphadenopathy outside the mesorectum, and T2-T3/N0-N1 stage tumors. There was a trend towards a higher pCR rate in EBT patients with 43% found to have no residual tumor at time of surgery, compared to 14% of patients treated with IMRT and 7% of patients treated with 3DRT. The pCR rate for EBT observed in our study (43%) was similar to the 29% observed by Vuong et al. [4]. All patients treated with EBT in our study had negative margins at resection, and 86% were able to undergo a sphincter preserving surgery (lower anterior resection). Toxicity was less for EBT compared to conventional methods and was rare at a grade 3 or 4 level, as seen in the McGill data. Overall survival and progression-free survival for EBT were noninferior to conventional chemoradiation; however, with the small sample size and short median followup, definitive conclusions regarding survival outcomes cannot be drawn.

Radiologic analysis according to RECIST showed similar tumor response rates in EBT, 3DRT, and IMRT patients. Radiologic complete response (rCR) was observed in 1 patient in the EBT and IMRT groups, while no patient in the 3DRT group had an rCR. Interestingly, pathologic complete responses (pCR), defined as absence of any residual tumor cells, occurred at higher frequency than rCR in all 3 groups, with 3 EBT patients, 2 IMRT, and 1 3DRT patient manifesting pCR at surgery. Of the 3 patients who demonstrated pCR in the EBT group, 1 had an rCR, 1 a radiologic partial response (rPR), and 1 had radiologically stable disease (rSD) (Figure 2). This suggests that lack of rCR following neoadjuvant EBT does not rule out pCR. These findings agree with a study performed by Branagan et al., which found that preoperative radiologic rectal tumor staging using MRI showed a poor correlation (Kappa statistic = 0.18) with

pathologic tumor stage of the resected specimen [26]. As microscopic pathologic examination of the TME specimen is the gold standard for assessment of tumor response, our data indicate that the radiologic response on preoperative MRI cannot be reliably used to predict degree of tumor response to EBT because even rSD can correlate with a pCR at resection. Positron emission tomography (PET) imaging may represent a more effective way to radiologically evaluate tumor response prior to surgery. Although a study performed at Stanford University showed that changes seen on PET have limited value in predicting for pathologic response of rectal cancer after conventional neoadjuvant chemoradiation, the utility of PET has not yet been examined in assessing tumor response to EBT [27].

One concern in treating rectal tumors with EBT instead of conventional external beam radiation is lack of sterilization of pelvic lymph nodes as a result of the rapid dose falloff associated with EBT, which covers only the mesorectal lymph nodes with little to no coverage of pelvic nodes. Thus, it is conceivable that EBT may lead to higher lymph node metastasis rates and local recurrence. For that reason, patients are selected for EBT based on pathologic lymph node status by imaging. Patients are excluded if positive lymph nodes are identified in the pelvis outside the mesorectum prior to treatment. It is encouraging that in our study preoperative MRI showed no development of pelvic node involvement for any of the 7 patients who received EBT. Furthermore, the one patient in the EBT group with radiologic involvement of mesorectal lymph nodes on pretreatment MRI exhibited complete resolution of nodal involvement on post-EBT imaging. Although limited in their generalizability by the small sample size, these findings suggest that when patients are carefully selected for neoadjuvant EBT (i.e., N0-N1 patients only), there is a low likelihood that they will develop radiologic evidence of N2 disease prior to surgery. This evidence confirms data presented by Vuong et al. documenting a 5-year local recurrence rate of 5% in N0-N1 patients treated with EBT, which likely indicates a 5% or lower rate of spread to pelvic lymph nodes prior to surgery [4]. However, longer followup and a greater number of patients are needed in our study before radiologic results regarding development of N2 disease prior to surgery can be correlated with local recurrence rates.

Radiation-induced injury to the rectum is well documented and characteristic histologic changes include architectural disruption and atrophy, goblet cell loss, shortened crypts, a thickened and distorted muscularis, intestinal wall fibrosis, serosal thickening, and vascular sclerosis [28, 29]. A study in mice that documented the histopathologic characteristics of radiation injury to intestinal tissue observed similar findings as those listed above [30]. Mice that received external beam radiotherapy showed mucosal ulcerations, fibrotic changes, serosal thickening, and marked vascular sclerosis. Effects on rectal tissue due to high-dose-rate (HDR) brachytherapy have not yet been published. However, an autopsy study evaluating the histological findings in prostate tissue treated with low-dose-rate brachytherapy showed similar results to our study [31]. The prostate specimens showed distorted glandular architecture, extensive fibrosis, and hyalinization of the blood vessels.

Our study is the first to describe the histologic differences in treatment effect of EBT compared to conventional external beam radiation seen on pathologic examination of rectal adenocarcinoma resection specimens. In general, the types of histologic changes induced by EBT and conventional external beam radiation were similar, consisting of mucosal ulceration, fibrosis and hyalinization of the lamina propria, degeneration of the muscularis propria, and vessel wall hypertrophy and sclerosis as well as formation of serosal adhesions. Notably, however, the distribution and degree of these changes throughout the layers of the rectal wall were distinct for EBT. TME specimens from patients who received conventional external beam radiation demonstrated moderate radiation-induced changes diffusely throughout the rectal wall. Specimens from patients treated with EBT, on the other hand, displayed these changes along a gradient, with intense treatment effect apparent in the superficial layers of the rectal wall (mucosa, lamina propria, submucosa, and muscularis propria interna), but progressively reduced treatment effect in each of the deeper layers (muscularis propria externa, subserosa, and serosa). These contrasting distributions of treatment effect suggest that EBT may achieve a more potent localized ablative effect on the tumor and immediately surrounding rectal tissue than does conventional external beam radiation, but may not be as effective in sterilizing the serosa.

It follows that careful patient selection is critical for successful implementation of EBT. Patients with T1–T3 lesions may derive considerable benefit from the high ablative potential of EBT and would be considered viable candidates because their tumors can be adequately covered with EBT without extreme doses to the rectal wall. If tumors are more than 3-4 cm from the rectal wall, EBT may cause increased proctitis. Our results, as well as the data reported by Vuong et al. [4], indicate that EBT likely achieves higher pCR rates than conventional external beam radiation. A growing body of evidence supports the notion that patients with pCR after neoadjuvant therapy have more favorable long-term outcomes compared to patients with lesser or no pathologic response [10, 17–22]. Thus, it may be possible to improve outcomes in patients with T1–T3 rectal tumors by treatment with EBT rather than conventional external beam radiation. Patients with T4 lesions, however, may have portions of tumor that extend beyond the effective range of the radioisotope used in EBT and are likely better suited to conventional external beam radiation, which we have observed in this study to affect all layers of the rectal wall, including the outermost serosa.

Modern staging performed with endorectal ultrasound (EUS) and pelvic MRI has been shown to attain a high degree of accuracy in determining the T stage of rectal tumors. EUS has demonstrated a sensitivity of 90% and specificity of 75% for identifying T3 tumors, while MRI has a sensitivity of 80–86% and specificity of 71–76% [32–35]. In predicting adjacent organ invasion (T4 tumor stage), EUS and MRI have demonstrated sensitivities of 70% and 74%, respectively, and high specificity at 97% and 96% [33]. The use of these staging modalities has become routine in recent years

as part of the workup for rectal cancer and can be utilized to discern patients well suited to EBT versus conventional external beam radiation in the clinical setting.

Finally, the limited range at which radiation treatment effects were observed for EBT on histopathologic examination in our study provides a rationale for the lesser degree of toxicity experienced by patients in the EBT group. Sauer et al. reported a 27% incidence of grade 3 to 4 acute toxicity as a result of neoadjuvant chemoradiation for rectal cancer [9]. More recent studies involving the addition of agents such as oxaliplatin to neoadjuvant chemoradiation regimens have been associated with rates of grade 3 to 4 acute toxicity as high as 36% [10–13]. The rate of acute toxicity in our study was well below this, with only one patient in the EBT group (14%) experiencing grade 3 proctitis. Thus, in addition to increasing the likelihood of achieving a pathologic complete response, EBT may also provide a less toxic mode of neoadjuvant therapy that appears at least as effective as long-course conventional chemoradiation as measured by short-term outcomes.

Study Limitations. Our study was primarily limited by a small number of patients and a short period of followup. These limitations precluded definitive survival analysis, but did not hinder evaluation of several clinical, radiologic, and pathologic outcomes of interest. The fact that only data on EBT patients was collected prospectively, while data on 3DRT and IMRT patients was collected retrospectively, introduces the biases inherent in retrospective studies to our analysis. It is also possible, though unlikely, that the difference in gender distribution between the EBT, 3DRT, and IMRT groups could confound our analyses, especially in regard to toxicity considering the different organs at risk in the pelvic region between males and females. Further followup of the EBT patients included in this study, as well as future EBT patients (trial enrollment goal is 30 patients), will be needed to determine median overall survival and thus estimate the impact of EBT on this primary oncologic outcome.

5. Conclusions

Comparison of preliminary EBT trial data to historical controls treated with conventional external beam radiation reveals that patients treated with EBT experience less toxicity and shorter time to surgery without compromising margin or lymph node status at resection. Followup was not sufficient for survival analysis, but EBT appears noninferior to 3DRT and IMRT at 6 months. EBT alone administered over 4 days achieves similar radiologic and favorable pathologic tumor response rates when compared to 5-6 weeks of conventional chemoradiation. EBT showed a more intense local ablative effect on histopathologic examination, suggesting a greater likelihood of achieving pathologic complete response and, consequently, improved long-term outcomes. Furthermore, radiation-induced changes due to EBT were tightly localized to the area of the tumor with greater sparing of normal tissues including small bowel, likely explaining the lower rate of toxicity observed in comparison to 3DRT and IMRT. Careful patient selection using EUS and MRI is necessary to ensure that patients with T4 tumors that extend beyond the range of the radioisotope used for EBT are not offered this therapy. In summary, EBT appears to be a promising mode of neoadjuvant treatment for low lying rectal adenocarcinoma. Longer followup and a larger multicenter study are needed to conclusively evaluate the potential of EBT to produce a survival benefit in this patient population.

Authors' Contribution

The authors contributed equally to this work.

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Review Article

Approach to Rectal Cancer Surgery

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Rectal cancer is a distinct subset of colorectal cancer where specialized disease-specific management of the primary tumor is required. There have been significant developments in rectal cancer surgery at all stages of disease in particular the introduction of local excision strategies for preinvasive and early cancers, standardized total mesorectal excision for resectable cancers incorporating preoperative short- or long-course chemoradiation to the multimodality sequencing of treatment. Laparoscopic surgery is also increasingly being adopted as the standard rectal cancer surgery approach following expertise of colorectal surgeons in minimally invasive surgery gained from laparoscopic colon resections. In locally advanced and metastatic disease, combining chemoradiation with radical surgery may achieve total eradication of disease and disease control in the pelvis. Evidence for resection of metastases to the liver and lung have been extensively reported in the literature. The role of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal metastases is showing promise in achieving locoregional control of peritoneal dissemination. This paper summarizes the recent developments in approaches to rectal cancer surgery at all these time points of the disease natural history.

1. Introduction

Rectal cancer is often camouflaged to be part of colorectal cancer with Australian statistics approximating 14 225 cases of bowel cancer in 2008 with a higher predominance among men and those above 50 years of age [1]. Meanwhile, the American counterpart recorded rectal and colon cancer to be the third leading malignancy plaguing both sexes in 2012 whereby 9% of deaths in each gender group was attributed to the disease [2]. The risk of death before age 75 has declined over the years from a high of 1 in 50 in 1987 to 1 in 91 in 2007 and this is attributed to better early detection of precancerous lesions and management of the disease [1, 2].

Treatment of rectal cancer is primarily surgical and is highly dependent on the preoperative staging [3]. Early cancers, especially T1 tumors, have been controversially proposed for local excision either via transanal excision or transanal endoscopic microsurgery (TEMS) [4–6]. While some report good outcomes measurable to radical surgery, others beg to differ prompting the need for salvage therapy [4–7]. Later stages of cancer usually follow the traditional approach of abdominoperineal resection (APR) or anterior resection and its success at reducing local recurrence is improved by total mesorectal excision (TME) [8, 9]. However, these procedures are associated with their own set of morbidity and mortality [10, 11]. Other therapeutic modalities such as chemotherapy and radiotherapy have been included in conjunction with surgery particularly in advanced cancers. They can be used preoperatively or postoperatively either to increase the chances of a sphincter-preserving procedure to allow better quality of life or with a curative intent [12–14]. An overall cancer-specific 5-year survival of 77% has been reported [15].

In this paper, we seek to discuss the modern approach to rectal cancer surgery at all disease time points from preinvasive and early rectal cancer, resectable rectal cancer, and locally advanced and metastatic rectal cancer with an emphasis on presenting some of the controversies and the accepted standards of treatment.

1.1. Local Excision of Preinvasive and Early Rectal Cancer. The advent of endoscopic mucosal resection (EMR) for rectal tumours could not have been timelier as the race to provide a treatment that is highly efficacious and of low morbidity continues. EMR has been in practice for a few decades now and is commonly used to address gastrointestinal pathologies such as a Barrett's oesophagus, and early gastric cancers (EGC) with a reported local recurrence rate of 2% in EGC [16–18]. The procedure focuses on removal of diseased mucosal tissue or at most, the superficial submucosa instead of a full-thickness excision [16, 19]. It can be done by means of a strip biopsy, local injection of hypertonic saline-epinephrine in the "inject, lift and cut" technique, "cup and suction" otherwise known as the EMR-cap technique or EMR with band ligation. If necessary, more than one of the aforementioned methods can be applied [16, 20, 21].

EMR is an alternative to the locally-approached transanal excision (TAE) and transanal endoscopic microsurgery (TEMS). Generally, local excision of rectal cancer is indicated for early disease that encompasses its precursor (dysplasia or adenoma), T1 tumours that display moderate-to-well differentiation and no lymphatic or vascular invasion [6, 16, 17, 22]. At present, it is known that EMR can be performed on flat, sessile, or lateral spreading rectal tumours [22–24]. The success of EMR is reflected through its high overall cure rate with some reporting 91% for treatment-naïve patients and others at 96% [23, 25].

One of the common consequences of EMR is bleeding which occurs from 1%–45% of cases [26]. The bleed can be minor and is easily manageable with haemostatic clips or severe requiring blood transfusions or even surgery [19, 24, 26]. 0.7% to 4% of cases are complicated with perforation which can appear later as abdominal distension and pain necessitating further operation [25, 26]. Other adverse events also include postprocedural abdominal pain and serositis [25].

While EMR is an excellent therapeutic option for rectal tumours, it is operator dependent. Identifying the lesion especially if it is a lateral spreading tumour can be challenging to the untrained eye as it displays subtle changes but this is improved by a dye-staining technique [22]. A meta-analysis showed that the chances of a complete en bloc resection is directly proportional to experiences if the operator [27]. Removal of diseased-tissue greater than 2 cm requires a piecemeal resection. The concern is that complete resection and a proper histological evaluation is rendered difficult with larger lesions, thus running a risk of local recurrence [23, 25, 28]. In spite of this, some studies showed that the success of the resection is not statistically different between the two techniques [26, 29].

Complicating the procedure further is the second attempt of EMR for recurrent lesions. Failure of the mucosa to lift during the "inject, lift and cut" technique may occur secondary to submucosal fibrosis. The success rate of a repeated resection is reduced from 91.0% in a treatment-naïve patient to 74.5% in a previously attempted lesion [25]. It is reported that the time for conversion of a precursor lesion to cancer is variable, with dwelling times in the adenoma state ranging from 4 years to as long as 48 years [30]. In fact, flat adenomas need not necessarily be treated as it is almost always noninvasive [22]. This questions the need for EMR in such lesions and more so, the implication on the patient who is no doubt heading for months of unwarranted anxiety.

Nevertheless, EMR is a safe and effective treatment modality that is minimally invasive and only requires conscious sedation [25, 26, 28]. It is also efficient with Moss et al. reporting a mean procedural duration of 25 minutes while another study accounted a range of 25–137 minutes [25, 29]. When possible, patients can be treated as an outpatient with discharges within the same day [31, 32]. A comparison between TAE and endoscopic resection showed that the latter was associated with a significantly shorter hospital stay of 2.7 ± 1.1 days with a mean difference of 6.2 days [19]. Similarly, TEMS recorded a range of 0–44 days of hospitalization while EMR had a range of 0–27 days [31]. EMR per se is not as costly as the other procedures available, thus allowing a cheaper and less invasive option for the patient. This translates into reduced expenditure for the spender [20, 29, 33].

On the other hand, TEMS and TAE are not as inferior as one might think. Lesions larger than 8 cm in diameter can be removed with good effect via TEMS [34, 35]. Where EMR may fail to completely remove the tumour, both TEMS and TAE can compensate for it [31, 36]. First attempt of TEMS for large rectal adenoma is reported to have a lower early local recurrence rate at 10.2% compared to EMR at 31.0% ($P < 0.001$) [31]. Meanwhile, low risk-T1 tumour recurrence rate following TEMS is 0–10% while Santos et al. reported a 12% recurrence rate following EMR [28, 37]. TAE is estimated to have a 15% local recurrence rate of the malignancy at five years [38]. It would seem that the recurrence rate following TAE is high compared to EMR but contradicting this is a 32-patient study by Lee et al. which showed no recurrences of cancer following either endoscopic resection or TAE at a median followup of 15 months (range 6–99) [19]. Studies evaluating the disease-specific and overall survival rates (TEMS versus radical surgery and TAE versus radical surgery) showed that the values were not statistically significant to one another indicating the efficacy of these procedures [5, 38].

EMR appears to be favourable as TEMS and TAE have the added adverse effects including wound breakdown, incontinence, urgency, strictures, neuralgia, and anovaginal fistula [34, 35, 37, 39]. Barendse et al. studied both EMR and TEMS and discovered that the former was associated with half the percentage (12%) of postoperative complications compared to the latter (24%) [31]. However, given the variable recurrence rates, there is some apprehension towards EMR. In view of this, no accurate decision can really be made. Instead, it is a judgment call by the surgeon and more importantly the patient himself based on the local expertise and the pros and cons of each option available. As we push the fort of combination treatment, it is likely that in the future, local excisional strategies will become a more commonly adopted strategy in complete or subcomplete responding tumors after chemoradiotherapy. However, the limitation of mesorectal sampling may mean that more

intensive followup is required to detect recurrence at the local excisional site and/or mesorectal lymph nodes.

1.2. Standardized Surgery in the Era of a Multimodality Approach for Resectable Rectal Cancer. Rectal cancer differs from colon cancer whose risk of local recurrence is low. Its proximity to the anal sphincter also makes this a major consideration into the surgical approach towards resection. In the localized setting, a multimodality approach has in recent years been developed and investigated in trials to improve local recurrence, disease-free and overall survival using a variety of sequences of chemotherapy and radiotherapy. Prior to surgery, adequate local staging is paramount in the surgical planning and accurate prediction of the extent of bowel wall involvement may be obtained through endorectal ultrasonography and magnetic resonance imaging may serve the similar purpose but also identify the involvement of lymph node metastases [40]. The aims of rectal cancer surgery are to remove the tumor with an adequate distal margin of a minimum of 2 cm in the case of a low rectal tumor with sphincter preservation or 5 cm in the case of a rectosigmoid/upper rectal tumor with restoration of intestinal continuity through an anastomosis. This operation is known as anterior resection. If a 2 cm distal margin cannot be secured, an abdominoperineal excision with enbloc resection of the entire anorectum and an end colostomy is required. Surgery should be performed using a "no-touch" technique with high ligation of the inferior mesenteric artery to achieve adequate lymphatic sampling through harvesting of the sigmoid mesentery and mesorectum. Tumors of the middle and lower rectum require a total mesorectal excision (TME) [41]. TME reduces the risk of local recurrence and although a prospective randomized trial has not been conducted to verify its efficacy, longitudinal data derived from The Netherlands where a TME trial was conducted following rigorous training of colorectal surgeons demonstrated that there was an observed reduction in rate of local recurrence from 16% to 9% with TME surgery being an independent predictor of overall survival [42]. Further, data from the MRC CR07 and NCIC-CTG CO16 randomized trials demonstrated that the plane of surgery achieved in patients undergoing rectal cancer surgery impacted on local recurrences with a 3-year local recurrence rate of 4% for patients whose surgery was completed with achievement of the mesorectal plane, 7% for intramesorectal plane and 13% for muscularis propria plane [43]. Pertinent also in low rectal cancers requiring abdominoperineal excision, to avoid a "coning effect" in the deep pelvis as the tumor is approached from both the abdomen and perineum, extended abdominoperineal excision incorporating resection of the levator muscles to reduce inadvertent bowel perforation and breaching of the circumferential resection margin [44].

1.2.1. Laparoscopic or Open Surgery. Today, in the current era of laparoscopic surgery where shorter postoperative hospital stays, reduction in pain scores, shorter time of return of bowel function, lower treatment cost, and improved cosmesis may be achieved, these standardized surgical resections have been demonstrated to be feasible in the laparoscopic approach [45]. Initially, the laparoscopic approach was first examined in colon cancer with at least 4 large randomized trials; COST Study Group trial from the USA, COLOR trial from Europe, MRC CLASICC trial from the UK, and a trial in rectosigmoid cancers from the Prince of Wales Hospital in Hong Kong demonstrating equivalent oncologic efficacy with similar overall survival, disease-free survival and local and distant recurrences [46–49]. These studies although predominantly examined in the setting of colon cancer were quick to translate into standard practice for rectal cancer despite limited large scale prospective randomized trials. However, there remain concerns over the ability to achieve adequate mesorectal excision and clear surgical margins in laparoscopic rectal cancer surgery. In the UK MRC CLASICC trial, there was a 34% conversion rate from laparoscopic to open surgery in the rectal cohort, increase performance of TME surgery to ensure adequacy of the distal resection margin in the laparoscopic group because of the inability to palpate the tumor for localization. Nonetheless, there was no difference in positive circumferential resection margin, local recurrence, disease-free, and overall survival in both the laparoscopic versus open anterior resection and abdominoperineal resection groups [48].

The Prince of Wales Hospital group from Hong Kong reported a small prospective randomized trial of laparoscopic assisted versus open abdominoperineal resection for low rectal cancer randomizing 99 patients (51 lap-assisted and 48 open) demonstrating earlier return of bowel function, decrease time to mobilization, lesser analgesia requirement, longer operative time, and higher direct cost in the lap-assisted group without difference in morbidity and mortality [50]. In an update of this trial, after 10 years of followup, the authors reported higher rates of bowel obstruction requiring hospitalization and intervention in the open group but similar oncologic outcomes were shown with 10-year survival of 83.5% and 78% ($P = 0.595$) and 10-year disease-free survival 82.9% and 80.4% ($P = 0.698$) in the lap-assisted and open group, respectively [51]. In the COREAN trial that randomized 170 patients in each arm to laparoscopic and open surgery for mid or low rectal cancer after preoperative chemoradiotherapy, the laparoscopic group had lower amount of blood loss, longer operative time, quicker recovery of bowel function, and a lesser amount of analgesic requirement. Surgical quality indicators including the circumferential resection margin, macroscopic quality of the TME specimen, number of harvested lymph nodes, and perioperative morbidity were similar between groups [52]. In a Spanish randomized trial of 204 patients of whom 78.6% in the open group and 76.2% in the laparoscopic group underwent sphincter-preserving surgery; blood loss was greater in the open surgery group, operative time was longer in the laparoscopic group, and return to diet and hospital stay was longer in the open surgery group. Complication rates were similar between groups but a larger number of lymph nodes were isolated in the laparoscopic group [53]. Together, these three small randomized trials suggest that the laparoscopic approach achieves improved short-term outcomes without compromising the surgical

quality of rectal cancer operations in skilled hands but a longer operative time is required. Longer followup of these trials and results of ongoing larger trials will confirm the long-term oncologic outcomes of laparoscopic rectal cancer surgery.

1.2.2. Sequencing of Multimodality Therapy. Thorough preoperative clinical staging is paramount in the sequencing of multimodality therapy for rectal cancer. For smaller tumors T1/T2, surgery alone with wide surgical resection of low anterior resection or abdominoperineal resection for distal lesions not amendable to low anterior resection may be performed. This allows sampling of mesorectal lymph node for accurate pathological staging. In patients who are medically unfit or who adamantly refuse to undergo standardized resectional surgery, local excision with or without chemoradiotherapy may be considered an option to palliate early-stage disease. This strategy fails to sample the mesorectal lymph nodes that are essential in disease staging. In a large single institution cohort study comparing their retrospective experience of 350 with stage I rectal cancer of whom 283 patients (80.9%) underwent standardized resection and 67 patients (19.1%) undergoing local excision, 5-year local recurrence was 14.1% in the local excision group compared to 3.3% in the standardized resection group [54]. This significantly higher local recurrence rate may then be salvaged through multimodality approach combining preoperative chemoradiotherapy and surgery. However, at times, these local recurrences may not be resected with standardized resectional surgery and may require radical surgeries such as a pelvic exenteration.

For clinically staged T3/T4 rectal tumors without clinically identified nodal disease (stage II) who undergo TME surgery with either a low anterior resection or abdominoperineal resection with harvesting of at least 12 lymph nodes examined and staged as pN0 chemoradiation is not required. Chemoradiation may be considered in the setting of pT3N0 tumors with adverse pathologic features, non-TME surgery or in those with fewer than 12 lymph nodes harvested. For T3/T4 tumors with lymph node metastases (stage III) identified clinically, treatment involves both chemoradiation with fluorouracil (5-FU) and total mesorectal excision (TME) based surgery. However, there remain enormous controversies regarding the optimal sequence of these therapies. Postoperative chemoradiation was shown to achieve superior results over postoperative radiation alone with a 34% reduction in recurrence rate with reductions observed for local recurrences and distant metastasis [55]. When postoperative chemotherapy was compared to radiotherapy in the NSABP R-01 randomized trial, postoperative chemotherapy appeared to improve survival and radiotherapy reduced the incidence of locoregional recurrence without survival improvements [56]. Given the benefits of chemoradiation in achieving local control as an adjunct to surgery, the German Rectal Cancer Study Group then conducted a randomized trial of 421 patients to determine the perisurgical sequencing of chemoradiation for rectal cancer. These investigators compared preoperative to postoperative chemoradiation and demonstrated that the 5-year cumulative incidence of local recurrence was 6% in the preoperative arm compared to 13% in the postoperative arm ($P = 0.006$) with fewer grad 3/4 acute and long-term toxic effects of chemoradiation observed in the preoperative arm compared to the postoperative arm [57]. In a smaller Korean trial, the improved effects of local control was not demonstrated in the preoperative compared to the postoperative chemoradiation arm, however, it was shown that an increased rate of sphincter preservative surgery could be achieved [58]. The exact type of preoperative therapy was also recently debated with a short course radiation (25 Gy in 5 fractions) followed by surgery a week after or a long course chemoradiation (50.4 Gy in 28 fractions combined with systemic chemotherapy) followed by surgery four to six weeks after. The brief use of radiotherapy in the short course setting has been argued upon its role in providing adequate tumor response to allow sphincter preservative surgery. Two randomized trials; Polish ($n = 312$) and Australian ($n = 326$) compared these two regimens and both trials showed a lower rate of early acute toxicity and reduce cost of treatment without any difference in long-term oncologic outcomes [59, 60].

After preoperative chemoradiation, guidelines recommend adjuvant chemotherapy for patients with node positive disease. However, the EORTC 22921 trial of 785 clinically staged T3/T4 rectal cancer patients randomized to receive adjuvant fluorouracil based chemotherapy after preoperative (chemo) radiotherapy and surgery showed no survival benefit of chemotherapy on disease-free survival. However, specific subgroup analysis was performed to determine the appropriate role of adjuvant chemotherapy and showed that pathologically staged T0-2 (ypT0-2) patients appeared to benefit in terms of both disease-free and overall survival from adjuvant chemotherapy compared to ypT3/T4 patients. Importantly, adjuvant chemotherapy did not appear to demonstrate any difference in outcomes of patients with ypN0 or ypN+ disease. This demonstrates that further benefits of adjuvant chemotherapy are only observed in responding patients (ypT0-2) [61]. Further trials are required in this area to determine the appropriate role of adjuvant chemotherapy and the selection of high-risk populations who may then benefit from other modern adjuvant agents.

2. Role of Surgery for Advanced and Metastatic Rectal Cancer

2.1. Locally Advanced or Local Recurrence. Tumors extending beyond the rectal wall with invasion into surrounding viscera are considered locally advanced rectal cancer. Often in patients who develop local recurrence, recurrent disease often similarly involve adjacent structures where the previously excised rectal tumor was located. Although its incidence has decreased following total mesorectal excision and the incorporation of preoperative chemoradiation, when it occurs, it remains a debilitating condition that is difficult to treat. Palliative radiotherapy may provide brief symptom relief for an average of 3 months with median survival

in these patients being between 12 and 24 months [62–64]. Surgery may provide a long-term palliation to the debilitating symptoms of pelvic recurrences. In the curative setting, delivery of long course preoperative chemoradiotherapy may induce tumor down-staging to facilitate surgical resection. In a randomized trial comparing neoadjuvant radiotherapy to chemoradiotherapy in 207 patients with locally unresectable T4 primary rectal or local recurrent rectal cancer, chemoradiotherapy compared to radiotherapy facilitated higher potential for an R0 resection (84% versus 68%; $P = 0.009$), improved local control in patients who underwent a R0 or R1 resection (82% versus 67% at 5 years; $P = 0.03$), improved time to treatment failure (63% versus 44%; $P = 0.003$), cancer-specific survival (72% versus 55%; $P = 0.02$) and overall survival (66% versus 53%; $P = 0.09$) [65]. The surgery involved necessitated pelvic exenteration where adjacent organs are resected with an aim to achieve clear margins. In patients with primary T4 rectal cancer and recurrent rectal cancer, 28% and 20% of patients in the chemoradiotherapy arm and 27% and 46% in the radiotherapy arm, respectively, required exenteration. Intraoperative radiotherapy (external-beam) (IORT) is another approach to improve local control. This treatment modality has been investigated in patients with locally advanced unresectable rectal cancer after chemoradiotherapy down-staging and surgery. Its application is best used in the setting of a complete resection. Valentini et al. reported 100 patients with T4M0 tumors undergoing R0 resection after down-staging by chemoradiotherapy and showed that 5-year local control was 90% in patients with R0 surgery and 100% in patients with R0 surgery and IORT. Further, IORT did not appear to compensate for suboptimal surgery with 5-year overall survival of 68% observed in patients with R0 surgery compared to 22% in R1 or R2 surgery [66]. Such radical surgery however is not widely performed and only available in specialized institutions. In a pattern of care study of the United States population through data identified from the Surveillance, Epidemiology and End Results (SEER) registry, only 33% of patients with locally advanced adherent colorectal cancer underwent multivisceral resection for which was shown to be associated with improved overall survival [67].

2.2. Liver Metastases. In patients with synchronous rectal cancer with liver metastases, there remains an enigma over the appropriate sequencing of chemotherapy, radiotherapy, and surgery. In a study from the Erasmus University, van der Pool et al. reported a consecutive series of 57 patients of whom 29 patients underwent resection of the primary tumor first, 8 patients underwent simultaneous rectal and liver resection and 20 underwent a liver-first approach achieving a median survival of 47 months and 5-year survival of 38%. This was achieved in a multidisciplinary setting where an individualized approach towards treatment was taken. In general, if resection of both primary tumor and liver metastases may be completed in one surgery, this approach may be favored. If the liver metastases are not completely resectable during the rectal surgery or are too advanced for hepatectomy irrespective, neoadjuvant chemotherapy is preferred followed by a liver-first approach followed by restaging and preoperative radiotherapy and rectal surgery. In patients with metachronous liver metastases, the evidence of hepatectomy is based on current literature available for colorectal liver metastases. Results of large clinical series have shown that median survival range from 43 months to 64 months with 5-year survival ranging between 37% to 51% [68, 69]. Of note, in a large international multi-institutional registry study, rectal primary tumor were associated with extrahepatic recurrences after hepatectomy for liver metastases, hence emphasizing the importance of local control in the pelvis [69]. However, there is no difference in colon or rectal based primary tumor site impacting outcomes after hepatectomy for colorectal liver metastases [70].

2.3. Lung Metastases. Epidemiological and observatory data from the followup of patients with curatively treated colorectal cancer have shown that rectal cancer patients have a higher preponderance to developing recurrence in the lungs [71–73]. In a large population based study of 30 years in Burgundy (France), Mitry et al. reported that lung metastases often accompanied liver metastases with synchronous lung metastases being more common in left colonic and rectal cancers [71–73]. Surgery for lung metastases is indicated if the lung metastases are the only site of disease and a complete resection may be achieved. Where extrapulmonary metastases are present, a highly selective approach should be taken often after adequate tumor response to systemic chemotherapy to select patients whose disease is amendable to resection of both lung and extra-pulmonary metastases. The highest level of evidence for resection of lung metastases comes from a large systematic review of 20 published studies for pulmonary metastasectomy for colorectal lung metastases. Pfannschmidt et al. report a median 5-year overall survival of 40% in this selected group of patients who underwent surgery [74]. Site of the primary tumor did not result in different survival outcome. However, given that the liver will often be involved when there is lung metastases, it is important that the selection of patients for pulmonary metastasectomy should include a sufficient disease-free interval from previous liver resection, use of prethoracotomy CEA levels and the absence of mediastinal lymph node involvement as a separate selection criteria in this group of patients. Presently, a randomized trial (PulMiCC) funded by Cancer Research UK is seeking to investigate if pulmonary metastasectomy contributes to improved survival of patients with colorectal lung metastases by randomizing patients with a history of resected colorectal cancer who are found to have pulmonary metastases to be randomly allocated to "active monitoring" or "active monitoring with pulmonary metastasectomy" with overall survival, relapse-free survival, lung function, and patient-reported quality of life as endpoints of this clinical trial [75].

2.4. Peritoneal Metastases. Shedding of tumor during the difficult abdominoperineal resection, low anterior resection

operation, or invasion of a large T3/T4 tumor in the upper rectum above the peritoneal reflection may result in the shedding of free peritoneal tumor cells within the abdominopelvic peritoneal cavity. The growth and implantation of these cells may result in the development of peritoneal metastases (carcinomatosis). Results of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) have shown that this combined modality technique allows complete excision of peritoneal tumors with locoregional control achieved through the chemoperfusate. In colorectal cancer, a randomized trial comparing cytoreductive surgery and HIPEC demonstrated a median survival of 22.3 months compared to 12.6 months in patients receive systemic chemotherapy with or without palliative surgery [76]. The two-fold survival benefit provides evidence of its efficacy. However, in this trial of 105 patients, only 12 patients had rectal cancer. Again, in a large registry study of the French experience of HIPEC in colorectal cancer, of 523 patients included, only 36 patients (7%) had primary colorectal tumor of rectal origin [77]. In another international registry of 506 patients with colorectal peritoneal metastases undergoing cytoreductive surgery and HIPEC, there were 40 patients (8%) with the primary tumor of rectal origin and the median survival of these patients was 19.2 months compared to 24 months in patients with tumors of sigmoid origin, 17 months for patients with tumors of the right colon and 20 months for patients with tumors of the left colon [78]. These results inform us that peritoneal metastases from rectal cancer is less common but prevent us from drawing any meaningful conclusion on whether there may be disparate survival outcomes for colon and rectal cancer patients with peritoneal metastases. Based on the currently available evidence, selected rectal cancer patients with limited peritoneal disease burden may be considered for cytoreductive surgery and HIPEC.

3. Conclusion

Rectal cancer surgery has made significant advancement at all-time points of the natural history of this disease. There are now minimally invasive local excision options that are currently being tested for efficacy as we await further clinical trials to verify its efficacy for pre-invasive and early lesions. Laparoscopic rectal cancer surgery incorporating total mesorectal excision is now emerging as the standard surgical approach with ongoing clinical trials that will confirm its short and long-term oncologic efficacy. There is now evidence based results from clinical trials for both preoperative short and long-course chemoradiation prior to surgery for resectable tumors for which has been shown to improve local control of disease albeit its aim achieving sphincter preservative surgery where possible. Ultimately, the goal of this being to achieve adequate sampling of mesorectal lymph nodes to provide adequate information for tumor staging and prediction of local and distant recurrences for which will guide treatment decisions. There is now evidence for resecting metastases from rectal cancer from local recurrences, liver, lung, and peritoneal metastases based on a body of retrospective clinical data with long-term followup.

Conflict of Interests

The authors declared that there is no conflict of interests.

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Review Article

Management of Rectal Cancer and Liver Metastatic Disease: Which Comes First?

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In the last few decades there have been significant changes in the approach to rectal cancer management. A multimodality approach and advanced surgical techniques have led to an expansion of the treatment of metastatic disease, with improved survival. Hepatic metastases are present at one point or another in about 50% of patients with colorectal cancer, with surgical resection being the only chance for cure. As the use of multimodality treatment has allowed the tackling of more complicated cases, one of the main questions that remain unanswered is the management of patients with synchronous rectal cancer and hepatic metastatic lesions. The question is one of priority, with all possible options being explored. Specifically, these include the simultaneous rectal cancer and hepatic metastases resection, the rectal cancer followed by chemotherapy and then by the liver resection, and finally the "liver-first" option. This paper will review the three treatment options and attempt to dissect the indications for each. In addition, the role of laparoscopy in the synchronous resection of rectal cancer and hepatic metastases will be reviewed in order to identify future trends.

1. Introduction

Rectal cancer is the fourth most commonly diagnosed malignancy in the United States, with approximately one-third of all colorectal malignancies arising in the rectum, considered as the last 15 cm of the large bowel. Of the 150,000 new cases of colorectal cancer (CRC) diagnosed in the United States every year, about 50% develop hepatic metastases during the course of their disease, with 20–25% of these presenting with synchronous liver metastases [1–3]. This is even more important if we consider that in about a one-third of the patients with synchronous or metachronous liver metastases, the liver is the only site of metastatic disease, meaning that around 15,000 patients per year are candidates for therapy of these lesions [4].

Just as important as the extent of the disease is the fact that the only potential therapy for cure in patients with CRC and hepatic metastatic disease is surgery [5]. Even though median survival of patients with untreated metastatic CRC is around 6 months to a year, advances in adjuvant treatment after the colorectal resection have shown the potential of a decrease in the number of metastatic cases [6]. Agents such as oxaliplatin, and newer targeted-therapy ones such as cetuximab and bevacizumab, have led to improved response rates and survival [7–9]. Even so, the two-year survival is limited to 40% at best, thus reiterating the primacy of surgery as part of the multimodal approach [10]. Limitations remain as only about 10–20% of patients with liver metastatic disease are candidates for surgical resection at presentation [11]. However, another 15–30% of previously considered unresectable patients can be converted and (despite the absence of randomized controlled trials) the majority of evidence supports a significant survival benefit with surgical resection, with overall 5-year survival rates after hepatic resection with curative intent ranging from 35 to 55% [12–16].

All of this progress in our understanding and management of patients with CRC and hepatic metastatic disease, not unexpectedly, has led to more questions. A central one is the timing and sequence of therapeutic interventions

in patients presenting with synchronous CRC and hepatic metastases. The classical approach has been to resect the CRC, continue with chemotherapy, and then proceed to the liver, provided that the patient is coping with the treatments and the hepatic disease burden is manageable. Improvement in surgical and anesthesia techniques and the accumulation of experience have allowed qualified surgical teams to proceed with the simultaneous resection of both the CRC and the hepatic metastases in selected patients. The realization that the liver metastases are actually what defines the prognosis of the patients, and because complications in rectal surgery are not uncommon after chemoradiation and can thus delay the start of appropriate metastatic therapy, the "liver-first approach" has been proposed in patients with locally advanced rectal cancer and synchronous liver metastases. This paper will attempt to dissect the different types of approaches and identify the patients that would be most served by each one. Finally, the role of laparoscopy will also be reviewed to identify future directions in the management of stage IV rectal cancer.

2. Chemotherapy and Resectability

There is a new paradigm in what is considered resectable liver metastatic disease, as previous standards having to do with the disease burden (how many lesions, location) have been replaced by newer ones that place the focus on what remains behind. Specifically, in order for hepatic metastatic lesions to be considered resectable it is important to be able to achieve a negative resection margin and to leave behind at least two contiguous segments with adequate size and function to avoid hepatic insufficiency after resection. The adequacy of the size of the liver remnant is dependent on its quality, which can certainly be affected by the preoperative chemotherapy.

This brings into the forefront the question of the ideal timing of surgery in patients with resectable disease. Preoperative chemotherapy used as neoadjuvant therapy offers the advantage of earlier treatment of micrometastatic disease and possible improved containment, as well as evaluation of tumor responsiveness, which is information that can also help shape future therapy [17]. Some argue that the presence of the whole liver may mean increased tolerability to the side effects of chemotherapy, compared to the hepatic remnant after resection. Tumor responsiveness can help determine future chemotherapy, as well as identify those patients with the best chance for resection, since progression while on chemotherapy is a bad prognostic factor [18, 19]. There are, however, complications which include chemotherapy-induced nonalcoholic steatohepatitis (NASH), steatosis, centrilobular necrosis and sinusoidal changes [20, 21]. More importantly, preoperative chemotherapy, due to the liver injury, can delay the resection or even simply make it very difficult to identify the lesion as a complete response does not necessarily mean that all cancer cells have been eradicated [22]. The advantages and disadvantages of preoperative chemotherapy mentioned above make it even harder to identify what the best sequence of therapies should be in patients presenting with simultaneous rectal lesions and resectable liver metastases. Even an expert consensus statement in 2006 failed to provide clear guidelines, stating that "either stages or simultaneous resections of the primary tumor and liver metastases can be considered depending on variable factors…" [23]. Even so, three main approaches (the classical staged one and the more novel synchronous and "liver-first" ones) have been identified and it is essential to understand the type of patient that each one is applicable for.

3. Simultaneous versus Staged Primary and Hepatic Metastases Resection

The classical approach in dealing with synchronous rectal cancer liver metastases has been the staged one, where colectomy is followed by chemotherapy and then by liver resection, provided that the disease passes the "test of time" [24–26]. Advocates of this approach believe that it allows the full metastatic load of the disease to be revealed, as well as the biological behavior or "aggressiveness" of the tumor. An added argument is the potential for increased morbidity and mortality from the combination of two major operations. However, several studies have shown that the synchronous colorectal resection does not lead to increased morbidity or mortality when combined with partial hepatectomy [27–30]. There are two caveats here; the first one is the fact that most studies refer to colorectal cancer as a whole and not just rectal cancer. The importance of this is that rectal procedures are technically more challenging than colon procedures, with a higher risk of morbidity and mortality. Despite that, a study (possibly the only one identified in the literature) looking at synchronous rectal and hepatic resection of rectal metastatic disease from the Mayo Clinic showed that combined rectal and hepatic resection is safe [31]. They reported overall survival at 1, 2, and 5 years of 88%, 72%, and 32%, respectively, as well as disease-free survival from local recurrence at 1, 2, and 5 years of 92%, 86%, and 80%, numbers that were comparable to those undergoing a staged procedure. Similar data were presented in another published study from the Memorial Sloan-Kettering Cancer Center, which reported prospectively on 240 patients undergoing synchronous resection of a primary colorectal carcinoma [32]. In that study rectal cancers were 38% of the patient population, but in the simultaneously resected population most hepatic resections were not of the major type.

The other caveat is that most studies comparing simultaneous and staged colorectal and hepatic resections are retrospective and, more importantly, patients undergoing the simultaneous procedure had fewer, smaller, and more often unilobar synchronous colorectal liver metastases [33]. These concerns have led to the recommendation that simultaneous procedures should only be pursued when they involve minor hepatic resections, while major hepatectomies should only occur in very carefully selected cases and by an experienced hepatobiliary team. Additionally, simultaneous hepatic resections should not be performed as part of an exploration for an emergent colorectal resection for bleeding or perforation or obstruction, because apart from the

severely increased morbidity, they can also lead to a higher chance of distant metastases [34]. Similarly, if there is chronic significant liver disease, or the possibility of a small liver remnant, simultaneous resections should not be performed to avoid the risk of postoperative hepatic insufficiency.

4. The "Liver-First Approach"

This approach is the latest and one that is most suited for patients with advanced rectal cancer. Approximately, 30% of patients with locally advanced rectal cancer have synchronous liver metastases. The locally advanced rectal disease is usually treated with a long course of chemoradiation of about five weeks and with at least six weeks going by before the patient can be operated upon. The result is that, and provided that there are no chemoradiation complications, three months will have passed before the liver disease is actually addressed. This is made harder by the high frequency of complications, which push any therapy for the liver disease even further down the road, as well as the fact that the liver metastatic disease is the one ultimately affecting the prognosis.

The "liver-first" or "reverse" approach consists of preoperative chemotherapy, followed by resection of the hepatic metastatic disease, and then by resection of the rectal primary at a second operation. The ideal patient is one with advanced synchronous liver metastatic disease and a rectal cancer [35]. The rationale for this approach is based on the fact that complications such as bleeding, obstruction, or perforation are rare in patients with stage IV colorectal cancer, as well as the fact that treatment of the metastatic disease is not delayed by the local therapy for the primary tumor [36, 37]. An increasing number of studies have examined this approach, with one of the earliest ones by Mentha and colleagues demonstrating the safety of this strategy with morbidity and mortality rates of 19% and 0%, respectively, and an overall 3-year survival of 83% [38]. Another study comparing all 3 strategies, revealed similar results with morbidity and mortality of 31% and 4%, respectively, and a 3-year overall survival of 79% [39]. Most importantly, that study showed that the classic, combined, or reverse surgical strategies in patients with synchronous colorectal lesions and hepatic metastases are associated with similar outcomes [39]. The "liver-first" or reverse approach is best suited for patients with advanced hepatic metastases and an asymptomatic primary.

5. The Role of Laparoscopy

We have seen that the optimal strategy for managing resectable synchronous colorectal liver metastases is being refined over time. Although the guidelines have been to perform the colorectal cancer and the liver resection separately because of potentially increased mortality, this has been changed in several cases to one of synchronous resection for patients with limited hepatic metastatic disease [40–42]. Similar reluctance was observed in the case of stage IV rectal cancer specifically, because of the fear of increased risk of morbidity and anastomotic leakage [43]. The institution of a concerted approach by colorectal and hepatobiliary surgeons has led to the successful application of simultaneous resection, even in the case of major hepatic resections [44].

Achieving a solid oncologic outcome in a safe manner further encouraged surgeons to the use of laparoscopic total mesorectal excision (TME) for stage IV rectal cancer combined with open or laparoscopic hepatic resection. One of the largest series for stage IV rectal cancer from Beaujon Hospital included 10 patients undergoing laparoscopic mesorectal excision, of which 3 underwent a simultaneous laparoscopic resection for the hepatic neoplasm and the other seven an open resection through a small incision [45]. In this pilot study it is suggested that laparoscopic rectal resection with synchronous resection of hepatic disease is possible with acceptable, low morbidity and a short hospital stay. Others have used a hybrid procedure, with the use of hand-assisted laparoscopic surgery for minor resections, whereas pure laparoscopic rectal and hepatic resections for stage IV rectal cancer have mainly appeared as case reports [46, 47].

These reports show that technical progress and an improving learning curve can play a critical role in the more widespread use of laparoscopic surgery for the simultaneous resection of stage IV rectal cancer. However, we need to be mindful of the fact that this procedure remains under evaluation, as the learning curve and the operative time are long, and no randomized controlled trials exist [48].

6. Conclusion

The optimal timing for surgical resection of synchronous colorectal liver metastasis and the primary tumor is a question that remains unanswered. The traditional approach of a staged approach with initial resection of the colorectal tumor, followed by chemotherapy and then by hepatic resection 2 to 3 months later, has been based on the argument that it is physiologically less stressful for the patient compared to the combined procedure. This becomes even more important in the case of rectal cancer, where resection of the rectal primary is a significantly more challenging procedure by itself with well-established morbidity. Advances in surgical and perioperative care have changed this mindset, with the result being that the simultaneous resection of the colorectal primary and the hepatic metastases is increasingly gaining ground, as it results in morbidity, mortality, and length of stay comparable to the staged resection, while at the same time leading to earlier completion of the surgical therapy and the ability to start adjuvant therapy. With increasing experience it has also been possible to better define the subset of patients that would benefit the most from this approach, which includes those patients that warrant a limited hepatic resection.

Further advances led to the institution of the "liver-first" approach, based on the belief that in patients with stage IV rectal cancer, the factor that defines survival is the ability to deal with the hepatic metastatic disease. In selected patients, where the primary rectal cancer is not a threat for

bleeding, obstruction, or perforation, there is the option of addressing the hepatic disease first before it progresses too far. Furthermore, laparoscopic surgery with the rapid progress that it is experiencing is playing a role even in the cases of simultaneous resection. From the above discussion it becomes evident that trying to answer the question of timing of surgery for patients with colorectal primary and hepatic metastatic disease allows us to see how far we can push the envelope in providing sound surgical treatment for these patients.

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Review Article

Analysis of Risk Factors for Lymph Nodal Involvement in Early Stages of Rectal Cancer: When Can Local Excision Be Considered an Appropriate Treatment? Systematic Review and Meta-Analysis of the Literature

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Background. Over the past ten years oncological outcomes achieved by local excision techniques (LETs) as the sole treatment for early stages of rectal cancer (ESRC) have been often disappointing. The reasons for these poor results lie mostly in the high risk of the disease's diffusion to local-regional lymph nodes even in ESRC. *Aims*. This study aims to find the correct indications for LET in ESRC taking into consideration clinical-pathological features of tumours that may reduce the risk of lymph node metastasis to zero. *Methods*. Systematic literature review and meta-analysis of casistics of ESRC treated with total mesorectal excision with the aim of identifying risk factors for nodal involvement. *Results*. The risk of lymph node metastasis is higher in $G \geq 2$ and $T \geq 2$ tumours with lymphatic and/or vascular invasion. Other features which have not yet been sufficiently investigated include female gender, TSM stage >1, presence of tumour budding and/or perineural invasion. *Conclusions*. Results comparable to radical surgery can be achieved by LET only in patients with T_1 N_0 G_1 tumours with low-risk histological features, whereas deeper or more aggressive tumours should be addressed by radical surgery (RS).

1. Introduction

Colon and rectal cancers have many features in common, including risk factors, symptoms, and screening procedure; however, anatomical, clinical-pathological, and genetic diversities call for them to be considered as two different diseases often requiring different forms of treatment [1–4]. The oncological outcomes of rectal cancer surgery are usually worse than those of colon cancer; one reason for this is the higher local recurrence rate after curative resection [5]. The advent of total mesorectal excision (TME) as an addition to radical resection (RS) has strongly decreased the risk of local recurrence; in spite of this favourable outcome following RS, there is a high rate of severe complications and of abdominoperineal resections (APRs) with permanent colostomy. Local Excision (LE), more recently flanked by Transanal Endoscopic Microsurgery (TEM), has been proposed as an option for patients with early rectal carcinoma in whom radical surgery and its complications may be avoided, as well as for high-risk patients not suitable for administration of general anesthesia. Nevertheless, reported oncological outcomes following local excision techniques (LETs) in rectal cancer are often unsatisfactory. Local recurrence rates after LET for T1 and T2 tumours can range from 6.6% to 18% and from 17% to 67% [6–11], respectively [3–7]. Bentrem et al. found that patients with T1 rectal cancer treated by local excision have a threefold to fivefold higher risk of tumour recurrence than those treated by radical resection [12].

Table 1: Inclusion and exclusion criteria for study selection.

Inclusion criteria
(i) Casistics of rectal cancer T1/T2 treated by radical resection with TME
Exclusion criteria
(i) Rectal cancer T3 or T4
(ii) Rectal cancer in IBD
(iii) Casistics of colon and rectal cancer together
(iv) Neoadjuvant therapies (radio/chemo)
(v) Radical resection of rectal cancer following LE/TEM
(vi) Radical resection of recurrent rectal cancer
(vii) Presence of distant metastasis (M1)
(viii) Studies focused only on selected histotypes (depressed polyps, pedunculated polyps, etc.)
(ix) Studies focused only on selected lymph node involvements (micrometastasis, lateral lymph node metastasis, etc.)

The reasons for these disappointing results can be attributed mostly to the high risk of the disease's diffusion to loco-regional lymph nodes even in ESRC, for which LET cannot provide radical treatment. In this context it is clear that indications for the use of LET in ESRC should ideally consider all those clinical-pathological features that may reduce the risk of lymph node metastasis to zero. In this study risk factors for lymph node metastasis in ESRC were analysed through a systematic literature review together with a meta-analysis of the data retrieved.

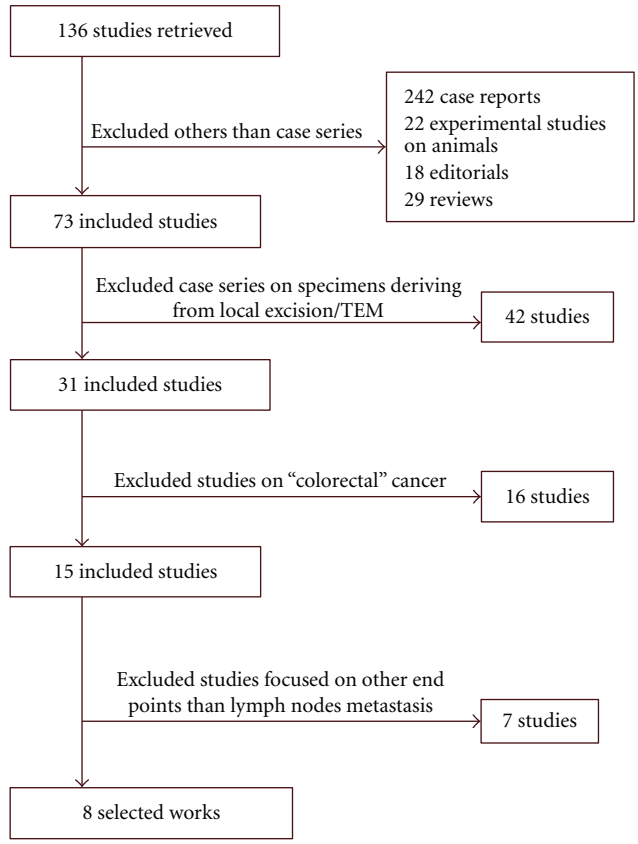

Figure 1: Quorum flowchart of the literature search.

2. Materials and Methods

2.1. Data Sources. Computerized search for mesh terms indicating risk factors for lymph node metastasis in rectal cancer up to December 2010 on Pubmed, Pubmed Central, OvidSP, BioMed Central, Chinal, Cochrane Library, Embase, SUMSearch, American College of Physicians (ACP) Journal Club, the most important Web Search Engines (Google, Google scholar, Yahoo, Lycos), grey literature, and references cited in the works selected.

A total of 136 studies were identified by the searches. By scanning titles and abstracts, 63 redundant publications, reviews, case reports, and editorials were excluded. After referring to full texts, 65 studies which did not satisfy the inclusion/exclusion criteria were removed from consideration. A total of 8 studies were left for analysis, involving a total of 1560 patients (Figure 1) [5, 13–19]. All 8 works were retrospective case studies of T1/T2 primary rectal cancer treated with RS and TME, ranging from 2++ to 2− according to the SIGN classification for grading evidence (Scottish Intercollegiate Guidelines Network) [13]. Unfortunately the objective of the work did not allow for other study designs apart from the analysis of retrospective studies. The inclusion and exclusion criteria are shown in Table 1.

Finally, the quantitative and qualitative data of 1560 patients were extracted from the works selected and reported in a cumulative data form. Variables collected for each patient included gender, age, tumour size, tumour grading, depth of tumour invasion, presence of lymphatic invasion, presence of vascular invasion, presence of perineural invasion, and tumour budding.

2.2. Statistical Analysis. Statistical analysis was carried out using Meta-DiSc (version 1.4). Study-specific ORs with corresponding 95% confidence intervals (CIs) for different clinical and pathological features (dichotomous variables) versus loco-regional lymph node positivity/negativity were extracted. The overall effect was tested using χ^2 with Yates correction or by Fisher's exact test (with significance being set at P-value ≤ 0.05). Meta-analysis was performed using fixed-effects (FEs) or random-effects (REs) models, depending on absence or presence of significant heterogeneity. Cochran-Q and Higgins I^2 statistics were used to check heterogeneity not only among studies but also between the subgroups included in this meta-analysis [14]. For the Cochran-Q statistic, P-value ≤ 0.10 indicated statistically significant heterogeneity. We defined statistical significance as P-value ≤ 0.10 rather than the conventional level of 0.05 because of the low power of this test [20]. I^2-values lie between 0% (no observed heterogeneity) and 100% (maximal heterogeneity); thus, an I^2-value greater than 50% may be considered to represent substantial heterogeneity [15]. In the absence of statistically significant heterogeneity, the fixed-effect method was used to

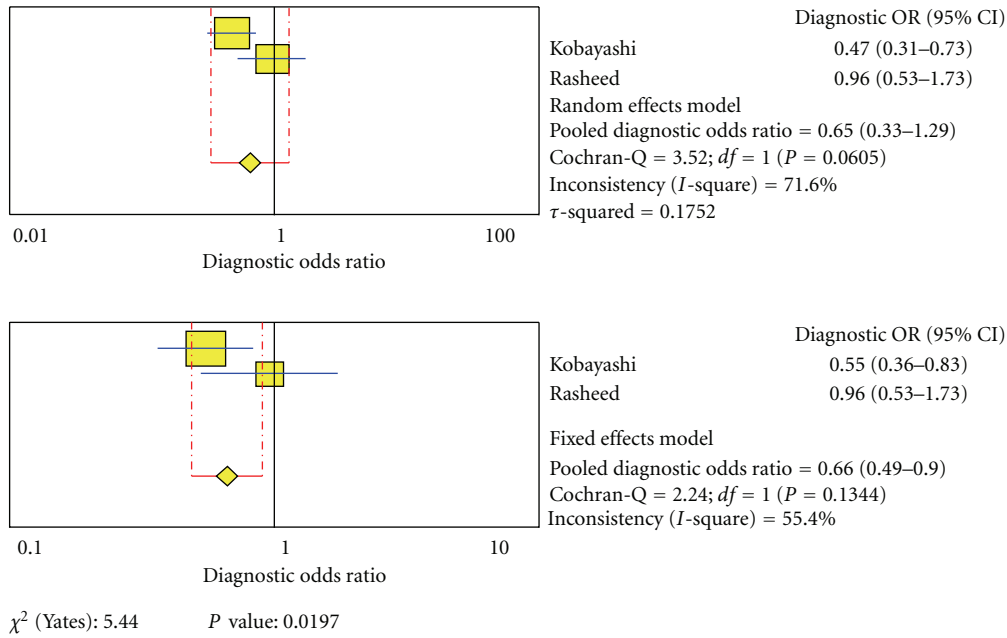

Figure 2: Risk of lymph node metastasis in males versus females.

combine the results. When heterogeneity was confirmed, the random-effect method was used.

3. Results

In our meta-analysis the rate of lymph node metastasis in ESRC is very high: about 10.53% for pT1 and 23.6% for pT2 cancers. Only two studies analysed gender as a prognostic factor for loco-regional lymph node metastasis (LNM), although the cumulative number of patients was quite substantial (870). Statistical heterogeneity between these studies was tested with Cochran-Q statistic (P-value =0.13, not significant) and with I^2 (I^2 = 55%, significant for presence of heterogeneity) (Figure 2). These contradictory results indicated that both fixed-and random-effect methods are useful to combine the results. In the first case the pooled OR for males vesus females in LNM was 0.66 (0.49–0.90), with a P-value of 0.0197, thus indicating a trend on the part of the female gender towards lymphatic spreading of the tumour. On the contrary, using a random-effect method, the pooled ORs for males versus females was 0.65 (0.33–1.29), with a P-value of 0.17; even though the OR was not statistically significant, it displays a comparable trend. Moderate/high tumour grading and vascular invasion were analysed in five studies resulting in a strong association with the presence of LNM; pooled OR were 0.40 and 0.46 respectively, with P-values of 0.000 for both (Figures 4 and 5). A relevant association with LNM was also found for lymphatic invasion (pooled OR 0.26; P-value 0,000) (Figure 6). Depth of tumour invasion also proved to be an important prognostic factor for LNM. T1 versus T2 stages were examined in all selected studies with a much clearer trend of T2 stages towards nodal involvement (pooled OR 0.44; P-value 0.000) (Figure 3). Other tumour variables such as tumour size, tumour budding, perineural invasion, depth of tumour invasion within the submucosal layer (Sm 1, 2, and 3), and distance from the dentate line were investigated either only in a single study or using heterogeneous parameters, thus preventing a reliable meta-analysis.

4. Discussion

Although colon cancer and rectal cancer share many features, there are important clinical-pathological and genetic differences between these two diseases, including in particular the tendency for rectal cancer, but not colon cancer, to recur locally; according to the majority of authors, this tendency towards local recurrence is a consequence of the tumour spreading through the *lymph* vessels. It has been clearly demonstrated that nodal involvement leads to an increased risk of local recurrence, overall survival, and disease-free survival [16–19, 21, 22]. In our meta-analysis the rate of lymph node metastasis in ESRC is very high: approximately 10.53% for pT1 and 23.6% for pT2 cancers. These outcomes stress how LET alone should not be considered as a radical oncological treatment in such a high subset of patients, unless future improvements in preoperative staging lead to the unequivocal identification of patients with nodal involvement. Unfortunately at present precise local tumour staging of rectal cancer is only possible after a surgical resection. The published literature shows that MR and US imaging, with an accuracy that does not exceed 70%, are not reliable enough to identify nodal involvement [20, 23–25]. A possible explanation for this trend is the frequent likelihood of metastasis of small lymph nodes (smaller than 5 mm), which are difficult to detect even by highly experienced radiologists. In a recent study of 101 cases of rectal cancer 45.3% of the metastatic lymph nodes were Smaller than 5

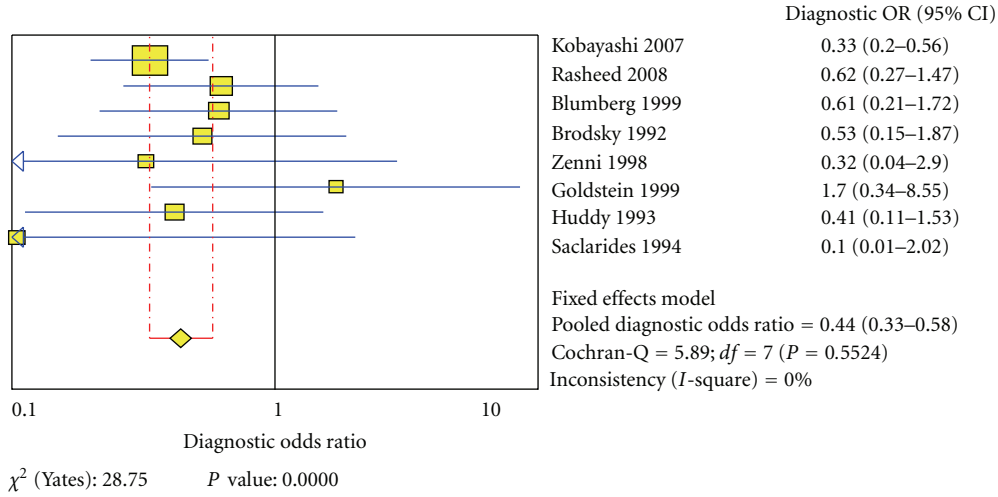

Figure 3: Risk of lymph node metastasis in T1 versus T2.

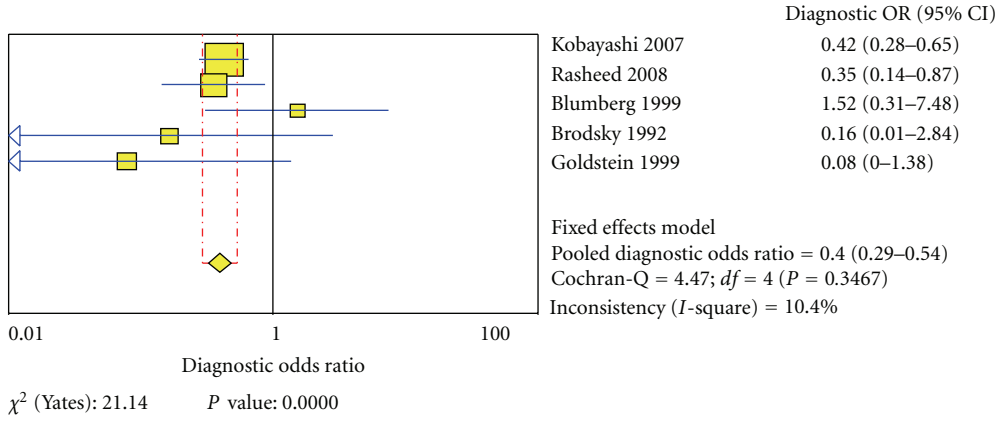

Figure 4: Risk of lymph node metastasis in G1 versus G2/G3.

millimetres in diameter; hence, a possibility of undetected nodal involvement even in T1 tumours does exist [23]. More recently MR supplemented with specific i.v. contrast medium (USPIO) was proposed by some authors as an alternative imaging technique offering high sensitivity and specificity in the identification of involved mesorectal lymph nodes. In the paper of Dow-Mu Koh based on 25 patients with rectal cancer the use of MR with USPIO resulted in an average sensitivity of 65%; specificity, 93%; positive predictive value, 43%; negative predictive value, 97%. The authors concluded that the use of MR with USPIO enhancement can achieve higher diagnostic specificity than but the same sensitivity as morphologic findings in pathologically matched mesorectal lymph nodes. Unfortunately given the shortage of trials addressing the outcomes of this amazing technique, its role in clinical practice still needs to be investigated in further studies. The sentinel lymph node technique has been more recently proposed by some authors as a means of evaluating loco-regional lymph node status; although interesting and promising, this technique is at present under development and has not yet been validated by scientific evidence [26, 27]. In the absence of a reliable technique to detect nodal involvement before surgery, research efforts are at present directed towards the identification of standard pathological variables capable of identifying tumours at risk of lymphatic spreading. Detecting a subset of patients who are likely to have LNM and who would possibly benefit from adjuvant therapies, abdominoperineal resection, or both would be of primary importance in the treatment of patients initially treated by local excision. Prior studies by other investigators have dealt with this issue through multivariate analysis of casistics of colorectal cancers operated on by radical surgery. Unfortunately these studies rarely discriminate colonic cancers from rectal cancers in their design. This differentiation is mandatory in our opinion, given the above-mentioned distinctions between these two diseases. To our knowledge, there are no systematic literature reviews with meta-analysis focused on risk factors for LNM exclusively in rectal cancer that deal with this problem. It is important to acknowledge the limitations of the present study: the retrospective nature and the restricted number of available studies investigating clinical-pathological tumour features could challenge our conclusions, but it must be said that the nature of this study per se does not permit any other kind of

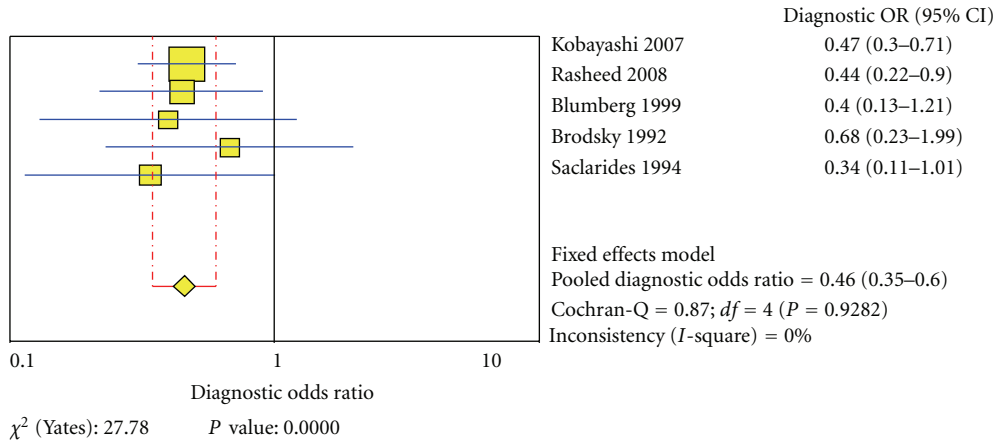

Figure 5: Risk of lymph node metastasis in Vascular Invasion.

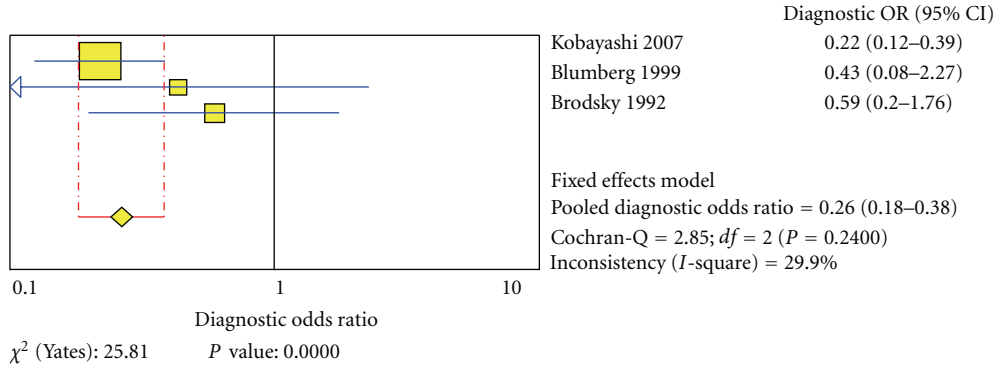

Figure 6: Risk of lymph node metastasis in lymphatic invasion.

analysis than the retrospective investigation of rectal cancer specimens. Furthermore, in order to reduce selection biases, we followed rigorous exclusion criteria in the study selection. Studies which considered colon cancer and rectal cancer together were dismissed. We also excluded studies which did not discriminate between primary malignant tumours and recurrent ones, radiochemotherapy-treated cancer and cancer related to IBD. In addition we did not consider works focused on specific types of rectal cancer (i.e., sessile polyps, pedunculate polyps) or particular kinds of LNM (i.e., micrometastasis, lateral lymph node). Some of the findings that emerge from the present work call for a number of considerations: it is noteworthy that the female gender appears to be related to an increased risk of LNM (pooled OR with fixed-effect method equal to 0.66; *P*-value 0.019), but this finding was not significant using random-effect method, especially because it is difficult to identify heterogeneity in a so small number of studies. Nevertheless an explanation to this trend was attempted. Hormone receptors expressed on colorectal cancer (CRC) cells could play an important role in this context. The presence of estrogen receptors (ERs) has been clearly demonstrated in 70% of CRCs [16]. Moreover, a number of other authors have shown that tamoxifen has a potent inhibitory action on metastatic cells from colo-rectal cancer in murine models [17]. It must be underlined that in our analysis this association is close to the inferior limits of the statistical significance and hampered by the fact that only two studies analyse this aspect (I2 : 55%). New studies are needed to support this interesting finding. As previously shown in other studies on colo-rectal cancer, our data confirm that the risk of lymph node metastasis is increased in moderate or not differentiated tumours (grading 2-3) (pooled OR 0.40; *P*-value 0.000) [28], invasion of the muscular layer of the intestinal wall (pooled OR 0.44; *P*-value 0.000) [29], lymphatic invasion (pooled OR 0.26; *P*-value 0.000) [30, 31], and vascular invasion (pooled OR 0.46; *P*-value 0.000) [32, 33]. The adequate number of studies included and the absence of heterogeneity between them mean that these outcomes have a high statistical significance. Other tumour variables such as tumour size, tumour budding, perineural invasion, depth of tumour invasion within the submucosal layer (Sm 1, 2, and 3), and distance from the dentate line were investigated either only in a single study or using heterogeneous parameters, thus preventing a reliable meta-analysis. The following clinical-pathological features are worthy of further consideration.

4.1. Tumour Size. Tumour size can be an indicator of technical difficulty and can prevent the risk of postoperative complications (stenosis, leakage) and local recurrence due

to the possibility of excision margin involvement. A tumour size of 3 cm involving <40% of the rectal circumference has been taken as the upper limit by many authors. Some authors reported a trend toward higher local recurrence rates with tumour diameters >3 cm, although without a statistically significant difference [34]. Blumberg et al. [14] studied 3318 patients with intramural cancers (T1 or T2). Tumours classified as large (>3 cm) did not have an increased risk of lymph node metastasis when compared with small lesions (≤3 cm) with a *P*-value of 0.77. Kobayashi et al. [5] analysed 567 consecutive patients who underwent radical resection for T1–T2 lower rectal cancer. The authors divided the lesions into two groups, smaller or equivalent to 2 cm and larger than 2 cm, and did not find any statically significant difference in the incidence of lymph node metastasis between the two groups. Brodsky et al. [15] investigated 154 patients with pT1 or pT2 rectal cancer treated by radical resection. The authors found that increasing tumour diameter did not correlate with increasing incidence of LNM.

4.2. Distance from the Anal Verge. Distance from anal verge is of critical value not only for an increased risk of lymphatic spread but also because it can determine the surgical approach chosen. Steup et al. [35] studied 605 patients with rectal cancer. Of these, 44 were T1, 132 were T2, and 429 had a more invasive cancer. Steup did not study only patients with early rectal cancer, but from the analysis of the authors' findings it can be concluded that lesions of the lower third of the rectum have a higher incidence of lymph node metastasis. Nascimbeni et al. [31] identified an analysis cohort of 353 patients. Only patients with sessile T1 adenocarcinoma who underwent a colo-rectal resection were included in the study. The study results show that of 29 lesions in the lower third of the rectum, 10 (34%) had lymph node metastasis; of the 54 patients with cancer in the middle third of the rectum, 6 (11%) had lymph node invasion; finally, of the 36 patients with a tumour in the upper third of the rectum, 3 (8%) had lymph node metastasis. The findings of the multivariate analysis (*P* 0.007) highlight that lesions of the lower third of the rectum have a higher risk of lymph node metastasis than the other rectal regions.

4.3. Sm 1-2-3. Some authors have analysed the relationship between the depth of invasion and the risk of lymph node metastasis according to Kudo's classification [36]. Nascimbeni et al. [31] studied histological specimens retrospectively from 353 patients undergoing colo-rectal resection for sessile T1 lesions. The authors reported a 1–3% risk of lymph node metastasis in Sm1 cancer and 8% in Sm2, while for Sm3 lesions the risk was 23%. Thus they concluded that the invasion of the lower third of the submucosa (classified as "Sm3") is a significant predictor of lymph node metastasis. Rasheed et al. [13] analysed 313 patients with T1 and T2 colo-rectal cancer operated by radical resection with TME. The statistical analysis of this study failed to demonstrate a strong association between depth of tumour invasion and the presence of lymph node metastasis in T1 colo-rectal cancer. The author's conclusion however is that if depth of mucosal invasion is to be used as a guide to determine the likelihood of successful local curative surgery for rectal cancer, it must be used together with other prognostic indicators of success such as degree of tumour differentiation and evidence of vascular invasion. When the T1 tumour is superficial (Sm1 or Sm2) but one of these additional risk factors is present, the clinician should consider either more aggressive curative resectional surgery or the use of adjuvant oncological treatment in the form of chemotherapy or chemoradiotherapy.

4.4. Perineural Invasion. Perineural invasion refers to cancer spreading to the space surrounding a nerve. Perineural invasion is a well-known risk factor for nodal involvement in different types of tumours. With regard to colo-rectal cancer, Huh et al. [30] identified perineural invasion as the only significant independent factor predicting both overall and disease-free survival in patients with T1 and T2 colo-rectal cancer ($P = 0.004$). They found that although the incidence of perineural invasion was only 4.5%, the odds ratio of lymph node metastasis increased 10-fold for patients who had perineural invasion, as compared with those who did not. In their study, Saclarides et al. [19] found the same relationship between perineural invasion and nodal involvement as Huh.

4.5. Tumour Budding. Tumor budding is defined as an isolated cell or a small cluster of up to four carcinoma cells in the invasive front, and the presence of more than 10 budding foci when viewed at a 200-fold magnification is considered positive for tumour budding, based on the data from Ueno et al. [37].

Several reports have suggested that tumour budding is probably the first histological event of invasion and metastasis in CRC. Okuyama et al. [38] reported that budding is a risk factor for lymph node metastasis in colo-rectal cancer, especially in the early stage. Homma et al. [39] examined tumour budding as a quantitative parameter to ascertain whether it could be used as an index for estimating the aggressiveness of early rectal cancers. He has found that a high tumour budding grade is a risk factor for lateral lymph node (LLN) metastasis and could be used as a criterion for LLN dissection. Goldstein and Hart [16] analysed 73 abdominal resection specimens and found a correlation between lymph node metastasis and tumour budding, even though with low statistical significance (*P*-value <0.01). He suggests that pathologists should scrutinise the leading edge of locally excised cancer for foci of microacinar nest tumour budding or undifferentiated cells, because a patient is at increased risk of lymph node metastasis if any of these features is extensively present.

The results of the above studies, although not yet proven to be statistically significant, serve as an incentive to intensify the search of risk factors for lymph node invasion and the development of mathematical models to determine how much the risk increases in the case of coexistence of two or more of these features. Further studies are necessary on large casistics of ESRC with multivariate analysis of all the above-mentioned clinical-pathological tumour features associated with lymph node invasion, in order to quantify the weight of each of these risk factors. A scoring system based on studies could be a good instrument to stratify patients into different

risk classes and direct them towards the most appropriate treatment.

5. Conclusions

(i) Only the absence of each of the variables identified in this study (high-grade tumours, invasion of the muscular layer of the intestinal wall, lymphatic and vascular invasion) can justify LET as a radical treatment for rectal cancer.

(ii) If one of these risk factors is present, the risk of lymph node metastasis N+ is real and the decision whether to refer the patient to an RS or an LE/MET in addition to radio-and/or chemotherapy should be taken in a multidisciplinary context, also taking into consideration patient characteristics and expectations.

(iii) A number of other tumour features are worthy of further investigation as potential risk factors for nodal involvement: gender, tumour size, tumour budding, distance from the dentate line, perineural invasion, and depth of submucosal invasion (Sm1, 2, and 3).

(iv) Further work is needed on large casistics of ESRC with multivariate analysis of all the above-mentioned risk factors in order to evaluate the weight of each of them and set up a scoring system to quantify the real risk of nodal involvement, stratify patients, and direct them to the most appropriate treatment.

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Review Article

Intersphincteric Resection for Low Rectal Cancer: An Overview

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The treatment of rectal cancer has evolved from being solely a surgical endeavor to a multidisciplinary practice. Despite the improvement in outcomes conferred by the addition of chemoradiation therapy to rectal cancer treatment, advances in surgical technique have significantly increased rates of sphincter preservation and the avoidance of a permanent stoma. In recent years, intersphincteric resection for low rectal cancer has been offered and performed in patients as an alternative to abdominoperineal resection. An overview of this procedure, including indications, oncological and functional results based on current literature, is presented herein.

1. Introduction

There has been an evolution in the treatment of rectal cancer in recent times. A few decades ago, rectal cancer treatment was solely a surgical endeavour. Nowadays, it has evolved into therapy involving several disciplines. Nevertheless, surgery remains the cornerstone of curative treatment. The incorporation and widespread use of total mesorectal excision (TME) as the standard mode of surgical resection of adenocarcinoma of the rectum has been the most important surgical development in outcomes improvement for this disease [1, 2]. Supervised teaching of TME, as well as the detailed pathological audit of resected specimens, has also led to better oncological results [3]. Advances in surgical technique with the use of either advanced stapling or manual coloanal anastomoses have allowed for achieving continuity of the gastrointestinal tract at levels closer to the anal verge than those achieved historically. The advent of adjuvant and neoadjuvant chemoradiotherapy has also increased local control of disease [4] and in some instances has led to increased survival [5].

Surgery for rectal cancer in recent years has focused on anatomic and functional preservation of the sphincter without compromising oncological outcomes. Radical surgical treatment of cancers in lower third of the rectum has traditionally included low anterior resection (LAR) and coloanal anastomosis, and abdominoperineal resection (APR). Historically, the decision-making for sphincter-saving procedures has been related to the distance between the tumor and the anal sphincter complex [6]. In the 1980s, a distal margin of 5 cm was required. In the ensuing decades, the "2-cm-rule" was accepted and adopted [6]. This rule has been challenged, however, and currently a distal margin of 1 cm is accepted as being appropriate for optimal oncologic outcome. This provides a greater proportion of rectal cancer patients with the possibility of sphincter preservation [7, 8]. Recently, adequacy of the circumferential resection margin is being considered of equal, if not greater, importance in the risk of local recurrence of rectal cancer [9]. In recent years, intersphincteric resection (ISR) has been proposed to offer sphincter preservation in patients with very low rectal lesions, as an alternative to APR. Of note, APR has consistently had higher rates of local recurrence rates (up to 22%) compared with LAR [10, 11].

2. Materials and Methods

A literature search for relevant articles in the English language associated with intersphincteric resection (ISR) between 2000 and 2012 was undertaken. All articles regarding intersphincteric resection were case series from single institutions or systematic reviews. Case reports were

excluded from this overview. Medline was the search engine utilized.

2.1. ISR: Definition. Schiessel and colleagues initially described the technique of ISR [12]. During ISR, a transanal division of the rectum, with removal of part or the entire internal anal sphincter (IAS) after TME, is performed, thus obtaining an adequate distal margin. Restoration of bowel continuity is achieved by performing a hand-sewn coloanal anastomosis.

3. Indications and Preoperative Evaluation

When planning for proctectomy with ISR for rectal cancer, careful patient selection is paramount. Tumor height, its relationship to each component of the sphincter complex, and the presence or not of regional lymph node or distal metastases needs to be evaluated. For this reason, a combination of a careful physical exam and imaging modalities is utilized. Preoperative evaluation by the surgeon by means of digital rectal exam and rigid proctoscopy provides information regarding the level of the distal edge of tumour relative to the "anal anatomic component of interest," which varies among experts in the literature [13, 14]. Anal anatomic components of interest include the anal verge, the dentate line and the anorectal ring. Specialized imaging is required to study the relationship of the IAS and external anal sphincter (EAS) with the tumour. Invasion of these structures by the lesion can also be depicted. Endorectal/endoanal ultrasound and magnetic resonance imaging (MRI) are performed for this reason. In addition, high-resolution MRI is accurate at estimating the circumferential margin; with an overall accuracy of 88% [15]. Additional cross-sectional imaging evaluates the presence of distal metastases.

Inclusion criteria for performance of ISR include the following:

(i) tumours located 30 mm from anal verge;

(ii) tumours located 15 mm from dentate line;

(iii) tumours located 1 cm from anorectal ring;

(iv) local spread restricted to the rectal wall or the IAS;

(v) adequate preoperative sphincter function and continence;

(vi) absence of distant metastases.

Contraindications to the performance of ISR are the presence of fecal incontinence, T4 lesions, undifferentiated tumors [10], as well as tumors invading the puborectalis and the external anal sphincter (EAS) [14].

A significant number of patients may require neoadjuvant chemoradiation therapy. In a systematic review of ISR involving 14 studies and 1289 patients who underwent ISR by Martin and colleagues, 44% of patients had stage III disease and 38% underwent preoperative chemoradiation overall [14]. Of note, in certain studies included in the review, preoperative radiation was a contraindication to performing ISR due to possible adverse functional effects. This is in contrast to a recent study by Denost and colleagues in which 93% of patients undergoing ISR received preoperative radiotherapy [16].

3.1. Surgical Technique. The principle of the ISR technique is based on an anatomic dissection plane between the IAS and EAS [17].

The technique incorporates a combined abdominal and perineal approach. Initially, high ligation of the inferior mesenteric vessels is done. This is followed by TME down to the level of the pelvic floor. TME can be performed through a laparotomy or laparoscopically [6]. Subsequently, a per anal resection of the IAS is undertaken. The distal resection line may be at the intersphincteric groove (total ISR), between the dentate line and the intersphincteric groove (subtotal ISR), or at the dentate line (partial ISR).

Additional maneuvers to reduce the risk of local tumor cell implantation include closure of the rectal stump, cytocidal washout, and pathological evaluation of the distal margin with frozen section analysis [18].

The specimen is usually delivered per anum. A hand-sewn coloanal anastomosis with construction of a colon J-pouch, transverse coloplasty, or straight anastomosis is performed.

Certain groups, especially in Japan, perform lateral pelvic lymph node dissection for TNM stage III tumors [13].

A defunctioning temporary stoma is fashioned, which is closed 6 weeks to 12 months from the primary operation.

3.2. Short-Term Adverse Events. The overall operative mortality associated with ISR is 0.8% [14]. The cumulative morbidity rate is reported to be 25.8%. Anastomotic leak was experienced after a mean of 9.1%, and the rate of pelvic sepsis was 2.4% [14].

The rate of clinically apparent anastomotic leakage following stapled anastomosis following anterior resection is in the range of 3–15%. Rates of leakage rise significantly for more distally sited anastomoses [19]. Anastomotic leakage is associated with postoperative anastomotic stricture, cancer recurrence, poor postoperative function, as well as increased operative mortality [20].

In conclusion, ISR can be performed with acceptable rates of anastomotic leakage and low operative mortality.

3.3. Oncologic Outcomes. Radical surgical removal of the tumor is the only chance for permanent cure of rectal cancer, despite all progress in the development of oncologic therapy [10]. Rullier and colleagues [6] reported a local recurrence rate of 2% in a series of 92 patients undergoing ISR. Most patients (78%) had T3 lesions, and 88% underwent long-course neoadjuvant radiochemotherapy. The overall 5-year survival rate was 81%, with a 5-year disease-free survival of 70%. Yamada et al. reported a similarly low 2.5% cumulative 5-year local recurrence rate, a 5-year disease-free survival rate of 83.5% for stage II patients and 72% for stage III patients [13].

Tilney and Tekkis performed a literature search to identify studies reporting outcomes following ISR. Twenty-one studies accumulating a total of 612 patients were identified [20]. The pooled rate of local recurrence was 9.5% with an average 5-year survival of 81.5%. Distant metastases occurred in 9.3%. In Martin's systematic review, the mean distal margin free from tumour was 17.1 mm, CRM-negative margins were achieved in 96% of patients, and the overall local recurrence rate was 6.7% (range : 0–23%). The 5-year overall and disease-free survival rate was 86.3% and 78.6%, respectively [14].

Rates of local recurrence following low anterior resection for the treatment of rectal cancer are commonly reported in the range of 2.6–32% following surgery alone [21]. Preoperative chemoradiation therapy has led to local recurrence rates in the 6% range [4].

Therefore, the performance of ISR for treatment of very low rectal cancer affords similar oncologic outcomes to those of conventional resections. Moreover, Saito et al. [22] compared outcomes of patients undergoing ISR with patients undergoing APR. Similar local recurrence rates (ISR = 10.6%, APR = 15.7%, P = NS) and 5-year disease-free survival (ISR = 69.1%, APR = 63.3%, P = NS) were reported. Patients undergoing ISR had significantly longer 5-year overall survival compared with patients undergoing APR (ISR = 80%, APR = 61.5%, $P < 0.05$). In conclusion, local and distant oncologic outcomes are not comprised with ISR. It is considered that the risk of local recurrence may be a function of circumferential margin involvement rather than distal margin involvement.

Risk factors for local and distant recurrence after ISR were reported by Akasu et al. [23]. Local recurrence rate was 6.7% and distant recurrence was 13%.

In the multivariate analysis, risk factors for local recurrence included positive microscopic resection margins, focal d-differentiation of tumor (tumor budding), and elevated preoperative levels of CA 19-9 (>37 U/mL). The identified risk factors for distant recurrence were pN1, pN2 disease, poor differentiation, and distance of tumor from anal verge, 2.5 cm.

3.4. Anorectal Physiology. An important goal of sphincter-preserving surgery is to reach acceptable quality of life levels by preserving fecal continence. The main concern of the ISR technique is functional outcome. Physiologic studies have shown that anal resting pressure is due to the IAS for 55%, the hemorrhoidal plexus for 15%, and to the EAS for 30% [24].

Total or partial excision of the IAS is bound to affect continence. Furthermore, preoperative radiation therapy may cause additional loss of sphincter function.

Kohler et al. reported a 29% reduction in resting anal pressure following ISR. Squeeze pressure recovered to preoperative levels after 12 months [25].

Rullier et al. compared outcomes in patients undergoing partial or subtotal IAS resection. Subtotal excision of the sphincter was associated with significant reduction in resting but not squeeze pressure after ISR [26]. Of note, there have been no studies assessing anorectal physiology and continence after neoadjuvant radiation and prior to ISR.

3.5. Functional Outcomes and Quality of Life. As an antithesis to an aphorism by the famed architect Louis Sullivan, in rectal cancer surgery, "function follows form" (the type of operation performed). Loss of a part of the sphincter complex, loss of the rectal reservoir, and radiation is bound to have adverse effect on continence and defractory function.

Bretagnol and colleagues reported that fecal continence measured by both the Kirwan and Wexner scores was significantly worse after ISR. In addition, the need for antidiarrheal medication was higher in patients undergoing ISR compared with patients that had undergone conventional coloanal anastomosis [27].

Frequency, urgency, the Wexner score, and the Fecal Incontinence Severity Index (FISI) were significantly improved following colonic J-pouch reconstruction compared with straight coloanal anastomosis [27].

Regarding quality of life (QOL), Bretagnol et al. used both the SF-36 and fecal incontinence quality of life (FIQL) to compare QOL between patients undergoing ISR and conventional coloanal anastomosis. There was no difference in the QOL scores between ISR patients and conventional coloanal anastomosis patients in the physical and mental subscales of the SF-36.

In Martin's systematic review, the mean number of bowel movements per day was 2.7. Nearly half (51.2%) of patients reported "perfect continence," about a third (29.1%) reported experienced fecal soiling, 23.8% had flatus incontinence, had 18.6% had urgency. In a large study assessing functional outcomes after ISR, Denost reported that half of the patients had a "good functional result," 39% had minor fecal incontinence, and 11% had major incontinence [16]. In the same study, the only independent predictors of "good" continence were a distance of tumour greater than 1 cm from the anorectal ring and anastomosis higher than 2 cm from the anal verge.

Possible technical modifications when performing ISR may improve functional outcomes. These include partial ISR (when possible) and construction of a colon J-pouch. These are known to improve function in the first year after surgery. However, the effect is not sustained after 2 years [14].

4. Conclusion

In order to be successful in treating rectal cancer, good oncologic outcome is the first priority. Equally important is the achievement of an acceptable quality of life for the patient. The avoidance of a permanent stoma and all of the concomitant morbidity associated with it may be of greater importance to the patient. Low anterior resection with intersphincteric dissection and partial or total excision of the IAS may be offered an alternative to APR in selected patients. The functional outcomes after ISR are expected to be inferior to those of conventional low anterior resection; this information needs to be frankly communicated to the patient. The morbidity, mortality, and oncological outcomes

after ISR are acceptable. Careful patient selection and sound operative technique, with emphasis on high-quality preoperative imaging and functional assessment, should lead to superior results. These principles have been closely examined at our own institution, and we have embarked on our first cases of intersphincteric resection in selected patients.

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Clinical Study

Glove Port Technique for Transanal Endoscopic Microsurgery

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Introduction. Despite initial enthusiasm, the use of transanal endoscopic microsurgery (TEM) is still quite limited at present because of the expense of highly specialized equipment and the complexity of the learning curve. Furthermore, some authors report a relevant, although temporary, effect on anorectal function because of the considerable anal dilatation which can even produce a rupture of the internal anal sphincter. The "glove TEM" proposes itself as an alternative to traditional TEM that could settle these problems. *Materials and Methods*. The technique is accurately described together with the necessary equipment to perform it. Between 2011 and 2012, we operated eight patients with this technique for rectal adenomas or early carcinomas achieving R0 resection in all cases and reporting no early or late complications during the first five months of followup. *Discussion*. This technique offers multiple advantages compared to the original TEM. (i) It allows the use of all available laparoscopic instruments. (ii) It gives a great manoeuvrability of the instruments in contrast to rigid rectoscope systems. (iii) Given the limited length of the device, it permits to operate on tumors closer to the dentate line. (iv) It is less traumatic to the anal sphincter. It is definitively much cheaper. *Conclusions*. We believe that this new technique is easy to perform, cost-effective, and less traumatic to the anal sphincter compared to traditional TEM.

1. Introduction

The transanal endoscopic microsurgery (TEM), originally designed by Buess et al., is a safe and minimally invasive surgical technique for the treatment of benign adenomas and early-stage carcinomas of the low, middle, and upper rectum not amenable to traditional colonoscopic excision [1, 2]. TEM satisfies two major aims: complete removal of the lesion and maintenance of sphincter function. Additionally, TEM offers the benefit of avoiding the trauma and morbidity of the conventional open surgery major leading to a better quality of life for the patient, less postoperative hospital stay, and reduced morbidity and mortality rates. The TEM procedure involves a transanal approach using a set of endoscopic surgical instruments that can reach further into the rectum than other forms of local excision together with a form of enhanced vision. The excellence of the image allows for more precise excision; according to many authors, this implies a better oncologic outcome and a lower reoperation rate [3, 4]. Following our experience with the laparoscopic single-port surgery (SILS) and particularly with a homemade device composed of a disposable wound retractor (Alexis) and a simple surgical glove [5], we recently started to use the same device for transanal endoscopic surgery. In this paper, we describe this technique, reporting the results of our first eight cases.

2. Materials and Methods

We use a wound retractor (Alexis) applied through a disposable circular anal retractor (Sapimed SpA) well fixed with skin stitches (Figure 1). A powder-free surgical glove is then put, air tight, on the wound retractor, and three or

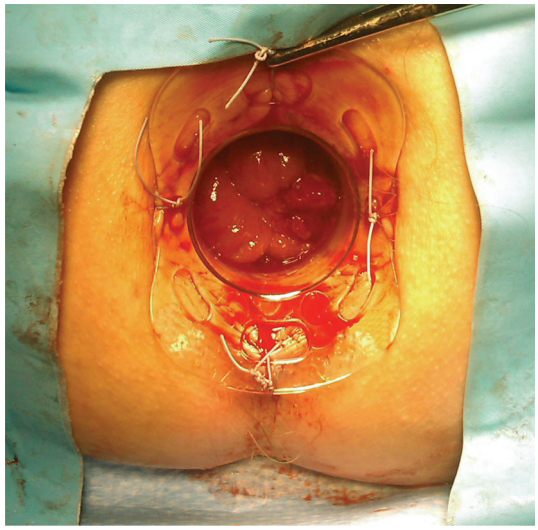

Figure 1: The disposable anal retractor is well fixed with four skin stitches.

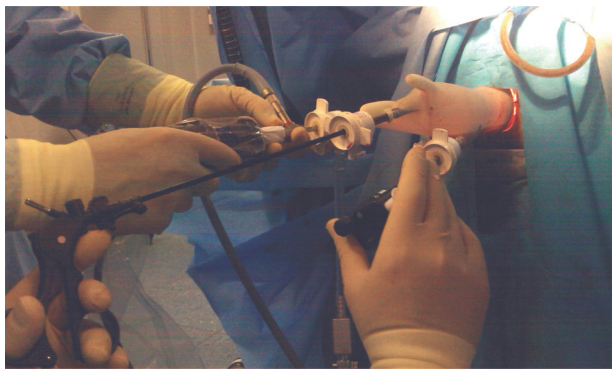

Figure 2: The laparoscopic camera is inserted via the middle finger port.

four trocars are inserted via the finger tips. A laparoscopic camera is inserted via the middle finger port (Figure 2). All laparoscopic standard instruments can be used without any bond or limitation in maneuverability since they are free to work through the wound retractor. The pneumorectum is maintained at almost 12 mmHg. The operation then proceeds exactly like in the traditional TEM, with the mucosal marking all around the lesion. The tumor is then resected dissecting the rectal wall along the marking deeply to the mesorectal tissue preserving wide safety margins all around the lesion. The smaller length of the anal retractor, compared to the traditional TEM, allows easily excising the distal margin of the specimen even at only 1.5/2 cm from the dentate line. The excisional area is then closed with an absorbable continue suture (Figure 3).

3. Results

We recently used this technique on eight patients, five large rectal adenomas, two T2 cancers of the proximal rectum not amenable for abdominal surgery, and one T1 cancer of the distal rectum, achieving R0 resection in all cases. The average distal margin from the anal verge was 6,5 cm (range 1,5–12 cm). The hospital stay was short, with all patients discharged in the first postoperative day. No early or late complications were reported during the first five months of followup.

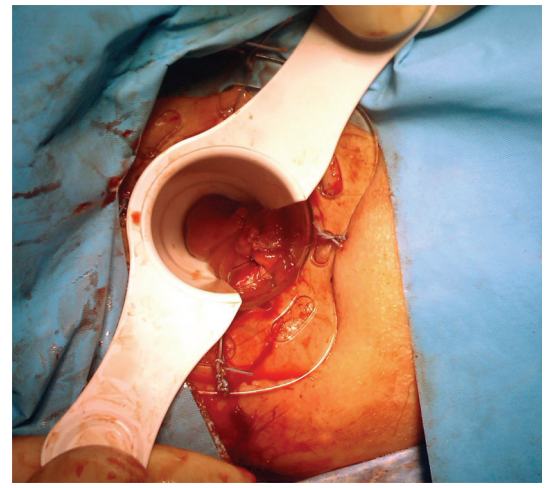

Figure 3: Final result after suturing the excisional area.

4. Discussion

The TEM approach offers patients with rectal lesions, an additional treatment option with several advantages: the major benefits of TEM include avoidance of a major abdominal operation, avoidance of a colostomy, visualization improved over that of customary transanal approach, and ability to expand transanal excision proximally. Nevertheless, despite these advantages, the use of TEM is still quite limited. The reasons for this unrealized potential are to be found mostly in the high cost of the equipment and in the complexity of the learning curve. The risks of TEM and local excision may include infection, bleeding, and perforation into the peritoneal cavity or vagina. These are fortunately rare but would require further surgery. Furthermore, some authors report a relevant, although temporary, effect on anorectal function because of the considerable anal dilatation due to the rectoscope wide diameter (40 mm wide). Gracia Solanas et al. found TEM procedure can result in a rupture of the internal anal sphincter (25% of cases on a casistic of 40 patients that), with the consequent decreasing in anal resting pressure, and in a dilatation without rupture of external sphincter what produces a decreasing of maximal squeeze pressure. The fall of anal pressures had minimal clinical repercussion when the sphincter is intact, but, when the internal anal sphincter is broken, a temporal incontinence develops [6]. In another study conducted by Herman et al. [7], the effects of TEM on anorectal motility and function are investigated. The authors report the results of anorectal motility studies (using pull-through anorectal manometry and rectal barostat) and endoanal ultrasound

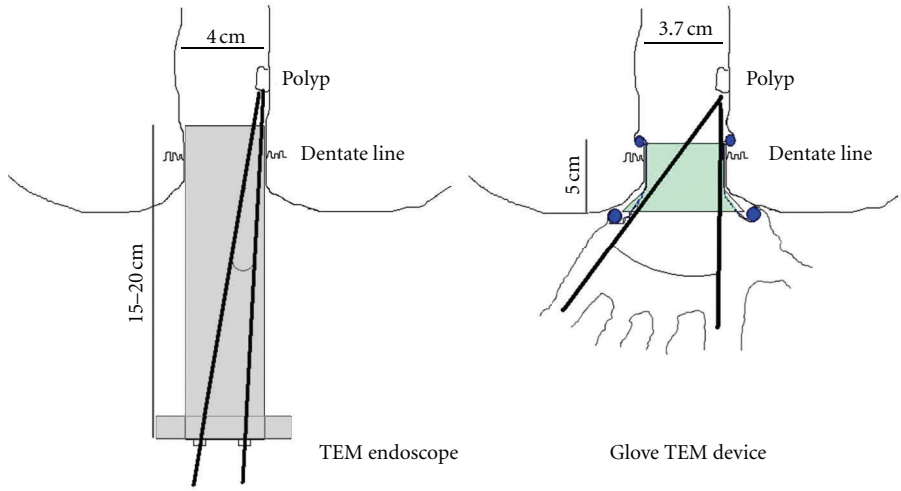

Figure 4: Traditional TEM endoscope versus Glove TEM device: dimensions and instruments working angles.

prior to surgery and 3 weeks and 6 months after TEM on 33 patients with rectal tumors. The authors conclude that TEM has relevant but temporary effects on anorectal motility; nevertheless, only few motility disturbances are reflected in continence results such as liquid stool/flatus incontinence, soiling, stool frequency, and urgency (21%), since 79% of patients following TEM reported perfect continence control.

In our opinion, the glove TEM technique offers multiple advantages:

(1) the possibility of using almost all available laparoscopic instruments with the maximum range of maneuverability in contrast to rigid and long rectoscope systems. As is shown in Figure 4 traditional TEM endoscope is 15–20 centimeters long depending on the model; the anal dilator utilized in the Glove TEM is only 5 centimeters long allowing to operate with a broader angle between the instruments especially when the lesion is in the lower rectum;

(2) the ability to operate on tumors closer to the dentate line till a minimum distance of 1,5/2 cm given the above-mentioned limited length of the Glove TEM device together with its great handiness;

(3) minor trauma to the anal sphincter due to the smaller size of the retractor which is only 3.7 centimeters compared to the 4 centimeters of the TEM endoscope. Although the two devices have a variation of no more than 3 mm in diameter, this entails a difference of almost 1 centimeter in their circumferences (11,61 cm versus 12,56 cm) which we believe could be sufficient to consider the glove TEM system less stressful to the anorectal function. Furthermore, even though our casistic is too small to gain statistical significance, we have to note that we did not report any clinically detectable anorectal dysfunction on the patients we operated with the Glove TEM;

(4) last but not least, the glove TEM is much cheaper than the traditional TEM [8] because it can be performed with the usual laparoscopic multiuse equipment through a simple homemade device whose cost is approximately 100 USD (one disposable anal dilator, one Alexis wound retractor, and a surgical glove).

Nevertheless, we have to report that some pitfalls emerged in our initially experience with this technique. Firstly, we strongly suggest to use thin (5 mm) and long laparoscopic camera (50 centimetres) in addiction to three slim trocars inserted through finger tips to avoid conflicts between instruments during the operation. Secondly, a hand support of the trocars and a visual assistance are necessary during each introduction and extraction of the laparoscopic instruments since the glove's flexibility and elasticity make these operations extremely troublesome and expose the glove to the risk of accidental perforation with consequent gas leakage. New devices developed for laparoscopic SILS (GelPOINT, OCTO Port) in substitution of the glove technique could probably settle these problems.

5. Conclusions

On the basis of our early experience, we believe that glove TEM is a promising surgical technique, safe, effective, and easy to install and to perform. It is made from commonly used and relatively inexpensive surgical equipment and offers the possibility to use all the conventional laparoscopic instruments with an amazing manoeuvrability thus avoiding long and complex learning curves for a laparoscopic surgeon. Our experience demonstrates that this technique can allow use of transanal endoscopic microsurgery in a broader spectrum of patients than maybe otherwise possible for economic and technical reasons.

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Review Article

Surgical Management of Locally Recurrent Rectal Cancer

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Developments in chemotherapeutic strategies and surgical technique have led to improved loco regional control of rectal cancer and a decrease in recurrence rates over time. However, locally recurrent rectal cancer continues to present considerable technical challenges and results in significant morbidity and mortality. Surgery remains the only therapy with curative potential. Despite a hostile intra-operative environment, with meticulous pre-operative planning and judicious patient selection, safe surgery is feasible. The potential benefit of new techniques such as intra-operative radiotherapy and high intensity focussed ultrasonography has yet to be thoroughly investigated. The future lies in identification of predictors of recurrence, development of schematic clinical algorithms to allow standardised surgical technique and further research into genotyping platforms to allow individualisation of therapy. This review highlights important aspects of pre-operative planning, intra-operative tips and future strategies, focussing on a multimodal multidisciplinary approach.

1. Introduction

Local recurrence of rectal cancer is difficult to treat, may cause severe disabling symptoms, and often holds a dismal prognosis. Surgery remains the cornerstone of management for the majority of primary rectal cancers. Despite a marked improvement in local control with the popularisation of Total Mesorectal Excision (TME) and the use of improved chemoradiotherapeutic regimen, recurrence continues to present a significant clinical problem. Refinements in management have, however, led to a decrease in locoregional rectal cancer recurrence rates from 25–40% to 4–8% [1]. Since 20% to 50% of these patients has local recurrence in the absence of distant metastasis, it is intuitive that surgical management represents a viable treatment option [2]. Surgery for locally recurrent rectal cancer, however, requires the undertaking of complex techniques in a hostile operative environment and in many cases requires input from other specialities such as urology, gynaecology and vascular teams. These surgeries should in principle only be performed in a tertiary centre with appropriate surgical, anaesthesiology, and intensive care expertise. Postoperative morbidity is high, ranging from 15–70% and increases with the complexity of resection performed [3, 4]. As a result, surgical management of local recurrence of colorectal cancer has not attained the international approval which has been bestowed upon resection of distant metastases such as hepatic disease. Despite many potential pitfalls, surgery remains the only therapy with curative potential and safe surgery is feasible. This paper highlights pertinent issues regarding surgical preparation and techniques with a focus on the importance of a multimodal approach.

2. Mode of Presentation and Risk Factors

In 70% of cases, recurrence of rectal cancer occurs within two years of primary surgery, while 85% occurs within 3 years [4, 5]. Mode of presentation is varied and may be dependent on the site of disease. Up to one-third of patients does not present with any symptoms [4, 5], emphasising the importance of a carefully designed and diligent schedule of postoperative followup. A recent population-based cohort study of 57 patients concluded that followup after rectal cancer surgery by annual clinical examination is not sufficient. They reported that at diagnosis of local recurrence 86% of

patients was symptomatic and 70% was diagnosed between scheduled follow-up visits [6]. The nature of this schedule is dependent on the type of primary resection performed. After sphincter-preserving surgery, surveillance to facilitate early diagnosis of recurrence should comprise digital rectal examination, sigmoidoscopy, and enquiry regarding symptoms of bleeding or changes in bowel habit. In contrast, the majority of local recurrences after abdominoperineal resections are diagnosed after detection of elevated CEA levels or upon report of pelvic pain [7]. When present, symptoms tend to be disabling and persistent. Refractory pelvic pain, tenesmus and malodorous discharge are common [8] and quality of life is often detrimentally affected [9, 10]. Pain on presentation has been identified as a significant predictor of inferior long-term survival [11, 12]. This is likely related to the association between extent of pain and degree of fixation in the pelvis, reflecting a more advanced stage of local recurrence at presentation and therefore worse prognosis.

Several risk factors are reported to be associated with local recurrence. These may be broadly grouped into pathological, anatomic, and surgical factors. Degree of lymphovascular invasion, differentiation, and tumour size has been associated with increased risk of local recurrence [13]. Anatomically, positive circumferential or distal resection margin at initial resection, including positive microscopic margins, increases risk. In patients who have received neoadjuvant chemoradiation, a margin of less than 1 cm is considered oncologically adequate [14]. Patients operated on in high-volume centres have also been reported to enjoy lower recurrence rates [15] and surgical technique may also play a role. In selected series, abdominoperineal resection (APR) has been associated with higher recurrence rates than sphincter-preserving surgery [16]. In addition, newer lower excision techniques such as transanal endoscopic microsurgery (TEMS) may also increase risk and patients should be carefully selected since recurrence rates are increased according to stage. A retrospective analysis of 74 patients with T1 and T2 rectal adenocarcinoma treated with TEMS and 100 patients with T1N0M0 and T2N0M0 rectal adenocarcinoma treated with radical surgery showed a statistical difference in 5-year local recurrence rates for T2 but not T1 cancers [17]. Elevation in serum CEA lacks sensitivity (59%) but has a specificity of 84% [18]. Recent efforts towards identifying novels biomarkers to predict recurrence in colorectal cancer have shown early promise [19]; however, further investigation is necessary.

3. Anatomical Classification

Although TME has contributed dramatically to improved management of primary rectal cancer, its popularisation decreases the likelihood that a recurrent neoplasm will remain confined to a specific compartment due to the absence of visceral rectal fascia [20]. Locally recurrent rectal cancer is generally grouped according to anatomic location. An alternative system, used at the Mayo Clinic, classified these tumours according to the presence of symptoms, with a particular focus on pain, as well as degree of fixation. Although the anatomical system may be imperfect, it is currently the most widely accepted method of classification. Due to the fact that surgical approach is largely dictated by the location of recurrence and relationship to surrounding structures, the use of an anatomical classification system is practical in this setting. Axial recurrences are confined to the pelvic organs without invading into bone or sidewall. This includes anastomotic recurrence after low anterior resection (LAR), recurrence after local excision procedures, such as, TEMS and perineal recurrence after APR [21]. Tumours in the presacral space which invade into the sacrum are grouped as sacral or posterior recurrences. Anterior recurrences may involve genitourinary organs. Sidewall or lateral recurrence is diagnosed when tumour invades iliac vessels, pelvic autonomic nerves, pelvic ureters or extends through the greater sciatic foramen [22]. A growing body of evidence shows prognosis varies according to site of recurrence. Moore et al. reported that lateral or sidewall recurrences were less likely to be curatively resected than axial or anterior [14].

4. Surgical Management: Preoperative Preparation

Without intervention, prognosis of recurrent rectal cancer is dismal with median survival typically 6-7 months [8, 23]. These patients endure symptoms which are catastrophic to quality of life including refractory pain, discharge, and tenesmus. Only 30% of patients achieve symptom control with radiotherapy alone and this treatment option rarely improves survival beyond one year [24]. Radical surgery offers the only hope of complete therapy and up to 50% of cases is confined to the pelvis and thereby labelled theoretically amenable to cure [25]. Additionally, in carefully selected patients, surgery may be of benefit even in the presence of distant metastases with metastatsectomy gaining favour [24]. Morbidity and mortality rates of radical surgery for recurrences are high and can reach 60% and 8% (at 3 months), respectively [5].

Surgery for recurrent rectal cancer is a challenging undertaking which should ideally be individualized and performed in a specialist unit with early involvement of a multidisciplinary team. A recent systematic review reported that the proportion of potentially curative resections has increased in recent years, probably due to improved staging, neoadjuvant treatment, and increased surgical experience in dedicated centres, which has resulted in improved survival [26]. Resections of this nature, however, remain vulnerable to complication and the operative environment is often hostile. Normal tissue planes are frequently obliterated, tissues may be friable from previous irradiation, dense adhesions are often present, and fibrosis may be extensive. Unexpected discovery of previously undiagnosed peritoneal or visceral metastases is not uncommon and is a poor prognostic indicator. As a result, as much information as possible should be gathered preoperatively and communication with the patient regarding inherent risks is crucial. A specialist colorectal nurse should be involved at an early stage as a link between the patient and the lead clinician. A systematic

approach is optimum and some guidance can be found in the literature. Bouchard and Efron recommend a full blood panel including carcinoembryonic antigen testing as well as thorough physical examination [21]. Where necessary this should be supplemented by digital rectal examination, vaginal examination, sigmoidoscopy, cystoscopy, or examination under anaesthesia. Full details of previous surgeries should be sought if not performed in the same centre. Mirnezami et al. advocate early assembly of a multidisciplinary which may include orthopaedic, urologic, gynaecologic, and vascular surgeons as well as colorectal specialists [24]. Plastic surgeons may also be required as recent technical improvements in reconstructive options have contributed significantly to outcome and quality of life.

Thorough preoperative staging is crucial to optimum planning and determination of resectability. Mirnezami et al. provide an excellent algorithm for initial approach to surgically resectable recurrent rectal cancer [24]. Computerized Tomography (CT) can be used to confirm the presence of a mass and investigate the presence of distant metastases. If a distant lesion is identified or if occult tumour or metastases are suspected, Positron Emission Tomography (PET) with fluorodeoxyglucose (FDG) may provide useful information to establish a diagnosis and to assess the location and metabolic activity. The ability of Magnetic Resonance Imaging (MRI) to differentiate soft tissue contrast resolution makes it useful in assessing the precise site of the tumour including relationship to vessels. Both MRI and CT demonstrate low sensitivity in accurate assessment of side wall involvement [21]. With MRI the danger of false-positive readings in patients who have received recent radiotherapy remains an issue and differentiation between fibrosis and malignant tissues is not definitive. A recent retrospective study assessing the accuracy of preoperative magnetic resonance (MR) imaging for identification of tumour invasion into pelvic structures in 40 consecutive patients found that MRI had a negative predictive value of 93%–100%. Interestingly, assessment failures were mainly because of misinterpretation of diffuse fibrosis, especially at the pelvic side walls [27]. For this reason, it is crucial to procure tissue for histological confirmation of the recurrence where possible either by colonoscopy-or CT-guided biopsy. In cases where this is not possible, a detailed and frank patient discussion is imperative, conveying the high-risk nature of surgery versus uncertainty regarding the diagnosis. If patient or surgeon is reluctant to proceed, watchful waiting is an alternative course of action [24].

5. Surgical Management: Timing, Contraindications, and Resectability

Determination of resectability should not only assess anatomic feasibility of performing an R0 resection but also ability to attain an acceptable level of morbidity and mortality. Careful patient selection is crucial and when surgery is planned, rigorous preoperative assessment of fitness is necessary. High patient comorbidity load often represents the first contraindication to surgery. If physical examination reveals lower limb oedema, a cause should be sought as lymphatic or venous obstruction represents an absolute contraindication to surgery. Other anatomic factors identified in preoperative imaging, such as, encasement of iliac vessels, bilateral ureteric obstruction of circumferential involvement of the pelvic wall. This is because ability to obtain negative margins is significantly compromised by involvement of these structures [14]. Tumours which involve the ureters or iliac vessels may also be associated with bony involvement at S1 and S2 level. Sacral invasion above the S2-S3 junction will almost invariably require the patient to undergo internal fixation due to sacroiliac instability. Relative and absolute contraindications are the subject of some controversy in the literature with many small studies reporting conflicting results. Henry et al., for example, conducted a retrospective analysis of single-centre experience and concluded that hydronephrosis should not constitute an independent contraindication to attempted curative resection [28]. Maslekar et al. also recently reported resection of recurrence with encasement of external iliac vessels [29]. With advances in surgical technique it is likely that in the future more and more contraindications may move from being categorised as absolute to relative.

If the patient is radiotherapy naive, at our centre, we administer long-course chemoradiotherapy (40–50 Gy) to improve local control and potential for curability. The timing of surgery may then be dictated by a 6–8 week wait after treatment followed by thorough restaging [30]. It is well recognised that the normal tissue tolerance of the intestine is often the dose-limiting factor in the administration of pelvic and abdominal radiotherapy.

6. Surgical Management: General Principles

Having completed the extensive preoperative phase, some general principles apply to operative approach. Aids such as ureteric stents, radiological tattooing of surface markings for the level of sacrectomy, and preoperative marking of stoma site may be helpful [24]. A multimodal strategy has gained favour in the recent past. If intraoperative radiotherapy is planned certain infrastructure is required, such as, a specialised table to enable patient positioning and optimum delivery. Generally, the patient is first put in the Lloyd-Davies position but may need to be moved to the prone position if sacral resection is planned. Exposure is critical and in our practice we generally make an incision from the xiphisternum to symphysis pubis. Wound protectors may be used to reduce potential for infection and deposit of tumour cells in the wound. Many surgeons favour a Bookwalter retractor for exposure. Complete mobilization of the small intestine is advised to rule out the presence of metastases. This phase may be time consuming due to the potential requirement for extensive adhesiolysis and the small bowel is often adherent within the pelvis. If a small bowel segment is adherent to the pelvic malignancy then it must be removed en-bloc. If ascitic fluid is present a sample is sent for cytology. In commencing pelvic dissection, Bouchard and Efron recommend beginning in a plane free of adhesions in an area away from the tumour where possible [21].

Intraoperatively, as with imaging, difficulties may arise in accurately distinguishing tumour from radiotherapy-related fibrosis. This conflict limits the use of less radical approaches significantly. There may a role for the use of frozen section intraoperatively if this helps in the decision to proceed to a more aggressive dissection versus conservative management. In many cases it may take several hours of exploration of the various planes before one can be confident that resection is feasible.

The decision regarding how to proceed with central or axial recurrences is heavily related to the involvement of urogenital organs and the primary procedure previously performed. In the case of involvement of urogenital organs, curative resection requires an en-bloc-extended radical approach according to the patient's gender. If the dome of the bladder alone is involved, a partial cystectomy will generally suffice. If the trigone is involved, and the prostate in males, total pelvic exenteration and en-bloc prostatectomy are the only curative option. In addition to MRI, cystoscopy performed prior to definitive surgery will help with surgical planning and patient consent, according to area of bladder involved. In females, involvement of the uterus or vagina requires hysterectomy. Reconstructive options, such as, an ileal conduit, colonic conduit, or vaginal reconstruction are possible. In the absence of urogenital involvement, the patient's primary procedure dictates management. In a patient who has undergone a previous anterior resection, Mirnezami and Sagar recommend radical resection outside the original plane of dissection [22]. If the primary surgery was an abdominoperineal resection (APR), a pelvic recurrence can be treated with resection of the mass and involved small bowel where necessary. With perineal recurrence, a transperineal approach may be possible and a posterior distal sacrectomy may be required. In the case of previous APR, the empty pelvis often contains involved loops of small bowel which must be resected en-bloc with the mass. The ensuing perineal defect will generally require a rectus abdominus or gracilis flap. There is currently no guidance in the literature regarding the extent of lymphadenectomy required and equipoise on this issue cannot be reached in the absence of a further clinical trials.

Presacral venous haemorrhage may be extensive, difficult to control with conventional haemostatic agents and potentially life threatening. Before embarking on a resection in this area, provisions should be made for the potential requirement of blood products, aggressive fluid resuscitation, synthetic haemostatic agents, and devices, such as, thumbtacks [31]. Sacral recurrence is best managed via two-stage-combined abdominosacral approach [22]. Dissection in the presacral plane is necessary until the mass is reached. If neural and vascular involvement is absent, limited, or confirmed to be compatible with resectability, the patient may be moved to the prone position, allowing good exposure If the tumour invades the sacrum at the S1 or S2 level we would deem this unresectable. Some centres may consider resection with subsequent internal fixation, but we believe that ensuing deterioration in quality of life could not justify the risk to benefit ratio. If the tumour is distal to S2 then a distal sacrectomy may be performed with en-bloc resection of the previously formed neorectum or mass. Stomas and ileal conduits are constructed and omentoplasty may be undertaken to fill the pelvis. This reduces the potential for small bowel to become adherent to the raw pelvic surface causing obstruction and reduces the potential for perineal wound breakdown. The more extensive the sacrectomy performed, the worse are the morbidity, mortality, and quality of life. After less extensive sacral amputation, some series report a more acceptable quality of life despite stomas and temporary pain owing to the resection of sacral nerves [32]. A recent small series from the Mayo Clinic reported promising results from high sacrectomy indicating that these surgeries may be safely performed in centres of excellence [33]. Despite a median operative time of 13.7 hours and median operative blood transfusion of 3.7 litres, thirty-day mortality was nil. The overall median survival was 31 months (range 2–39 months), and all deaths were due to metastatic disease. Although only nine patients were included in this study, similar reports are emerging from other centres [34] and potentially indicate that high sacrectomy that achieves clear margins in patients with recurrent rectal cancer is feasible. Primary closure of the skin and fat is vulnerable to wound complications, and therefore a myocutaneous flap using the rectus abdominus or the gluteal muscles may be employed [26, 35].

The group associated with worst prognosis and resectability potential is the group involving the lateral pelvic sidewall [20]. A recent review reported that the more widespread use of TME has increased the incidence of pelvic sidewall recurrence [26]. Extensive involvement is a relative contraindication to operative intervention as key structures such as the ureters, iliac vessels, and sciatic nerve may be involved. Resection of the iliac vessels is associated with significant bleeding and as discussed, preoperative stenting of the ureters is advisable to facilitate dissection and identification of the ureters during the first phase of the surgery which should begin at the pelvic brim [36]. Early control of vessels and other key structures such as the obturator nerve, is imperative to success and progression to extended radical resection is usually required [24].

7. Palliation for Recurrent Rectal Cancer

In patients not fit for surgical intervention or with disease deemed unresectable, radiotherapy may play a role [37]. It is very effective in the treatment of pelvic pain and ongoing bleeding. The use of external beam radiotherapy has been reported to control pelvic pain in over 90% of cases and thus provide improved quality of life for affected patients. In patients with impending obstruction the use of self-expanding metal stents (SEMSs) is effective [38]. If the tumour is very low or the stent fails then a laparoscopic defunctioning stoma may be required to alleviate impending instruction. In patients with bilateral hydronephrosis ureteric stents either retrograde or antegrade will relieve the obstruction and prevent renal failure. If the ureters are completely obstructed then nephrostomy tubes are required.

8. Surgical Management: Multimodal Approach

While it is widely agreed that multimodal therapy is the future of management of recurrent rectal cancer, the use of Intraoperative Radiotherapy (IORT) remains controversial. IORT may be advantageous when bony involvement precludes the possibility of R0 resection [5]. Indeed, several studies have demonstrated a benefit in survival with IORT, particularly in combination with preoperative chemotherapy [12, 39]. IORT has been shown to result in significantly better three-year survival, disease-free survival, and local control in IORT-multimodal groups compared with historical control groups [40]. The overall survival after multimodal therapy at 5 years is approximately 30% at present [41] and when IORT is used as a component of this treatment, an increased survival rate of 15% can be demonstrated [39, 42].

9. The Future

Given the relatively poor prognosis despite multimodal treatment, the future of recurrent rectal cancer management lies in scientific progress, optimised technique, new treatments, and carefully designed clinical trials. The first case of transrectal high-intensity focused ultrasonography as a therapeutic option for advanced recurrent rectal cancer has recently been reported [43]. Potentially promising ongoing work includes identification of novel biomarkers as predictors of recurrence [19], discovery of novel alleles for use in targeted screening and personalized prevention [44–46], and development of systematic clinical algorithms [24]. Individualization of therapy in the future may be possible with next-generation genotyping platforms [47]. Although the popularisation of TME has resulted in decreased incidence of recurrence in rectal cancer, pelvic sidewall recurrence has increased, and tumours are less likely to be contained within defined compartments. Advances in imaging modalities and technical progress, however, have facilitated better selection of candidates for resection and substantially improved outcome as a result. Strategies for early detection require improvement and surgical techniques should be standardised. At present, best practice should include meticulous preoperative planning and adoption of a multimodal approach in centres of excellence with early involvement of a multidisciplinary team. A considerable amount of time must be spent counselling the patient and their family to facilitate thorough understanding of inherent risks and to ensure realistic expectations.

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Review Article

The Current State of Targeted Agents in Rectal Cancer

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Targeted biologic agents have an established role in treating metastatic colorectal cancer (CRC), and the integration of targeted therapies into the treatment of CRC has resulted in significant improvements in outcomes. Rapidly growing insight into the molecular biology of CRC, as well as recent developments in gene sequencing and molecular diagnostics, has led to high expectations for the identification of molecular markers to be used in personalized treatment regimens. The mechanisms of action and toxicities of targeted therapies differ from those of traditional cytotoxic chemotherapy. Targeted therapy has raised new insight about the possibility of tailoring treatment to an individual's disease, the assessment of drug effectiveness and toxicity, and the economics of cancer care. This paper covers the last decade of clinical trials that have explored the toxicity and efficacy of targeted agents in locally advanced and metastatic CRC and how their role may benefit patients with rectal cancer. Future efforts should include prospective studies of these agents in biomarker-defined subpopulations, as well as studies of novel agents that target angiogenesis, tumor-stromal interaction, and the cell signaling pathways implicated in rectal cancer.

1. Introduction

Over the past 30 years, the management of rectal cancer has undergone many significant changes. Until the 1980s, surgery was the mainstay of therapy for patients with rectal cancer confined to the bowel and regional lymph nodes [1]. However, local recurrence occurred in approximately 25% to 50% of patients with T3 or lymph node-positive rectal cancer [2]. These local failures, as well as distant metastases, were a serious problem in locally advanced rectal cancer (LARC).

To reduce these high failure rates, multiple trials evaluated different strategies of adjuvant radiation and 5-fluorouracil- (5-FU-) based chemotherapy [1, 3, 4]. Trial results demonstrated postoperative adjuvant chemoradiotherapy improved local control and survival compared with surgery alone, leading to the routine integration of adjuvant combined modality therapy into standard practice. At the same time, total mesorectal excision (TME) was introduced and further decreased local failure rates to less than 10% [5]. Subsequently, the landmark trial conducted by the German Group established superior local control, reduced treatment-related toxicity, and an improved sphincter preservation rate with neoadjuvant chemoradiotherapy compared with adjuvant 5-FU-based chemoradiation [6].

Today, although not proven to provide survival advantages (except in the pivotal Swedish trial), preoperative chemoradiotherapy with concurrent infusional 5-FU and more recently the oral fluoropyrimidine, capecitabine, followed by TME has become the standard of care for patients with T3 or lymph-node-positive rectal cancer, especially in tumors of the mid- and lower rectum [7, 8]. The use of targeted agents in patients with advanced colorectal cancer has led to further improvements in disease-free (DFS) and overall survival (OS), and further investigation in various settings is underway [9–12]. These "targeted" agents are now being studied in the treatment of rectal cancer and are discussed below.

2. Targeted Agents

Targeted therapies block the growth of cancer cells by interfering with specific targeted molecules needed for carcinogenesis and tumor growth [13]. Targeted cancer therapies may also be more effective by being potentially less harmful to normal cells. Two main categories of targeted therapy exist: small molecules (-nib) and monoclonal antibodies (-mab), both of which can be further subdivided as either signal transduction pathway inhibitors (imatinib mesylate, trastuzumab, cetuximab) or angiogenesis inhibitors (bevacizumab, sunitinib).

Increasing knowledge of tumor growth and dissemination pathways has turned more attention to the use of targeted agents coupled with chemotherapy in the treatment of metastatic colorectal cancer (mCRC). For these patients, phase III trials have shown improved disease-free and overall survival rates using epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) inhibitors when combined with conventional chemotherapy [9–12]. In this paper, we have reviewed VEGF and EGFR receptor inhibitors selectively and how their use may or may not be beneficial in the setting of rectal cancer as a radiosensitizer or in the adjuvant setting of rectal cancer. The majority of novel trials discussed are in phase II development and are presented here due to their potential benefit in rectal cancer.

2.1. VEGF Receptor Inhibitors. Bevacizumab is a humanized monoclonal antibody that targets the vascular endothelial growth factor (VEGF), particularly VEGF-A, a ligand with a key role in angiogenesis. Angiogenesis is required for tumor growth and malignant progression, and VEGF is a crucial regulator of this process. Indeed, high VEGF expression has been linked to a statistically higher risk of local recurrence and metastasis [18]. Thus, the inhibition of VEGF is a logical target for the treatment of patients with CRC. In addition, anti-VEGF antibodies enhance the capacity of radiotherapy to reduce tumor vascular density and interstitial fluid pressure (IFP) in xenografts [19].

These findings taken together support what is known as the vascular normalization hypothesis [20]. According to this hypothesis, an excess of proangiogenic factors within tumors leads to functionally and structurally abnormal vasculature that promotes increased IFP, a known barrier to drug delivery to tumors, and impaired delivery of oxygen and macromolecules, a known barrier to the effective radiation therapy [20–22].

One theory is that by "normalizing" this abnormal vasculature, transient antiangiogenic therapy reduces IFP and thereby increases the concentration of oxygen and penetration of cytotoxics, improving the overall effectiveness of combined modality therapy [20]. In the same study, a variety of plasma and circulating cell biomarkers were measured. Both VEGF and placenta-derived growth factor (PIGF) were found to be significantly elevated by bevacizumab alone and by combination therapy. These molecules may prove to be potential biomarkers for anti-VEGF therapy, as increases of pretreatment soluble VEGF receptor-1 (s-VEGFR1) and PIGF levels have also been associated with poor pathologic tumor downstaging after preoperative chemoradiation [29, 30].

2.2. EGFR Receptor Inhibitors. The epidermal growth factor receptor (EGFR) is a cell surface 170,000 daltons tyrosine kinase transmembrane receptor of the ErbB family, whose members play a critical role in oncogenesis [31]. In particular, EGFR has been shown to participate in the progression of CRC, as it is essential for tumor growth and division [32]. Some CRCs have been shown to overexpress EGFR, and overexpression of EGFR is associated with poorer prognosis [33, 34], and with resistance to radiation therapy. EGFR has, therefore, become an attractive target for therapy, and two different classes of biologic agents have been evaluated: the EGFR monoclonal antibodies (cetuximab and panitumumab) and the small-molecule tyrosine kinase inhibitors (gefitinib and erlotinib).

The efficacy of both cetuximab and panitumumab has been clearly demonstrated to depend upon the KRAS mutation status. Multiple analyses have demonstrated that responses to either cetuximab or panitumumab occur exclusively within the 60–70% of patients without activating mutations in codon 12 and 13 of KRAS [23, 24, 28, 35]. The activating V600E BRAF mutation is present in an additional 10% of patients, and it may be predictive of a lack of response to anti-EGFR therapy [36] in addition to a clear poor prognostic factor. The anti-EGFR monoclonal antibodies and their predictive biomarkers have taken CRC treatment another step closer to personalized therapy. However, the recent results of the large UK COIN study and a Belgian study have not confirmed a benefit in terms of PFS or OS from the addition of cetuximab to oxaliplatin-based chemotherapy in wild-type KRAS patients versus 5-FU and oxaliplatin alone [37, 38]. Therefore, more thoughtfully designed studies about potential negative predictive factors such as KRAS, BRAF, NRAS, PIK3CA mutations, and EGFR gene copy numbers would be beneficial.

3. Clinical Uses of Targeted Agents

3.1. Metastatic CRC. Bevacizumab, cetuximab, and panitumumab have been proven to be effective in different combined chemotherapy treatment settings for metastatic colorectal cancer and are briefly described here (Tables 1 and 2) [9–12].

3.1.1. Bevacizumab. Bevacizumab, a monoclonal antibody against the vascular endothelial growth factor ligand (VEGF-A), has demonstrated efficacy with significant improvement in progression-free survival (PFS) and OS in patients with metastatic colorectal cancer [9, 16, 39]. Results from a pivotal phase III trial of bevacizumab (5 mg/kg) showed a significantly greater OS, PFS, and response rate (RR) when used in combination with irinotecan, bolus 5-FU, and leucovorin (IFL), in 813 patients with previously untreated colorectal cancer [9]. The median OS was 20.3 months in the patients treated with bevacizumab, compared to 15.6

Table 1: Pivotal randomized clinical trials of bevacizumab in mCRC.

Author	Phase	Study design (regimen)	N +Bev/−	Results	Comment	Reference
1st line						
Hurwitz	III	IFL ± bevacizumab	402/411	20.3 versus 15.6 mo OS	RR,PFS,OS benefit	[9]
Scappaticci	II	5FU/LV ± bevacizumab	104/105	9.2 versus 5.5 mo PFS	No difference in OS, IFL was included in control group	[14]
Czito	III	IFL ± bevacizumab	249/251	17.9 versus 14.6 mo OS	RR,PFS,OS benefit	[15]
Saltz	III	CAPOX or FOLFOX ± bevacizumab	699/701	9.4 versus 8.0 mo PFS	No difference in OS	[16]
2nd line						
Giantonio	III	FOLFOX ± bevacizumab	286/291	12.9 versus 10.8 mo OS	RR,PFS,OS benefit, No benefit in Bev alone group	[17]

RR: Response rate, PFS: Progression-free survival, OS: Overall survival.

Table 2: Pivotal randomized clinical trials of cetuximab in mCRC.

Study	Phase	Study design(regimen)	N +Cet/−	Results	Comment	Reference
1st line						
CRYSTAL	III	FOLFIRI ± cetuximab	599/599	No difference in OS	PFS,OS benefit in KRAS-WT	[23]
OPUS	II	FOLFOX ± cetuximab	169/168	46 versus 36% RR	No difference in OS	[24]
CAIRO-2	III	CAPOX + beva ± cetuximab	377/378	9.4 versus 10.7 mo PFS		[25]
COIN	III	CAPOX or FOLFOX ± cetuximab	815/815	17 versus 17.9 mo OS	No difference in PFS,OS in KRAS-WT	[26]
NORDIC VII	III	FLOX ± cetuximab	194/185	19.7 versus 20.4 mo OS	No difference in PFS,OS in KRAS-WT	[27]
2nd line						
BOND	II	Irinotecan ± cetuximab	218/111	22.9 versus 10.8% PR		[10]
CO.17	III	Cetuximab versus supportive care	287/285	6.1 versus 4.6 mo OS	9.5 versus 4.8 mo OS in KRAS-WT	[11, 28]

RR: Response rate, PFS: Progression-free survival, OS: Overall survival. KRAS-WT: KRAS wild type.

months with the placebo-containing regimen ($P < .001$), and response rates were 44.8% and 34.8%, respectively ($P = .004$). Also of note was the phase III Bevacizumab plus Irinotecan in Colorectal Cancer (BICC)-C trial, consisting of two-arms: FOLFIRI(infusional FL) plus bevacizumab, versus mIFL (Bolus FL) plus bevacizumab. The median OS with the addition of bevacizumab was longer with FOLFIRI than with mIFL (28.0 versus 19.2 months; $P = .037$) [40, 41]. These findings led to the U.S./European Union approval of bevacizumab as a first-line-therapy component for mCRC with any 5-FU- based therapy.

The most commonly used bevacizumab-based first-line treatment in the USA continues to be FOLFOX plus bevacizumab. It was presumed that the benefit of adding bevacizumab to FOLFOX would be similar to that demonstrated with the IFL regimen, and that the addition of bevacizumab to FU-based combination chemotherapy would result in a significant and clinically meaningful improvement in survival among patients with mCRC [39]. Except in cases of major contraindications for bevacizumab, such as severe vascular disease or prior arterial thrombotic events, bevacizumab can be integrated with first-line chemotherapy in patients with metastatic CRC. In the event that a bevacizumab-naïve patient fails first-line chemotherapy, bevacizumab may be considered as a second-line treatment. In fact, the Bevacizumab Regimens: Investigation of Treatment Effects and Safety (BRITE) observational study confirmed that a notable OS benefit was demonstrated in those patients who continued bevacizumab therapy (5 mg/kg every 2 weeks) in combination with chemotherapy, after disease progression following a bevacizumab-based regimen (median OS, 31.8 months) [42]. The ARIES study validated the findings of BRiTE and reported a median OS of 24.7 months [43]. Furthermore, a recent randomized phase III

European trial (TML) suggests continuation of bevacizumab improves OS with final results to be reported at a later date [44].

3.1.2. Cetuximab. Cetuximab plus irinotecan is the standard treatment in irinotecan-refractory patients based on pivotal data from the Bowel Oncology with Cetuximab Antibody (BOND) trial, which established this as an effective regimen regardless of prior treatment history [10]. This trial confirmed the activity of cetuximab with response rates of 22.9% and 10.8% for combination therapy and monotherapy, respectively. In addition,there was a significantly longer time to tumor progression in favor of the combination arm (4.1 versus 1.5 months).

In a subsequent retrospective analysis of patients with KRAS wild-type tumors, there was an OS benefit for patients in favor of cetuximab (9.5 versus 4.8 months) [28]. Given cetuximab's demonstrated efficacy in the chemotherapy treatment-resistant setting, several studies were undertaken to evaluate its efficacy in the treatment-naive setting. The randomized, phase III CRYSTAL trial evaluated 1198 patients treated with FOLFIRI chemotherapy either with or without cetuximab, and noted improvement in PFS for the cetuximab-treated group [23]. However, it was also noted that no OS benefit was associated with the cetuximab-treated arm, potentially due to the fact that there was a difference in subsequent poststudy anti-EGFR therapy (23% in the FOLFIRI arm received subsequent cetuximab therapy, compared to 5.2% in the FOLFIRI + cetuximab arm) [49]. Retrospective tissue analysis on the CRYSTAL study revealed that the benefit from cetuximab was restricted to those patients with KRAS wild-type tumors and that it improved the PFS to 9.9 months compared to 8.4 months in the control arm. Subsequent analysis of the 666 patients with KRAS wild-type tumors who were enrolled has shown an OS improvement from 20 months in the control arm to 23.5 months in the cetuximab arm [50].

The randomized Phase II OPUS trial demonstrated similar findings when cetuximab was used with oxaliplatin-based chemotherapy; cetuximab, when combined with FOLFOX-4 chemotherapy, led to an improvement in PFS, when compared to those treated with FOLFOX-4 chemotherapy alone [51]. Similarly, the benefit derived from this therapy was limited to those patients with KRAS wild-type tumors (7.7 versus 7.2 months). However, these results have not been replicated in the phase III MRC-COIN study, where cetuximab was added to FOLFOX or CapeOX (capecitabine/oxaliplatin) in the first-line setting; those treated with capecitabine-based therapy fared worse [37]. Based on currently available data, it appears to be advantageous when cetuximab is added to irinotecan-based regimens while the advantage of combination with oxaliplatin remains less certain [26, 52]. Cetuximab can lead cancer cells to G1 or G2/M cell cycle arrest and upregulate several genes involved in proliferation (PIK31, CGREF1, and PLAGL1) with a reduction in Ki-67 [38]. But if only a small proportion of cells arrest in G0/G1 or G2/M, slowing down the cell cycle time may actually increase the amount of time available for DNA repair prior to mitosis, and thus could increase resistance to chemoradiation.

3.1.3. Panitumumab. Two phase III trials have determined the benefit of panitumumab in combination with chemotherapy relative to chemotherapy alone. The final reported results were selected for KRAS wild-type status as a predictive marker for anti-EGFR therapy in both studies. The Panitumumab Randomized Trial in Combination with Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy (PRIME) was a phase III randomized trial of FOLFOX with or without panitumumab in previously untreated patients [53]. The PFS time was longer in the panitumumab arm (9.6 versus 8.0 months, $P = .02$). The role of panitumumab was also investigated in combination with FOLFIRI for second-line treatment [54]. The primary endpoint of a PFS difference (5.9 versus 3.9 months; $P = .004$) was fulfilled with the addition of panitumumab but the OS endpoint was not met.

3.2. Adjuvant Setting

3.2.1. Bevacizumab. In the adjuvant treatment of colon cancer, two phase III trials did not demonstrate any benefit from the addition of bevacizumab to standard oxaliplatin-based chemotherapy in stage II/III colon cancer [55, 56]. From the results of the NSABP C-08 trial, in which bevacizumab in combination with FOLFOX6 did not improve DFS in the adjuvant setting in patients with stage II/III colon cancer, it seems that bevacizumab's efficacy may be maximal in a setting of more advanced disease [1]. The AVANT (Avastin adjuvant) study compared FOLFOX4 versus FOLFOX4 with bevacizumab versus XELOX with bevacizumab in 3,451 patients with stage II or III colon cancer. The study did not meet its primary objectives, and survival in the bevacizumab arms was inferior to the chemotherapy-alone arm [57].

3.2.2. Cetuximab. Two adjuvant trials have evaluated the potential benefit of cetuximab in combination with FOLFOX in a KRAS wild-type population: NO147 and PETACC8. There was no improvement in DFS or OS with the addition of cetuximab to FOLFOX. The NO147 trial compared 12 cycles of the modified FOLFOX6 to the same regimen with cetuximab [58, 59]. The 3-year DFS was even better with FOLFOX alone: 75.8% versus 72.3% for FOLFOX plus cetuximab. There was also a trend for 3-year OS inferiority: 87.8% with FOLFOX alone versus 83.9% for FOLFOX plus cetuximab. The subset of 717 patients with KRAS-mutated tumors did poorly with cetuximab. These observations raise questions about the manner of interaction between targeted therapies and chemotherapies and the mechanisms of inducing chemoresistance in some patients. The PETACC8 trial aims to increase the DFS in wild-type KRAS tumor patients. The trial has completed enrollment with final results to be presented at a later date.

Thus far, we have provided a general overview of the currently FDA approved role for targeted agents in metastatic colorectal cancer as well as the investigational status of targeted agents in locally advanced colon cancer. Overall,

of the targeted agents discussed, many of them have been analyzed to a much smaller extent in rectal cancer versus that of colon cancer in phase I/II clinical trials.

4. Locally Advanced Rectal Cancer

Overall, challenges remain in improving the treatment of locally advanced rectal cancer. Recent data from 3 phase III trials including NSABP R-04, STAR, and ACCORD 12 [60–62] have failed to provide a definitive role for oxaliplatin as a radiation sensitizer. Targeted agents in combination with fluorouracil-based treatment continue to remain an area of investigation.

4.1. Neoadjuvant Chemoradiation. Randomised phase III trials of neoadjuvant preoperative chemoradiation (CRT) in resectable rectal cancer show that the addition of 5-FU to preoperative radiation increases the pathologic complete remission (pCR) rate over radiotherapy alone and improves loco-regional control but has not extended DFS or OS [6, 63–65]. Several small phase I/II studies have since been created in the hopes of improving the pCR rate further by using combined chemotherapy with cytotoxic chemotherapy or targeted agents. It should be noted that pCR remains a common endpoint for many of current and prior trials in development. To date, none of the targeted agents have proceeded to phase III development as a radiation sensitizer with only one proceeding to the adjuvant setting of rectal cancer.

4.1.1. Bevacizumab. Given the data supporting the efficacy of bevacizumab therapy in metastatic colorectal cancer [17], it was postulated that combining bevacizumab with chemoradiation may increase antitumour efficacy by maximizing inhibition of the VEGF pathway. In an early trial of bevacizumab plus infusional 5-FU and radiation in stage II/III rectal cancer, bevacizumab administered as a single agent 14 days prior to chemoradiation induced normalization of tumour vasculature and reduced interstitial fluid pressure [66]. Willett et al. first reported on a phase I trial of bevacizumab in combination with preoperative 5-FU and radiation. Surgery was scheduled 7–9 weeks later. A pCR rate of 16% was reported, and an additional 72% of patients had only microscopic foci remaining after treatment in their phase I/II study of patients with T3/T4 tumors [29]. Crane et al. reported results of a single institution phase II trial of neoadjuvant bevacizumab, capecitabine, and radiation in 25 patients with locally advanced rectal cancer [47]. The pCR rate was 32%, with an additional 24% of patients having near-complete responses (less than 10% viable tumor cells). Toxicity was generally mild, although wound dehiscence was seen in 12% of patients (Table 3).

It should be noted that bevacizumab was to be evaluated in the adjuvant setting following definitive chemoradiation therapy in locally advanced rectal carcinoma patients (ECOG 5204). This was a randomized phase III trial of adjuvant FOLFOX +/− bevacizumab. However, this study closed prematurely due to slow patient accrual but would have closed eventually given the results of NSABP C-08.

4.1.2. Cetuximab. EGFR is also a rational target in combination with radiotherapy. Data from a variety of experimental models and human tumors suggest that EGFR signaling promotes resistance to radiotherapy by activating cell survival signals through Akt [73, 74]. Moreover, retrospective analyses demonstrated shorter DFS and smaller pCR rates in patients with rectal cancers expressing EGFR who were being treated with neoadjuvant radiotherapy [75, 76]. These data suggest the possibility of enhancing radiosensitivity with EGFR-directed therapy.

A landmark randomised phase III study in patients with locally advanced head and neck cancer showed that cetuximab in combination with radical radiotherapy significantly improved overall survival [77] compared to radiation alone [78]. Many mechanisms for this advantage have been proposed, including inhibition of repopulation during the latter phase of radiotherapy [79, 80]. Chung et al. treated 20 patients with ultrasound-staged (u)T3 to 4, clinical T4, or locally recurrent rectal cancer with weekly cetuximab and 5-FU during 5.5 weeks of pelvic radiotherapy, followed by an additional 4 weeks of cetuximab [81]. Patients underwent surgical resection 1 to 3 weeks after the completion of therapy. Cetuximab in conjunction with 5-FU and radiotherapy was feasible without synergistic or unexpected toxicities; the pCR rate was 12%. According to the meta-analysis of 13 reports, the addition of cetuximab to fluoropyrimidine-based CRT schedules suggest an overall pooled pCR of 9.1%, compared with an overall pCR rate of 13.5% seen with fluoropyrimidine-based chemoradiation schedules in a recent review (Table 4) [82]. The pCR rates have been disappointingly low, perhaps because anti-EGFR therapy is most effective in inhibiting the accelerated repopulation observed after the higher doses of radiotherapy used in patients with head and neck cancer [47].

Alternatively, cetuximab-induced inhibition of mitogenic signaling through the extracellular signal-regulated kinase (Erk) pathway may mitigate the radiosensitizing effect of S phase-specific chemotherapy. Cetuximab can lead to G1 or G2/M cell cycle arrest, and if only a small proportion of cells within the tumour are affected, this decrease in proliferation could impact the chance of achieving a pCR [38]. This process might also affect oxaliplatin, which is mainly active in S phase but would be less likely to affect irinotecan. Thus, preclinical data suggests that the sequencing of chemotherapy may have some significance but given the prolonged half-life of cetuximab, it may not necessarily apply to the clinical setting [83]. In light of this hypothesis, a phase I/II study (XERXES) created to compare a schedule of capecitabine-based chemoradiation with a cetuximab sandwich approach amended their protocol [84].

4.1.3. Panitumumab. Panitumumab was administered before the start of CRT, and every 2 weeks in combination with 5FU-oxaliplatin with concurrent RT(StarPan/STAR-02 study) [85]. Rate of pCR was 21.1% and pathological downstaging occurred in 57.9% of the patients. Higher pCR rate in comparison with the results of previous neoadjuvant rectal cancer trials with antiepidermal growth factor receptor monoclonal antibodies supports further studies necessary

Table 3: Clinical trials of bevacizumab in preoperative treatment of rectal cancer.

Author	Phase	Study design(regimen)	*N*	RT dose (Gy)	pCR rate	Major wound Cx	Reference
Machiels	I	Cape + oxali + bevacizumab	11	50.4	2/11(18%)	NS	[45]
Willett	II	5FU + bevacizumab	32	50.4	5/32(16%)	1/32(3%)	[29]
Rodel	II	5FU + bevacizumab	35	50.4	10/35(29%)	3/20(15%)	[46]
Crane	II	Capecitabine + bevacizumab	25	50.4	8/25(32%)	3/25(12%)	[47]
Mourad	II	Xelox + beva then cape + beva + RT	47	50.4	16/47(36%)	11/47(24%)	[48]

RT: Radiotherapy, pCR: Pathological complete response.

Table 4: Clinical trials of cetuximab in preoperative treatment of rectal cancer.

Author	Phase	Study design(regimen)	N	RT dose (Gy)	pCR rate	Diarrhea (≥ G 3)	Reference
Kuo	I	5FU+ cetuximab	20	50.4	2/17(12%)	2/20(10%)	[67]
Bertolini	I	Caplri + cetuximab	20	50.4	5/20(25%)	2/10(20%)	[68]
Velenik	I/II	Capecitabine + cetuximab	40	45	2/40(5%)	6/40(15%)	[69]
Horisberger	I/II	CAPOX + cetuximab	48	50.4	4/48(8%)	9/48(19%)	[70]
Chang	II	Cetuximab then 5FU + cetux	40	50.4	3/40(7.5%)	3/40(7.5%)	[71]
Rodel	II	Capecitabine + cetuximab	37	45	3/37(8.1%)	4/37(11%)	[72]
Oncofacts.com	II	Caplri + cetuximab	50	50.4	4/50(8%)	15/50(30%)	[44]

RT:Radiotherapy, pCR: Pathological complete response.

to understand the possibility of optimal regimens and sequences with CRT.

4.1.4. Tyrosine Kinase Inhibitors of the EGFR. Though it would appear to be intuitive that a tyrosine kinase inhibitor of the EGFR receptor would be of potential benefit, early data for their role in mCRC has not been defined and was determined to be more toxic [67, 86]. However, the small molecule tyrosine kinase inhibitors have radiosensitization properties. A phase I trial of a combination of erlotinib and bevacizumab with preoperative chemoradiotherapy of capecitabine demonstrated an impressive pCR(44%) [87].

Similar preliminary results were also reported of a phase I/II trial of bevacizumab and erlotinib in combination with 5-FU and pelvic radiotherapy for patients with clinical T3/4 rectal cancer [88]. No dose-limiting toxicities were reported and erlotinib at a dose of 100 mg was chosen as the MTD. At the time of last followup, the reported pCR was 47% and there were no local recurrences reported in patients who completed study therapy. Thus, based on these phase I/II trials, bevacizumab and erlotinib in combination with 5-FU or capecitabine and radiotherapy appear to be well tolerated and a potentially active preoperative regimen for patients with LARC.

4.2. Induction Chemotherapy. While modern rectal cancer trials with trimodality therapy have reported locoregional recurrence rates of less than 10%, especially with TME, systemic treatment can be delayed for up to 3-4 months following the original diagnosis [89, 90]. The problem, therefore, remains the persistent high rate of distant metastasis (30–35%) in this disease [91, 92]. Reasons for this higher rate of distant failure may be complex. One such reason, the biological response of tumors to radiation, may provide explanation in that tumors that are not completely eradicated undergo accelerated repopulation [93].Thus, integrating more effective systemic therapy into combined modality programs is the challenge and induction chemotherapy has the advantage of earlier administration of systemic therapy and may improve distant control. Theoretically, tumour shrinkage with chemotherapy potentially allows improved tumour vascularity and improved oxygenation and higher intratumoural levels of cytotoxic drugs. These factors in turn may enhance tumour sensitivity to chemotherapy or radiation [94]. Therefore, newer generation chemotherapeutics as well as targeted agents (cetuximab, bevacizumab) have been incorporated into phase I-II studies [95, 96].

Interestingly, early results from the phase III ACCORD 12/0405-Prodige 2 and STAR trial did not confirm a significant improvement of the primary endpoint, pCR rate, with the addition of oxaliplatin to preoperative 5-FU-based CRT [91, 92]. However, induction-capecitabine-based CT prior to CRT reported eventual pCR rates as high as 24% [97, 98]. In a randomized comparison of induction versus adjuvant capecitabine plus oxaliplatin, no difference in clinical outcomes was observed between the two treatment regimens, although the induction regimen resulted in a more favorable safety profile [99]. To date, the 3-year DFS and OS remain unchanged versus the control arm [100].

In the AVACROSS study, treatment consisted of bevacizumab and XELOX, followed by concomitant radiotherapy plus bevacizumab and capecitabine. pCR was achieved in 36% of the patients but the rate of postsurgical complications and cardiac toxicity was not negligible. Most were associated

with wound-healing complications with 24% of patients requiring further surgery; note that patients with a previous history of stable angina, arrhythmia, and coronary syndrome should be excluded [101]. Emerging evidence from several phase I-II trials indicate that induction chemotherapy for rectal cancer patients is feasible and does not compromise CRT or surgery, but only an adequately powered phase III trial will answer the question definitively.

An interesting multinational randomised phase II study, EXPERT-C trial (NCT00383695), compares neoadjuvant therapy comprising oxaliplatin, capecitabine, and CRT with or without cetuximab in 164 patients. It was designed on the basis of earlier single-arm phase II study (EXPERT), in which patients received 12 weeks of neoadjuvant capecitabine and oxaliplatin followed by chemoradiotherapy with capecitabine, TME, and 12 weeks of postoperative adjuvant capecitabine [97]. Radiological response rate after neoadjuvant chemotherapy and chemoradiotherapy was 89% (93/105) with a reported pCR of 20%. Three-year PFS and OS were 68% and 83%, respectively. Early results of the EXPERT-C trial indicate that improved 3-yr OS in patients receiving the investigational arm with CRT was 96% compared with 81% among those who received neoadjuvant chemotherapy and chemoradiation alone [102]. In the KRAS wild-type group, there was no statistically significant difference in PFS (81 versus 80%) and pCR (7 versus 11%) [7]. Though a phase II trial, the results of EXPERT-C have potentially renewed interest of investigators for oxaliplatin and cetuximab in the treatment of rectal cancer; results will need to be validated in a phase III trial.

4.3. Novel Targeted Agents in Phase III Clinical Trials. Several novel agents are being studied in phase III trials for the treatment of metastatic colorectal cancer: aflibercept, ramucirumab, regorafenib, perifosine, and brivanib. Of these, aflibercept and ramucirumab are specific VEGF-directed therapies, whereas the remaining three are associated with approaches to intracellular signal blockade.

Aflibercept is a fully human, recombinant fusion protein that functions as a soluble decoy receptor for VEGF, with affinity for VEGF-A, VEGF-B, and placental growth factor [103]. The VELOUR trial is a randomized, placebo-controlled study investigating the combination of FOLFIRI plus aflibercept versus FOLFIRI in the second-line treatment of mCRC [104]. Ramucirumab is another human monoclonal antibody directed against VEGFR-2, which is considered to be the primary VEGFR mediating the process of tumor angiogenesis [105, 106]. It is currently in phase III development in 2nd-line metastatic colorectal cancer in combination with FOLFIRI [107].

Regorafenib is a diphenylurea oral multikinase inhibitor that targets a variety of kinases implicated in angiogenic and tumor growth-promoting pathways and has been investigated as a single-agent activity in the phase III CORRECT trial in refractory mCRC [108]. The final results of the CORRECT trial noted improved OS versus best supportive care alone (6.5 versus 5.0 mo, $P < .0052$) [109]. Perifosine is an oral alkylphospholipid that inhibits several key signal transduction pathways, including Akt, JNK, and NF-κB. Inhibition of NF-κB signaling by perifosine has been reported to restore 5-FU chemosensitivity [110, 111]. The Xeloda plus Perifosine Evaluation in Colorectal Cancer Treatment (X-PECT) trial with a target enrollment of 430 patients has recently completed accrual [112]. Perifosine has been evaluated preclinically in prostate and glioma as a radiation sensitizer [113, 114]. Brivanib is an oral receptor tyrosine kinase inhibitor that specifically inhibits the VEGF and fibroblast growth factor (FGF) signaling pathways [115, 116]. Recent phase III data failed to show a benefit in OS when brivanib was added to cetuximab in KRAS-WT metastatic CRC patients [117]. Brivanib continues to be investigated in combination in a single institutional trial with irinotecan in an enriched patient population with a focus on plasma fibroblast growth factor (pFGF) [118].

Currently, perifosine appears to be the only targeted agent in phase III development with some potential as a radiation sensitizer based on preclinical studies. Hence, though greater than 50 novel agents are being investigated in phase II trials, only a small percentage of these agents will proceed to phase III clinical trial development with a minority eventually investigated for their radiosensitization properties. Therefore, it is important to identify predictive biomarkers for chemotherapy and radiation sensitivity, a task that should involve close cooperation and discussion between basic scientists, clinical, and translational investigators.

5. Adverse Events Associated with Targeted Therapy

5.1. Bevacizumab. Bevacizumab is accompanied by a manageable safety profile. Early-phase II and pivotal-phase III studies in CRC utilizing bevacizumab have identified hypertension (11%–32%), bleeding (mainly epistaxis; 30%–53%), proteinuria (10%–38%), arterial thromboembolism (ATE) (1%–10%), gastrointestinal perforation (0.3%–2%), and wound healing (1.3%–3.7%) as bevacizumab-associated adverse events.

Hypertension is the most commonly reported associated toxicity of patients treated with bevacizumab [9, 42]. The mechanism of bevacizumab-related HTN is unclear and has been attributed to possible alterations in the nitric oxide signaling pathway and the endothelial dysfunction of the renin-angiotensin system [48, 119]. There are no clear guidelines for the management of hypertension in patients receiving bevacizumab, but patients who develop more than grade 2 HTN during bevacizumab therapy should be managed using standard antihypertensive therapy.

Incidence of grade 3/4 proteinuria in recent phase III trials with bevacizumab in metastatic CRC have been reported in less than 2% of patients [9, 42]. The mechanism of proteinuria is not fully understood but may be related to the effects of VEGF on the renal glomerular capillaries. It is advisable that patients with proteinuria of more than 2+ on a dipstick should have a 24-hour urine check for quantification of protein. If patients develop proteinuria of more than 2 g/24 hours, bevacizumab administration should

be interrupted until proteinuria improves. Patients should be evaluated for ACE inhibitors or angiotensin-receptor blockers as initial treatment in the case of development of proteinuria with hypertension.

Bleeding from mucocutaneous membranes is common with bevacizumab and occurs in 20% to 40% of patients [120], the most significant type being gastrointestinal bleeding (6%) and the most common being self-limited epistaxis (46%). Note that the BRiTE study did not exclude patients on antiplatelet therapy or full-dose anticoagulation [121], so it is relatively safe in terms of risk of serious bleeding complications.

Thrombosis is a more potentially serious adverse event. In the pivotal phase III trial in patients with metastatic CRC evaluating the IFL regimen with and without bevacizumab, the incidence of all venous and ATE was 19.4% versus 16.2% in the nonbevacizumab arm [9]. It has been speculated that the blockade of the VEGF receptors leads to apoptosis of endothelial cells in the vasculature, thus exposing the subendothelial collagen and initiating a coagulation cascade resulting in an increased risk for thrombus formation [122]. Thus, the Food and Drug Administration (FDA) described that the rate of ATE is increased in patients with prior events of ATE or patients aged more than 65 years during bevacizumab therapy.

Other less common but serious reported toxicities may include gastrointestinal perforation (2%) and wound-healing complications. Patients who underwent surgery within 14 days of receiving bevacizumab are at a higher risk of developing wound healing complications [14]. Based on available data, bevacizumab should not be initiated within 30 days after surgery. Elective surgeries should be planned 6 to 8 weeks after last dose of bevacizumab, though chemotherapy alone can be continued until 2 to 3 weeks before surgery. Furthermore, it has been suggested that extended use of bevacizumab can increase the long-term risk of wound healing complications for up to 6 months after its cessation [55, 123].

The incidence of GI perforations may be slightly higher in patients with an intact primary tumor, prior adjuvant radiation therapy in rectal cancer, long-term nonsteroidal anti-inflammatory drug (NSAID) therapy ($\geq$1 month of use), peptic ulcer disease, diverticulosis, and previous gastrointestinal surgery [9, 100, 124]. An extensive meta-analysis reported an incidence of GI perforation under bevacizumab treatment of <1%, resulting in a mortality of 22% [125]. Reversible posterior leukoencephalopathy syndrome (RPLS) has been reported in clinical studies (with an incidence of < 0.1%) and in postmarketing experience [126]. RPLS is a neurological disorder, which can present with headache, seizure, lethargy, confusion, blindness, and other visual and neurologic disturbances. Discontinuation of bevacizumab and aggressive management of hypertension is indicated in patients developing RPLS.

5.2. Cetuximab. The most frequently observed toxicity with the use of cetuximab is the development of a rash; all patients experience some degree of xerodermatitis. The majority will develop a nonscarring, noninfectious, acneiform rash most prominent on the malar aspect of the face, chest, and back; it is exacerbated by sunlight. But the severity of the rash has been correlated with improved response to cetuximab therapy [127]. In view of this finding, a randomized, Phase I-II study (the "EVEREST" trial) was developed, with the experimental arm consisting of dose escalation of cetuximab to rash development in those treated patients who failed to develop a grade 2 rash following initial exposure to cetuximab. While a higher radiographic response rate in the experimental arm of this trial (the cetuximab dose escalation to rash) was observed, this did not lead to an improvement in PFS or OS advantage [128].

Cetuximab has also been frequently associated with renal magnesium wasting leading to hypomagnesemia, with this occasionally becoming symptomatic [129, 130]. When symptomatic, repletion with enteral or parenteral magnesium is indicated; it is not clear that magnesium replacement is beneficial in an asymptomatic patient [131]. Paronychial inflammation and fissuring of the distal fingertips are a class effect of these agents. If left unaddressed, severe paronychial infections may develop. Instances of elevated cases of allergic hypersensitivity reactions have been reported regardless of the premedications provided [132]. The development of IgE antibodies was noted and varied depending on the geographic location with greater instances in the in the Southern USA.

5.3. Panitumumab. In contrast to cetuximab, which is a chimeric monoclonal antibody that may produce severe hypersensitivity reactions in some patients, panitumumab is a fully human monoclonal antibody and is less likely to result in allergic hypersensitivity reaction.

6. Pharmacoeconomic Considerations

Targeted therapy also introduces new economic considerations. Targeted therapy is often used in addition to traditional chemotherapy. If targeted therapy includes monoclonal antibodies, costs can escalate exponentially. Pharmacoeconomic studies looking at health care systems have demonstrated that the cost per life-year gained with biologics is relatively high, compared with other interventions [133–136]. For example, multidrug colorectal cancer treatment regimens containing bevacizumab or cetuximab cost up to $30,790 for eight-weeks of treatment, compared with $63 for an eight week regimen of 5-FL, the standard treatment until the mid-1990s [137, 138]. The Cost of Care Task Force of The American Society of Clinical Oncology recently released a guidance statement emphasizing the importance of physician-patient discussion regarding the cost of care and the creation of decision-making tools to allow patients to make informed and educated decisions about their treatment [139].

7. Conclusions

Advances in rectal cancer therapy remain stagnant despite new existing cytotoxic and targeted agents in the treatment of metastatic colorectal cancer. Traditionally, agents that have been incorporated into rectal cancer trials are those that have

demonstrated promise in advanced and locally advanced colorectal cancer. However, to date, the role of cytotoxic agents as radiation sensitizers (i.e., oxaliplatin) have not demonstrated improved efficacy versus the standard of care, fluorouracil. Similarly, targeted agents have a definitive role in the treatment of metastatic colorectal cancer. Yet, its role in the treatment of rectal cancer as a radiation sensitizer has yet to be determined. In short, therapeutic developments in rectal cancer may lag behind because rectal carcinoma is not a commonly pursued area of pharmaceutical development. Furthermore, whether pCR is the optimal endpoint remains controversial versus the more traditional outcome of DFS or OS. Retrospective analyses have suggested that pCR is a potential surrogate for DFS or OS [71, 72]. These findings must be validated prospectively in a phase III trial.

Targeted agents continue to be evaluated in the phase I/II setting with promising potential but have yet to be proven to be superior to the standard of care, fluorouracil-based radiotherapy. Currently, the use of targeted agents is best suited in the setting of a clinical trial. Future developments in rectal cancer should focus on the identification of molecular factors that have prognostic and predictive significance to improve treatment outcomes. Research efforts focusing on additional biomarkers will refine our ability to use these agents specifically in patient populations that derive a meaningful benefit. With concerns about health care costs, it is also critical to create a pharmacoeconomic framework guiding the clinical use of these agents. The introduction of new therapeutic agents and the discovery and validation of prognostic and predictive markers along with new screening tools will enable oncologists to tailor patient-specific chemotherapy by maximizing drug efficacy and minimizing adverse and possibly severe side effects.

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Review Article

A Primer on the Current State-of-the-Science Neoadjuvant and Adjuvant Therapy for Patients with Locally Advanced Rectal Adenocarcinomas

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Patients with rectal cancers, due to the unique location of the tumor, have a recurrence pattern distinct from colon cancers. Advances in adjuvant therapy over the last three decades have played an important role in improving patient outcomes. This article serves to review the clinical studies that lay the basis for our current standard-of-care treatment of patients with locally advanced rectal cancer, as well as touch upon future ongoing experimental clinical trials of adjuvant chemoradiation therapy.

1. Introduction

Over one million people are diagnosed with colorectal cancer each year world-wide [1]. Patients with rectal cancers comprise approximately one-fifth of all patients with colorectal adenocarcinomas [2]; the unique anatomic location of the rectum with respect to the colon puts these patients at far higher risk of local recurrence [3]. Although adenocarcinoma is the most common cancer pathology of the rectum, squamous cell [4], adenosquamous [5], carcinoid cancers [6], and melanomas [7] also arise from the rectum, although with much lower prevalence. Anatomically the superior rectum is defined by the expansion of the taenia coli of the sigmoid colon to form a circular layer of muscle; inferiorly it is defined by the anorectal line (dentate line) [8]. The rectum is approximately 10–15 centimeters in length and endoscopically starts at 3 centimeters from the anal verge, extending to 15 centimeters, with significant person-to-person variation [9]. Patients with rectal cancer represent a subset of colorectal adenocarinoma patients that have been shown to have higher rates of recurrence after surgery alone when compared with more proximal portions of the colon secondary to its largely extraperitoneal situation [10]. Given the high rate of locally recurrent disease, multimodality therapy with a combination of total mesorectal excision (TME), radiation and chemotherapy (combined modality therapy, CMT) has now become the standard-of-care in locally advanced rectal cancer [11]. This paper seeks to review the seminal data that supports this approach, as well as touch on current controversies in the multimodality care of patients with locally advanced rectal cancer.

2. The Dawn of Adjuvant Therapy in Rectal Cancer

For many years, surgical resection was the only approach for patients with locally advanced rectal cancer. For patients with stage I disease, this continues to be the definitive treatment with a five-year overall survival (OS) rate of approximately 75% and a 7% or less local recurrence rate; however, patients with transmural penetration or nodal metastases have a higher risk of both local and distant recurrence, leading to inferior survival outcomes [12]. Given the high burden of local recurrence, efforts were initially placed into incorporating radiation therapy into the management of these

patients as a means to improve local control. Chemotherapy was also incorporated into therapy to address potential micrometastatic disease (distant failure) as well as a tumor radiosensitizer [13].

In 1985, the Gastrointestinal Tumor Study Group (GITSG) published a randomized trial addressing the role of adjuvant radiation, chemotherapy, and chemoradiation in the treatment of locally advanced rectal cancer. A total of 227 patients were randomized after receiving surgical resection to four different groups including: (1) no adjuvant therapy, (2) adjuvant radiation alone at either 40 or 48 gray (Gy) dose, (3) adjuvant chemotherapy with semustine and 5-fluorouracil (5-FU), or (4) adjuvant combined modality therapy (CMT) with either 40 or 44 Gy radiation with concurrent 5-FU followed by post-radiation semustine plus 5-FU. At a median follow-up time of 80 months, patients in the control group had a local recurrence rate of 55% compared with only 33% in the adjuvant CMT arm. Additionally, progression-free survival (PFS) differed significantly amongst all four groups with the CMT arm being the most favorable ($P < 0.04$). In the initial report, there was a trend towards an OS benefit when comparing the control group to the CMT group ($P = 0.07$) [14]. In 1986, a follow-up report for this study showed that patients in the CMT group had a 24% estimated improved survival benefit at seven years ($P = 0.005$) [15].

After this study, there was still the question as to whether or not adjuvant CMT was truly superior to adjuvant radiation therapy alone. This was addressed in a prospective study of 204 post-operative patients with T3, T4 or node-positive rectal cancer who were randomly assigned to receive either adjuvant radiation or CMT. The adjuvant radiation arm was treated with 45 to 50.4 Gy, while the combined group received the same dosage of radiation with concurrent 5-FU. The CMT group was treated with one cycle of semustine-plus fluorouracil before and after radiation followed by an additional cycle of 5-FU. Patients in the radiation alone arm had an estimated five-year recurrence of 62.7% compared with 41.5% in the combination group. ($P = 0.0016$). More importantly, there was a 29% reduction in the overall death rate in the CMT group [11].

3. Chemotherapy versus CMT

As a result of these promising trials, the National Institute of Health (NIH) published a Consensus Statement in 1990 advocating the use of combined CMT for adjuvant treatment in stage II and III rectal cancers [17]. The National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol R-01 trial demonstrated that patients who received adjuvant radiation when compared to surgery alone had an overall reduction in local recurrence, but no difference in DFS and OS. Meanwhile, patients who received adjuvant chemotherapy had an improvement in DFS and OS when compared with patients who received only surgery [18]. Given these findings, the NSABP conducted a study, R-02, which randomized 694 patients to receive chemotherapy with or without radiation. Chemotherapy was given as either a regimen with bolus 5-FU modulated with leucovorin or with the MOF regimen which included semustine, vincristine, and 5-FU. Much like the NSABP Protocol R-01 trial, the addition of radiation to adjuvant chemotherapy did not improve disease-free survival ($P = 0.90$) or overall survival ($P = 0.89$) but did decrease the five-year incidence of local relapse from 13 percent to 8 percent ($P = 0.02$) [19].

4. Neoadjuvant Radiation

Since these trials were unable to demonstrate an OS benefit with postoperative radiation, many groups started to explore the use of radiation in the preoperative setting. In 1997, the Swedish Rectal Cancer Trial became the first trial to show survival benefit with the addition of preoperative neoadjuvant radiation [20]. In this trial, 1,168 patients were randomly assigned to receive either surgery alone or preoperative short-course radiotherapy followed by surgery. The radiation was given over 5 days for a total of 25 Gy within one week prior to surgical resection. Patients in the study in the radiation group had a much lower 5-year local recurrence rate of 11% versus 27% ($P < 0.001$). Meanwhile, the five-year survival rate was 58% in the radiation group compared with only 48% in the surgery alone group ($P = 0.004$) [21]. Long-term followup continued to show an OS benefit at 13 years [22].

Around the time that the Swedish Rectal Cancer Trial was being conducted, total mesorectal excision (TME) was being established as the gold-standard for surgical resection in rectal cancer [22]. The impressive results of TME called into question many of the previous neoadjuvant and adjuvant trials that did not utilize the optimal surgical method. The Dutch Colorectal Cancer Group (DCCG) addressed this by conducting a trial similar to the Swedish Rectal Cancer Trial comparing short-course radiotherapy (25 Gy over 5 fractions) with TME versus TME alone. At two years, the rates of local recurrence were 2.4% in the radiation group versus 8.2 percent in the TME only group ($P < 0.001$) [23]. At five years, local recurrence rates were 5.6 percent versus 10.9 percent ($P < 0.001$), but overall survival was only 64.2% in the radiation with TME group versus 63.5% in the TME only group ($P = 0.902$) [24].

5. Neoadjuvant CMT

Given the potential of neoadjuvant radiation and the prior success of postoperative chemoradiation, the next step in the treatment of locally advanced rectal adenocarcinoma was the exploration of neoadjuvant CMT in the preoperative setting [25]. The first of these was the German Rectal Cancer Study Group, which compared neoadjuvant CMT with adjuvant CMT in patients with T3, T4, or node-positive disease. The study enrolled 823 patients from 1995 to 2002. Patients assigned to the neoadjuvant CMT group received five weeks of preoperative chemoradiation (50.4 Gy given in 18 Gy per day over 28 fractions, five days per week). Patients were also given 5-FU as a protracted venous infusion at 1000 mg/m^2 per day for five days on weeks one and five. A TME was then performed within six weeks of completion of neoadjuvant CMT. Patients in the adjuvant arm started four weeks after surgery and received the same schedule of CMT, with the exception of a 5.4 Gy boost. Both groups then received

postoperative 5-FU at 500 mg/m^2 per day for five days over four weeks. The study found no difference in 5-year OS between the two groups (76% for the neoadjuvant group and 74% for the adjuvant group, $P = 0.8025$). However, there was a lower local recurrence rate in the neoadjuvant group, 6% compared to 13% ($P = 0.006$). Additionally, it was found that the neoadjuvant group had significantly less long-term toxicities, particularly with regards to diarrhea, small bowel obstruction, and strictures at the anastomotic site [25].

The European Organization for Research and Treatment of Cancer (EORTC) published the results of Trial 22921 which also attempted to assess the addition of chemotherapy to preoperative radiotherapy. This trial randomized 1,011 patients to four different arms: (a) preoperative radiotherapy, (b) preoperative CMT, (c) preoperative radiotherapy with postoperative chemotherapy, or (d) preoperative CMT with postoperative chemotherapy. Radiation was given as 45 Gy delivered over 25 fractions; the 5-FU was given as a continuous infusion, modulated by leucovorin, for five days weeks one and five for the arms receiving preoperative CMT. Postoperative chemotherapy was given every three weeks for four cycles with the same regimen used preoperatively. The primary endpoint was OS between the two preoperative modalities and the two postoperative modalities. Ultimately, there was no difference in OS between the two groups that received preoperative radiation versus the two groups that received preoperative chemoradiation [26]. However, the group that did not receive any chemotherapy had a 5-year local recurrence of 17.1%. This was significantly higher than the preoperative CMT, the preoperative radiation with postoperative chemotherapy, and the preoperative CMT with postoperative chemotherapy groups, which had local recurrence rates of 8.7%, 9.6%, and 7.6%, respectively ($P = 0.002$) [26]. The trial was not designed to detect a difference in OS between the four groups, so this was not reported. Also of note, the trial ran for six years before it was required for patients to have a TME; thus, less than half of the patients were documented as having a TME.

The NSABP R-03 trial attempted to solidify the role neoadjuvant chemoradiotherapy as the treatment of choice for patients with stage II and III rectal cancer; in this study 267 patients were randomly assigned to either neoadjuvant CMT or adjuvant chemoradiation. Patients in the neoadjuvant group initially received a bolus of 5-FU with leucovorin once per week for six weeks. This was followed by radiation given as 45 Gy over 25 fractions with a 5.4 Gy boost. 5-FU and leucovorin were given on days 1–5 and days 21–25 of radiation. Patients then proceeded to surgery followed by 24 more weeks of weekly 5-FU and leucovorin. Patients in the adjuvant group followed the same treatment course with six weeks of chemotherapy, five weeks of CMT, and 24 weeks of chemotherapy all following initial surgery. Five-year disease-free survival (DFS) for the neoadjuvant group was 64.7 percent compared with 53.4 percent for the adjuvant group ($P = 0.011$) [27]. Additionally, there was observed a trend towards superior 5-year OS that was seen with 74.7% versus 65.6%, respectively ($P = 0.65$) [27]. Another interesting finding in this study was the 15% of patients in the neoadjuvant CMT group who obtained a complete pathologic response. In this small subset of patients, none of them had a recurrence. In this study it was not a requirement that all patients in this trial undergo a TME, which may have potentially confounded some of the results.

6. Optimizing Neoadjuvant Treatment

While questions still remain, for the most part, the results have established neoadjuvant CMT followed TME as the standard treatment in stage II and III rectal cancer with no contraindications to surgery or CMT. Subsequent trials have now tried to focus on optimizing both the length and types of chemotherapy and radiation used to improve survival and decrease toxicities.

6.1. Semustine. Many of the initial trials that favored adjuvant chemoradiation using 5-FU and semustine had concerns over the long-term toxic effects of semustine. In the first GITSG study [11], one patient who received semustine developed acute myelogenous leukemia (AML). The concerns over this toxicity led two trials to evaluate the benefit of adding semustine to 5-FU and radiation. Both studies found no differences in OS and semustine was ultimately excluded from future clinical studies.

6.2. 5-FU. The use of continuous infusion 5-FU over bolus 5-FU has become the standard of care in the perioperative treatment of rectal cancers primarily for its advantageous toxicity profile. In rectal cancer, the North Central Cancer Center Treatment Group (NCCTG) confirmed this by comparing adjuvant CMT with bolus 5-FU versus protracted venous infusion (PVI) [28]. Four-year relapse-free survival (RFS) was 53% in the bolus group and 63% in the continuous infusion group ($P = 0.01$), and four-year OS was 60% in the bolus group as compared with 70% in the continuous infusion group ($P = 0.005$) [28]. There was also significantly more diarrhea seen in the continuous infusion group versus more leucopenia in the bolus group.

6.3. Capecitabine. The backbone systemic therapy in CMT in the past has been 5-FU; while initially given as bolus therapy over 30 minutes, both prior to, with radiation, and following CMT, a randomized study demonstrated superiority of PVI 5-FU, in terms of decrease local relapse and improved OS [29]. Given the convenience of administration of the oral fluropyrimidines, and the fact that their administration which had similar pharmacokinetics to PVI 5-FU, capecitabine was studied in combination with radiation in the neoadjuvant CMT in rectal cancer patients. Phase I studies determined that the recommended phase II dose of capecitabine when combined with 50.4 Gy radiation preoperatively was 1800 mg/m^2 daily given orally in two daily divided doses [30].

For most medical oncologists, capecitabine has become an acceptable equivalent alternative to 5-FU in the perioperative CMT treatment of rectal cancer. Much of this approach is extrapolated from the demonstrated efficacy of capecitabine in the adjuvant treatment of colon cancer [31].

Two randomized phase III studies evaluated the efficacy of capecitabine as a neoadjuvant radiosensitizing agent. The German trial compared the use of 5-FU to capecitabine in the perioperative CMT setting. Patients in the capecitabine arm received preoperative chemoradiation with 50.4 Gy and capecitabine 1,650 mg/m^2 (in two divided doses) on days 1 through 38 plus capecitabine 2,500 mg/m^2 days 1–14 every 21 days for five additional cycles. Patients were also assigned to receive the five additional cycles of capecitabine either before or after TME. Patients assigned to the 5-FU arm received neoadjuvant chemoradiation with 50.4 Gy and either 5-FU 225 mg/m^2 daily or given as 1,000 mg/m^2 on weeks one and five of radiation. Patients were also given four additional cycles of bolus 5-FU 500 mg/m^2 for five days every 28 days. This was given either in the preoperative or postoperative setting. The five-year OS rate was 75.7% for the capecitabine group and 66.6% for the 5-FU group. This was significant for noninferiority ($P = 0.0004$) with a trend towards significance for superiority in favor of capecitabine ($P = 0.053$) [32].

A second randomized study, the NSABP R-04 trial, compared the use of capecitabine to continuous infusion 5-FU (both with or without oxaliplatin) during CMT. 5-FU was given as a 225 mg/m^2 daily PVI during radiation and capecitabine was given at 1650 mg/m^2 orally in two divided doses daily on the days of radiation only. No differences were seen with regards to pathologic complete response, surgical downstaging, or sphincter-saving surgery [33]. Local recurrence and overall survival have yet to be reported.

6.4. Oxaliplatin. Given the efficacy of oxaliplatin in the adjuvant [34] and metastatic [35] treatment of colon cancer, several recent trials have assessed the use of oxaliplatin in the perioperative treatment of rectal cancer. The Studio Terapia Adiuvante Retto (STAR)-01 trial has so far demonstrated a significant increase in toxicity, mainly diarrhea, without a benefit in local tumor response [36]. Similarly, the NSABP R-04 trial evaluated the addition of oxaliplatin with chemoradiation and found no improvement in pathologic complete response, surgical downstaging, or sphincter-saving surgery but did see a significant increase in grade 3 and 4 diarrhea ($P < 0.0001$) [33].

The German CAO/ARO/AIO-04 Trial showed that patients who received oxaliplatin with 5-FU during radiation had a pathologic complete response of 17.6% as compared with 13.1% ($P = 0.033$) for the group that received 5-FU alone during radiation [37]. The ACCORD 12/0405-Prodige Trial, which compared capecitabine with or without oxaliplatin during chemoradiation, demonstrated a similar statistical trend towards benefit with oxaliplatin, with pathologic complete response favoring the group receiving oxaliplatin, 13.9% compared to 19.2% ($P = 0.09$) [38]. Given no prospect clinical trial has demonstrated a survival advantage with the addition of oxaliplatin to CMT, preoperative oxaliplatin is currently not standard-of-care. Longer term followup for all of these studies is needed to evaluated DFS and OS before the efficacy of preoperative oxaliplatin can be assessed.

7. The Role of Additional Chemotherapy after Chemoradiation and Surgery

To date, there have not been any trials that have explored the use of further additional chemotherapy in rectal cancer after neoadjuvant chemotherapy and surgical resection. For the most part, medical oncologists use data from the adjuvant chemotherapy trials in stage II and III colon cancer as evidence and typically aim for a total of six months of perioperative treatment. The Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin (FOLFOX) in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators published the definitive trial that established the addition of oxaliplatin to 5-FU and leucovorin, the FOLFOX regimen, as the standard of care in the adjuvant setting [39]. Capecitabine with oxaliplain (CapeOx) has been shown to be superior to bolus 5-FU modulated by leucovorin (Mayo regimen) [16]. An equilvelance phase III study comparing FOLFOX with CapeOx is currently ongoing; safety data from this adjuvant trial suggest CapeOx is reasonably well tolerated [16]. It is generally recommended that patients with stage III or high-risk stage II colon cancer receive additional postoperative systemic fluropyrimidine-based adjuvant chemotherapy [11]. However, at this point, it is unknown whether or not patients with stage II rectal cancer truly benefit from additional adjuvant chemotherapy or if there is a subset of these patients who do not benefit from further treatment, similar to what is observed with the standard risk patients with stage II colon cancer.

8. Monoclonal Antibody Therapy in Neoadjuvant Treatment of Rectal Cancer

Monoclonal antibody therapies directed at circulating vascular endothelial growth factor (VEGF) and against cell receptor epidermal growth factor (EGFR) have become standard treatments in advanced colorectal cancer [40–42]. The anti-VEGF monoclonal antibody bevacizumab has been combined with capecitabine in a neoadjuvant CMT phase II single center study of 32 patients, with acceptable tolerance and a pathologic complete response rate of 32% [43]. Similar results were observed in another phase I/II single center trial, with promising clinical downstaging and a complete pathologic response rate of 23% (5 of 22 patients) [44]. Bevacizumab has also been combined with both oxaliplatin and capecitabine, in CMT; six of 25 (24%) patients achieved a complete pathologic response although there was noted to be significant gastrointestinal toxicity [45]. At this time no phase III trials evaluating the preoperative efficacy of bevacizumab are actively enrolling. Bevacizumab, cetuximab, and capecitabine are being combined with radiation preoperatively, in an ongoing current trial of KRAS non mutant rectal cancer patients [46]. The EXPERT-C trail was a randomized phase II study of preirradiation CAPOX followed by radiation therapy with capecitabine followed by TME, followed by postirradiation CAPOX; the experimental arm involved weekly concurrent monoclonal anti-EGFR therapy (cetuximab) administered with CAPOX. Of the 164

patients 90 (60%) were KRAS and BRAF non mutant. In this subset of patients the three-year OS was superior in the cetuximab-treated arm (96% versus 81%, $P = 0.035$), although there were no differences in the pathologic complete response rate [47].

9. Future Combined Modality Approaches to Locally Advanced Rectal Cancer

It is recognized that cancers in the upper one-third of the rectal have a lower risk of local recurrence when treated with surgery alone [48]; thus it is possible that some cancers, based on their anatomic location, may not benefit from the addition of radiation to chemotherapy and might be adequately treated with perioperative chemotherapy alone. However, this would have to be confirmed by randomized clinical trials before altering the current standard-of-care. A four-stage combined modality approach (chemotherapy, chemoradiation, surgery, and postoperative chemotherapy), as demonstrated by the EXPERT-C trial referenced above [47], is also being actively evaluated. The duration of preoperative chemotherapy is also being addressed in studies; a three arm trial of chemoradiation, versus chemoradiation and two cycles FOLFOX chemotherapy, versus chemoradiation and 4 cycles FOLFOX chemotherapy, demonstrated a higher pathologic complete response rate associated with the more preoperative FOLFOX chemotherapy, without increasing the surgical complication rates [49]. Whether or not this approach will lead to higher OS rates is currently unclear.

10. Conclusions

The multidisciplinary management of rectal cancer, with the incorporation of radiation and chemotherapy into the treatment plan, has had a significant impact on survival outcomes. Future approaches will likely tailor therapies and approaches based upon the anatomic location of the tumor, the molecular features, and possibly the pathologic response to neoadjuvant therapy. While 5-FU and capecitabine remain the standard therapy for combination with radiation, future studies may define a role for subsets of patients who benefit from the addition of oxaliplatin and 5-FU or capecitabine combined with radiation. The optimal preoperative dose of radiation, treatment schedule, and type of radiation treatment planning techniques continue to be evaluated prospectively in clinical trials. Future significant advances in systemic therapies hold the prospect of decreasing the necessity of surgery or radiation in rectal cancer.

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Clinical Study

Abdominoperineal Resection for Rectal Cancer: Is the Pelvic Drain Externalization Site an Independent Risk Factor for Perineal Wound Healing?

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Aim. The aim of this paper is to investigate if the insertion of the pelvic drainage tube *via* the perineal wound could be considered as an independent risk factor for perineal healing disorders, after abdominoperineal resection for rectal malignancy. *Patients and Methods*. The last two decades, 75 patients underwent elective abdominoperineal resection for malignancy. In 42 patients (56%), the pelvic drain catheter was inserted through the perineal wound (PW group), while in the remaining 33 (44%) through a puncture skin wound of the perineum (SW group). Patients' data with respect to age ($P = 0.136$), stage ($P > 0.05$), sex ($P = 0.188$) and comorbidity ($P = 0.128$) were similar in both groups. 25 patients (*PW* versus *SW*: 8 versus 17, $P = 0.0026$) underwent neoadjuvant radio/chemotherapy. *Results*. The overall morbidity rate was 36%, but a significant increase was revealed in *PW* group (52.4% versus 9%, $P = 0.0007$). In 33.3% of the patients in the *PW* group, perineal healing was delayed, while in the *SW* group, no delay was noted. Perineal healing disorders were revealed as the main source of increased morbidity in this group. *Conclusion*. The insertion of the pelvic drain tube through the perineal wound should be considered as an independent risk factor predisposing to perineal healing disorders.

1. Introduction

The abdominoperineal resection (APR) was first described by Miles in 1908, but early clinical trials reported operative morbidity rates as high as 40% [1–4]. Nissan et al. [5] reported an overall morbidity rate of 50–60% in patients undergoing APR for carcinoma. After the rectum is excised, the sacral cavity forms a large wound area that cannot be efficiently reduced. That area is prone to retention and infection. Besides, it is well documented that postoperative complications of the perineal wound and their long-term residuals comprise the major morbidity factor, especially when combined with neoadjuvant radio/chemotherapy [6–8].

According to published data, some authors recommend the pelvic drain externalization through an abdominal stab incision, while others bring out the tubes directly through the perineum—either *via* a separate skin incision or *via* the perineal wound [9–11]. With regards to our technique, we believe that a perineal externalization site produces better results due to the gravity. To our knowledge, there are no studies up to date concerning the effects of the pelvic drain externalization site on the morbidity rates.

The aim of this study is to investigate whether the insertion of the pelvic drainage tube *via* the perineal wound could be considered as an independent risk factor for perineal healing disorders, following APR for rectal malignancy.

2. Patients and Methods

Between 1991 and 2010, elective abdominoperineal resection for rectal carcinoma was performed in 75 patients (47 males

and 28 females) with a mean age of 69 years (range, 22–82 years). The preoperative assessment for all patients included blood tests, chest X-ray, colonoscopy, and abdominal computed tomography. Since 1995, pelvic MRI was also routinely used for staging purposes. The mean distance of the tumors from the dentate line was 3.1 cm (max: 4 cm, min: 0.5 cm).

Preoperative bowel preparation with polyethylene glycol was routinely performed. Antibiotic prophylaxis consisted of intravenous 2nd generation cephalosporin and metronidazole, given at induction. During procedures lasting more than 2 hours, another dose was administered. No further postoperative antibiotics were used, unless a postoperative complication had arisen that needed treatment. All procedures were performed by one senior colorectal surgeon. Before the beginning of the procedure, randomization of the patient to either one of the two groups found place using a computer-generated ballot.

With regards to the technique used, we performed both abdominal and perineal approaches with the patient in modified lithotomy position. The abdomen was entered through a midline incision, extending from the pubis cephalad to just above the umbilicus. This approach allows adequate visualization of the abdomen, as well as the extension of the incision cephalad, should the splenic flexure need mobilization. A total mesorectal excision with high ligation of the inferior mesenteric vessels and preservation of the pelvic plexuses was performed.

Ninety-two percent of the interventions (69 patients; 38 of the *Perineal Wound* and 31 of the *Skin Wound* group) were performed with curative intent, whereas in 6 patients (8%), 4 of the PW and 2 of the SW group, the procedure was palliative. In one patient of the *Perineal Wound* group, the posterior vaginal wall was also resected *en bloc* with the rectum. In a further *Perineal Wound* group patient, two metastases of the right hepatic lobe were enucleated using radiofrequency ablation. With regards to the *Skin Wound* group, one patient underwent total hysterectomy and resection of the posterior vaginal wall, one underwent resection of the posterior bladder wall, and a third patient underwent resection of the posterior vaginal wall.

A 30-Fr passive drainage was inserted and the peritoneal pelvic floor was reconstructed. This device, also known as gravity drainage system, consisted of a plain tube and a 350 mL volumetric bag (Figure 1). The perineal wound was primarily closed in a two-layer fashion. In 42 patients (56%), the pelvic drain was inserted through the perineal wound, whereas in the remaining 33 patients (44%), the drain was inserted *via* a puncture skin wound to the left lateral portion of the perineum. The puncture site used was due to surgeon's preference. Dermatological anomalies that would not allow the positioning of the puncture wound at this point were not observed in any patient. The pelvic drain was left *in situ* until either the daily fluid amount was less than 50 mL, or the drain had been *in situ* for 5–7 days and the patient was ready for discharge. In the latter case, the drain was removed irrespective of the daily output amount of the drain.

Twenty-five patients, 8 of the *Perineal Wound* and 17 of the *Skin Wound* group ($P = 0.0026$), underwent neoadjuvant chemoradiation. Surgery was performed six to eight weeks after preoperative radio/chemotherapy (Table 1). Patients' data with respect to age, sex, and comorbidity were similar in both groups (Table 2).

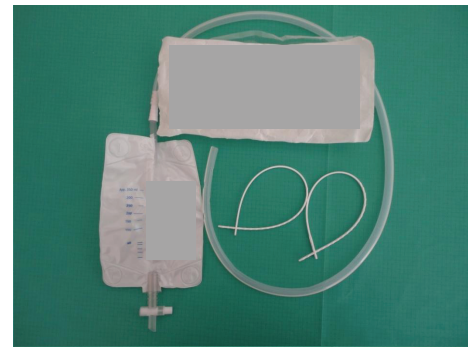

Figure 1: Type of a 30-Fr passive drainage system.

3. Statistical Analysis

Fisher's exact test was used for the comparisons between proportions. All the statistical analyses were performed using the SPSS v.15.0 statistical package (SPSS Inc, Chicago, IL, USA), enhanced with the modules exact tests.

4. Results

All patients were followed-up in our clinic on a weekly basis following their discharge for the first month and monthly thereafter. During follow-up, all patients had their baseline observations taken and a thorough examination of the perineal wound was performed by the operating surgeon and one assistant surgeon. Signs of localized infection, cellulitis, or delayed healing (such as redness, discoloration, swelling, warmth, etc.) were noted and recorded.

Most tumors in both groups were classified as BII according to Duke's classification and most of them were moderately differentiated. The detailed classification and differentiation of all tumors in the two groups is presented in Table 3.

Postoperative complications were observed in 22 patients of the *Perineal Wound* as well as in 5 patients of the *Skin Wound group*. With regards to surgery-specific complications, 20 were noted in patients of the *Perineal Wound* group, as well as 3 in patients of the *Skin Wound* group (PW versus SW: 47.6% versus 9%, $P = 0.0002$). The incidence of perineal wound healing disorders was significantly higher in the *Perineal Wound* group (PW versus SW: 33.3% versus 0, $P < 0.001$). In detail, 14 patients of the *Perineal Wound* showed a delay in perineal wound healing; in 11 of these patients, the perineal wound healing process was completed in 25–40 days (mean 31.2 days), while in three patients a permanent fistula was formed. In the *Skin Wound* group the mean time until complete perineal wound healing was 10 days and no case of healing disorder was noted. On the other hand, the number of patients who underwent neoadjuvant radio/chemotherapy was significantly higher in

Table 1: Patients treated by APR for a low rectal cancer ($n = 75$).

Group	PW ($n = 42$)	SW ($n = 33$)	P value	Significance level
Age*	67.2 (22–81)	71.3 (41–80)	0.157	NS
Sex ♂/♀	26/16	21/12	0.1878	NS
Tumor loc.**		3.1 (0.5–4)		
Indication				
Curative	38 (90%)	31 (94%)	*0.2935*	NS
Palliative	4 (10%)	2 (6%)	*0.2935*	NS
Neo-adjuvant RT/CT	*8*	*17*	*0.0026*	Sig.
Adjuvant RT/CT	21	8	*0.0147*	Sig.

* yrs: value I median (range).
** cm from the dentate line: value is mean (range).
(NS: non-significant; P value >0.05; Sig.: significant, P value <0.05).

Table 2: Risk factors associated with increased morbidity after APR; comparison of the study groups.

Group	PW ($n = 42$)	SW ($n = 33$)	P value	Significance level
Age (>55 yrs)	29	26	0.136	NS
Comorbidity	30	27	0.128	NS
Diabetes	11	7	0.191	NS
Cardiopulmonary dis.	4	5	0.212	NS
Vascular dis.	8	9	0.153	NS
Obesity (B.M.I. >30 kg/m^2)	12	9	0.203	NS
Neo-adjuvant RT/CT	*8*	*17*	*0.0026*	Sig.

NS: non-significant, P value >0.05; Sig.: significant, P value <0.05.

the *Skin Wound* group (SW versus PW: 51.5% versus 19%, $P = 0.0026$), and it is widely known that the incidence of wound healing abnormalities is reported to be higher in these patients. The rate of nonspecific, postoperative complications was exactly the same in both groups (Table 4).

The overall morbidity rate was 36%, but the statistical analysis revealed a significant increase in the *Perineal Wound* group (PW versus SW: 52.4% versus 9%, $P = 0.0007$). 5-year follow-up was completed for 49 patients, with a nonsignificant comparison between the study groups (SW versus PW: 26 versus 23, $P = 0.1336$). With regards to the survival rates, no significance was revealed after the pairwise comparison (SW versus PW: 73.07% versus 73.9%, $P = 0.253$), while the overall rate was 73.4% (Table 5).

5. Discussion

The abdominoperineal resection of the rectum is one of the most demanding procedures in gastrointestinal surgery and has undergone only slight technical modifications since its first description [12–15].

In patients undergoing APR and especially for carcinoma, multiple specific complications may arise either in the short or long term. According to published data, the overall morbidity ranges from 50 to 60% after an APR [16]. Murrell at al. [17] reported that the most common immediate postoperative complication, with a frequency of 32%, is the formation of an intra-abdominal or pelvic abscess. In our study the incidence of this complication was extremely low, as only one case of abscess in the presacral space was noted, which was treated successfully with computed tomography-guided drainage and intravenous antibiotics. Other known complications include nerve injury, ureteric injury, complications from the colostomy site, as well as perineal wound complications [18, 19].

In the past, when blunt dissection was used with little appreciation to the fine pelvic anatomy, sexual dysfunction was seen in up to 75% of men and 40% of women, while bladder dysfunction was seen up to 80% of cases. Nowadays, following the introduction of TME, these rates—even though influenced by age, tumor location, and comorbidity—are reported to be 10–30% for sexual dysfunction and less than 5% for bladder dysfunction [20, 21]. Moreover, postoperative radiation tends to exacerbate male sexual dysfunction [22]. In our study, 2 cases (2.7%) of urinary but no case of sexual dysfunction was noted, as sharp dissection in the proper planes helped avoiding injury to the nerve plexuses.

The perineal wound poses a unique risk, predisposing to major postoperative complications. Despite improved surgical techniques, the rates of perineal wound dehiscence are reported to be higher than 10%, as it was also shown in our data. Furthermore, it is observed in 30–40% of patients who undergo neoadjuvant radiation [23–26]. The anatomy of the pelvic floor and the inherent potential risk of infection secondary to rectal surgery are associated with a high rate

Table 3: Staging and differentiation.

Group	PW ($n = 42$)	SW ($n = 33$)	P value	Significance level
Staging (Duke's)				
In situ	2	—	*0.310*	NS
A	3	3	*0.311*	NS
BI	6	5	*0.254*	NS
BII	14	13	*0.165*	NS
CI	3	3	*0.311*	NS
CII	11	7	*0.191*	NS
D	3	2	*0.351*	NS
Differentiation				NS
Well	10	4	*0.107*	NS
Moderate	28	23	*0.189*	NS
Poor	4	6	*0.149*	NS

NS: non-significant, P value >0.05.

Table 4: Complications, morbidity, and mortality.

Group	PW ($n = 42$)	SW ($n = 33$)	P value	Significance level
Complications	22	5	*0.0007*	Sig.
Surgical (specific)	20	3	*0.0002*	Sig.
Abdominal wound dehiscence	2	2		
Pelvic abscess*	1	—		
Ostomy necrosis**	—	1		
Evisceration/reoperation	1	—		
Perineal healing disorders	**16**	—	***<0.001***	Sig.
Delay in perineal healing	14	—		
Perineal wound dehiscence	2	—		
Medical (nonspecific)	2	2	*0.374*	NS
Pneumonia	1	—		
Urinary dysfunction	1	1		
Atrial fibrillation	—	1		
Morbidity	**52.4**%	**15.2**%	***0.0007***	Sig.
Mortality		0		
Overall morbidity		**36**%		

* In the presacral space, treated with CT-guided drainage.
** treated with primary relocation.
(NS: non-significant, P value >0.05; Sig.: significant, P value <0.05).

of perineal healing abnormalities following an APR. Besides, perioperative chemoprophylaxis fails to provide sufficient protection, because vessel ligature and electrocoagulation result in reduced perfusion and consequent disorders in microcirculation of the sacral cavity [27].

A confounding issue is the different opinions as to what risk factors impair the perineal wound healing. According to Christian et al. [28], higher rates of major wound complications were associated with increased body mass index, diabetes, and stage, while preoperative radiation and primary closure were not associated with increased complications. On the other hand, Luna-Pérez et al. [29] demonstrated that the main cause of morbidity was perineal wound infection, influenced by postoperative radio +/− chemotherapy administration and patient age over 55 years.

In our patient group, the overall morbidity rate was 36%, while perineal healing disorder was noted to be the most common postoperative complication (59.3% of all case complications). Primary healing of the perineal wound, meaning no formation of seroma or hematoma and no signs of inflammation, was seen in 78.7% of patients. In the *Perineal Wound* group, the morbidity was significantly higher compared to the *Skin Wound* group (52.4%; 22/42 of patients, $P = 0.0007$). Perineal wound healing abnormalities were the main source of increased morbidity in this group (72.8%; 16/22 of complicated cases, $P = 0.001$). There were

Table 5: Local recurrence and survival.

Patients (n)	SW	PW	Overall		P value*	Significance level
Compl. 5-year follow-up	26	23	49		0.1336	NS
Deaths	7	6	13		0.2831	NS
Cause of death				*Time after APR (months)*		
LR**	1	1	2	12, 24		
LR** + hepatic metastases	—	1	1	6		
Hepatic metastases	3	2	5	12, 12, 14, 18,38		
Brain metastases	1	—	1	24		
Lung + hepatic metastases	1	1	2	18, 24		
Hepatic + brain metastases	1	—	1	24		
Stroke	—	1	1	36		
Survival (%)	73.07	73.9	***73.4***		0.253	NS
Local Recurrence (%)	3.8	8.7	***6.1***		0.357	NS

* SW versus PW.
**LR: local recurrence.
NS: non-significant, P value >0.05; Sig.: significant, P value <0.05.

14 cases (33.3%) of delayed perineal healing, as well as 2 cases (4.8%) of perineal wound infection/dehiscence, which were treated conservatively.

Apart from the pelvic drain externalization site, patients in both groups showed no statistically significant differences with regards to population data, comorbidities, disease stage, and intraoperative conditions. As mentioned before, these parameters have been reported to affect perineal wound healing in many publications [30, 31]. Moreover, it is shown that even though the number of patients who underwent neoadjuvant radiation was significantly higher in the *Skin Wound* group, the rate of perineal wound healing abnormalities was significantly lower in these patients compared to those of the *Perineal Wound* group. This fact correlates with recently published studies suggesting the lack of any relation between pelvic irradiation and perineal healing abnormalities [26]. According to these findings, it is clearly demonstrated that the insertion of the pelvic drain tube through the perineal wound constitutes an independent risk factor affecting perineal wound healing, which results in increased postoperative morbidity rates in patients undergoing APR for rectal cancer.

6. Conclusion

The insertion of the pelvic drain tube through the perineal wound should be considered as an independent risk factor following an APR, predisposing to perineal healing disorders.

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