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Management of locally recurrent rectal cancer

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ABSTRACT

The diagnosis and management of recurrent rectal cancer is surgically and oncologically challenging. Recurrence usually presents within 1–3 years of treatment for primary tumor, and diagnostic workup should assess pelvic resectability and workup for metastatic disease. Treatment includes neoadjuvant chemotherapy and/or radiotherapy, as well as surgical resection when an R0 resection is feasible. Neoadjuvant chemotherapy and radiotherapy is recommended in chemo/radiotherapy naïve patients. Preoperative or intraoperative reirradiation is feasible, but the long term impact on likelihood of R0 resection and survivability is controversial. Chemoradiation may also be used to palliate unresectable disease.

Introduction

The treatment of locally recurrent rectal cancer (LRRC) poses significant oncologic and surgical challenges. Approximately half of rectal cancer recurrences are locoregional, with an expected 43,030 new cases in 2018.[1] Recurrence has been associated with positive nodes, distal margin less than 1 cm, venous invasion, anastamotic leak, intraoperative disruption of the tumor, and lack of adjuvant chemotherapy and/or radiotherapy.[2–5] The Dutch TME trial demonstrated that patients who undergo total mesorectal excision (TME) with preoperative radiotherapy have a 4.6% recurrence rate, while patients without radiotherapy have an 11% recurrence rate.[2,6] A history of prior surgery, chemotherapy, and/or radiotherapy can obfuscate the diagnosis of recurrence, as fibrosis can obscure recurrence on pelvic MRI. Prior surgical resection, particularly total mesorectal excision, will disrupt anatomic planes and make subsequent surgical intervention more difficult. Decisions regarding neoadjuvant, intraoperative, and adjuvant therapy must consider patient history of chemotherapy and/or radiotherapy in the setting of heterogenous data regarding outcomes. While R0 surgical resection is the most significant predictor of outcomes of LRRC, successful treatment must consider factors including patient health, history of treatment and anatomy of the tumor. There are multiple considerations when approaching diagnosis, neoadjuvant treatment, and surgical resection of LRRC.

Presentation, workup and diagnosis

Recurrence of rectal cancer can present with pain or gastrointestinal symptoms, on surveillance imaging (pelvic MRI, PET-CT), on proctoscopy, and/or with rising CEA levels. Recurrence usually presents within 1 to 3 years of treatment for the primary tumor.[6–8] A 2012 study found that over 86% of LRRC were symptomatic at the time of presentation, with the primary symptom being pain.[9] When there is concern for LRRC, further workup includes evaluation of pelvic resectability and workup for metastatic disease.

The diagnosis of recurrence is ideally made via a tissue biopsy, but this is not always possible in the setting of previous surgical resection. High-resolution pelvic MRI is considered the optimal imaging modality for preoperative staging and surgical planning.[10] Preoperative MRI is associated with a negative predictive value of 93–100% when assessing invasion into structures, with a positive predictive value of 53–100%. Diffuse fibrosis, particularly in the pelvic side wall, can be difficult to differentiate from recurrent tumor and can obscure assessment of tumor invasion.[11,12] An estimated 40–50% of patients with LRRC present with synchronous metastases, therefore CT of the chest, abdomen, and pelvis should be performed before treatment.[13,14] Additional imaging may include PET-CT scan and/or high-resolution ultrasound for operative planning.

The patient with LRRC should also be referred to a multidisciplinary team which provides surgery, oncology, radiology, and pathology expertise to evaluate the optimal approach.[15,16] When assessing the need for preoperative, intraoperative, or postoperative radiation and/or chemotherapy, up to 26% of cases may benefit from such collaborative discussion, and thorough interdisciplinary communication may significantly improve the likelihood of achieving an R0 resection.[16,17]

Neoadjuvant, intraoperative, and adjuvant therapy

The utilization, choice and timing of chemotherapy and/or radiotherapy for LRRC is highly variable across institutions. Approximately 52–80% of patients with LRRC have a history of prior chemotherapy

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and/or radiotherapy for their index cancer treatment.[18,19] The 2013 Beyond TME Collaborative included consensus statements regarding neoadjuvant chemoradiation, but was inconclusive regarding the practice of re-irradiation for LRRC.[15]

In patients with no history of chemotherapy and/or radiotherapy for their primary tumor, perioperative chemoradiotherapy is recommended, and may improve the odds of R0 resection. Neoadjuvant chemotherapy is most often dosed during preoperative radiotherapy treatments, though some centers give additional postoperative chemotherapy with the guidance of the consulting oncologist.[20,21] Chemotherapy can include 5-fluorouracil and capecitabine with or without oxaliplatin or leucovorin, and several current regimens include only capecitabine.[7,20–22] A 2016 study found that chemotherapy did not significantly impact survival in patients with an R0 resection, but did improve survival of patients with R1 and R2 resection.[8]

The literature on LRRC is inconclusive and nuanced regarding reirradiation for LRRC patients with a history of prior chemoradiotherapy. In a much-cited study, Yu et al. evaluated tumor response to radiotherapy in patients with primary and recurrent rectal cancer, finding that recurrent rectal cancer was significantly less responsive to radiotherapy. Perioperative radiotherapy, either index or re-irradiation, has been shown to increase the likelihood of R0 resection to 43% and 50%, respectively when compared to patients without radiotherapy (26% R0 resection).[23] Radiation dosing is dependent on a history of prior radiation, and is given pre or intra-operatively (IORT). Neoadjuvant radiation dosing of patients without a history of prior radiation ranges from 45 to 54 Gy, delivered in fractions of 1.5–2.3.[7,20,21,24,25] In patients with a history of prior radiation, preoperative reirradiation is delivered at a decreased dose of 27–39.6 Gy in fractions of 1.7–2.2.[7,20,21,26] Finally, IORT is used in some centers in relation to resection margin, with doses of 10–17 Gy tailored to for R0, R1, and R2 resections.[7,20,21,24,27,28] Few groups give postoperative radiation.[26]

Multiple studies have questioned the overall oncologic impact of re-irradiation for LRRC. Dresen et al. found that patients who received radiation (either index or re-irradiation) as part of their treatment for LRRC had longer survival than those who were not irradiated.[24] Alberda et al. compared 139 patients with LRRC undergoing perioperative radiotherapy and surgical excision of their recurrent tumors. Patients with a history of prior radiotherapy were more likely to have R1 resection for LRRC, but had similar overall survival after resection and re-irradiation.[20] Bosman et al. described the reirradiation of 135 patients with LRRC, performed prior to reoperation, and found no significant difference when compared to patients undergoing index radiotherapy at the time of treatment for LRRC. In this study, index radiation dosing was 50.4 or 50 Gy, while reirradiation was dosed at 30 or 30.6 Gy, and additional IORT was given at 10, 12.5, or 15 Gy for R0, R1, and R2 resections, respectively.[7] Owens et al. similarly showed trends toward clinical improvement with re-irradiation, but no improvement in local control or overall survival.[18] A 2018 study of over 1000 patients showed that negative margins and bone resection influenced overall survival, while neoadjuvant therapy did not influence survival and increased complications.[19] In this study, 20.3% underwent bone resection during surgery. R0 resection was 67.4% in patients who had bone resection, and 56.2% in patients who did not ($p=0.0006$). Neoadjuvant therapy was associated with increased 30-day complication rates (OR 1.53, 95% CI 1.19–1.97), was not associated with R0 versus R1 versus R2 resection, and was not associated with increased survival on multivariable analysis.

While the efficacy of reirradiation is still under investigation, reirradiation is feasible, the utilization of intraoperative radiotherapy (IORT) may permit more targeted treatment in the setting of previous radiation, and hyperfractionated radiotherapy is recommended in previously irradiated fields.[29] Radiation toxicity is highly variable and dose-dependent, experienced in 5–50% of patients.[26,30] The major risk of reirradiation is radiation toxicity, which is inconsistently captured in studies examining reirradiation. Radiation toxicity is divided into acute and chronic toxicity. It can include diarrhea, ureteral or urethral stricture, nausea and vomiting, skin breakdown, and fistula formation. Rates of Grade 3 or greater radiation toxicity range from 4.6% to 22%, with the most common symptom being chronic, severe diarrhea in up to 17% of patients.[26,30] Surgery is usually performed 10–16 weeks after completion of chemo/radiotherapy.[7,8,21]

Surgical considerations

Multiple studies have established R0 resection as the single most important factor in successful treatment for LRRC. Successful R0 resection ranges from 53% to 66% and is dependent on surgical technique and the location of the tumor.[7,21,24,31–33] Only 18–30% of patients have resectable disease at presentation of LRRC.[18] Development of surgical specialty centers and collaboration with other surgical specialties have allowed specialists to pursue resection of tumors previously considered unresectable. As up to 50% of patients present with previously undetected peritoneal disease, diagnostic laparoscopy may significantly impact operative approach, including the decision to proceed with laparotomy.[34] Laparoscopic approach may allow for less comorbid procedures but was associated with decreased R0 resections in a prospective study of primary rectal cancers (81.7% laparoscopic vs. 86.9% open).[35]

In a 2013 Delphi study, most surgeons considered poor baseline performance status, bilateral sciatic nerve involvement, and circumferential bone involvement as absolute contraindications to surgical intervention.[15] Relative contraindications included extension of tumor through the sciatic notch, encasement of the external iliac vessels, high sacral involvement, irresectable distant metastases, and predicted R2 resection. Involvement of the S1/S2 nerve roots is considered a contraindication to surgical approach.[12,15]

Location of recurrence

The location of LRRC as it relates to adjacent pelvic structures has historically been a significant factor in achieving R0 resection. Relationship to the anterior, sacral, or lateral regions of the pelvis confer increasing difficulty with resection and associated worse outcomes. Several groups have sought to categorize the nature of recurrence and associated outcomes. However, a 2013 Delphi study revealed significant variation in surgeon assessment of risk and resectability as associated with tumor location. While anterior and axial compartments were considered resectable, there was less agreement on the posterior and lateral compartments.[10]

An early school of classification used tumor fixation, including categories for no fixation, one site, two sites, or three or more sites. Fixation of a LRRC indicated advanced recurrence, decreased likelihood of R0 resection, and poor prognosis in comparison with mobile tumors.[25,36] Wanebo et al. categorized LRRC based on bowel wall invasion, from local/minimal invasion to local/fully extensive invasion.[37]

The majority of recent studies describe recurrence as it relates to the bony structures of the pelvis and native rectum. An evaluation of the Dutch TME study divided recurrences into presacral, anterior, anastomotic, lateral, or perineal. Presacral recurrences are the most common location in patients with and without a history of radiotherapy, and lateral recurrences account for approximately 20% of LRRC.[6] Presacral tumors without bony invasion may be amenable to en bloc resection with periosteal elevation, though these have an increased risk of hemorrhage and must be approached carefully.[14] Presacral tumors with high bony invasion to the coccyx and sacrum may require pelvic reconstruction after extensive bony resection, and should be approached in coordination with orthopedic services. Lateral tumors may have significant structural involvement of vascular and neurologic structures, with associated high morbidity and poor prognosis.[12,38] R0 resection is significantly more likely in anterior and

axial LRRC.[39] Patients with central and/or anastamotic tumors may be amenable to laparoscopic approach.[14]

Advanced surgical techniques

Invasion of LRRC into the lateral pelvic wall is considered significantly comorbid and a potential contraindication to surgical intervention. Pelvic exenteration with *en bloc* lateral wall resection has been described with a 53–66.5% rate of R0 resection. This technique had high associated morbidity, with *en bloc* resection of the obturator internus and piriformis muscles, sacrotuberous and sacrospinous ligament, and sacral nerve roots, as well as necessary bony structures.[31,40]

The invasion of tumor above S2/S3 levels has historically been considered prohibitive to R0 resection. Resection above this level requires pelvic reconstruction, usually performed in conjunction with orthopedic specialty services. In a specialty center, this procedure carries a significant morbidity of 76%, but a R0 resection achieved in 74–93% and 5-year survival of 46%.[41,42]

While these techniques may confer improved survival potential to patients, they should be performed in specialty centers with available expertise and consulting professionals

Prognosis

Outcomes after treatment for LRRC are dependent upon achieving R0 resection.[8,25] Two year overall survival after surgery for LRRC ranges from 50% to 75%, while 5 year survival has been described as 17% to 42%.[7,20,21,25,43] One 2016 study found five year survival is approximately 44% for patients with R0 resection, 26% for R1 patients, and 10% for R2 patients.[8] Morbidity is dependent on the extent of resection and reconstruction, ranging from 26% in standard TME to 82% after high sacrectomy.[25,42] In patients undergoing re-resection and re-irradiation for LRRC, factors associated with inferior progression-free survival included a history of stage III disease at primary diagnosis, positive margin at primary surgery, synchronous or previously resected metastases, and lateral or sacral type recurrence.[21]

Treatment of unresectable LRRC may include chemotherapy, radiation, palliative surgical intervention including intestinal diversion, and hypoxic pelvic perfusion.[41,44] Radiotherapy has been shown to decrease pelvic symptoms including pain and rectal incontinence up to 83%.[45,46] Chemoradiation for unresectable symptomatic disease has been shown to have significant impact on pain.[47] In patients with unresectable disease, chemoradiation was shown to extend life by 10-12 months, but was never curative.[48]

Limitations

The standardized treatment of locally recurrent rectal cancer is significantly hampered by heterogeneous treatment protocols across multiple centers, including contraindications to surgery, chemotherapy regimens, and the utilization and timing of re-irradiation. Furthermore, many studies lump locally advanced primary rectal cancer with LRRC, despite significantly different rates of R0 resection (91% vs 62%) and disease free survival (76% vs 57% at 3 years).[32]

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