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Favorable Postoperative Complication Rate after Neoadjuvant Therapy and Transanal Full Thickness Local Excision for Rectal Cancer

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Abstract

Purpose: Full thickness Local Excision (LE) for patients with Moderately Advanced Rectal Cancer (MARC) whose tumors respond favorably to neoadjuvant therapy is one approach for organ preservation. Some authors have suggested abandoning LE due to frequent and severe postoperative complications. We report post-operative complications following neoadjuvant therapy and LE for MARC after modifications to the LE surgical technique and radiotherapy field and dose.

Methods: Between May 2017 to October 2020, 14 patients were diagnosed with MARC; 9 were treated in a phase II prospective trial and received neoadjuvant therapy, followed by limited full thickness LE with no/minimal Margins (LLE) after Complete Clinical Response (CCR) of their tumors. Five additional patients were treated off protocol and received only chemoradiotherapy followed by LLE. The radiation therapy dose ranged from 45 Gy to 54 Gy.

Results: Two patients with tumors extending to the dentate line experienced grade III postoperative complications of severe pain, infection, and fistula formation. One patient was treated with a seton and the other had a complete abdominoperineal resection due to residual tumor post-LLE of the 12 remaining patients with tumors located 3 cm to 8 cm from the anal verge, only two patients (17%) developed grade II toxicity requiring non-operative management. In both cases, symptoms resolved within 1 week.

Conclusion: Managing MARC with LE after neoadjuvant therapy with CCR should not be abandoned. Modifying the preoperative radiation field and dose, along with LLE and avoiding resection into the dentate line, produces acceptable post-operative complications. This approach remains a viable option for achieving 3 organ preservation for select patients.

Keywords: Chemo-radiotherapy; Local excision; Rectal cancer

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Introduction

Neoadjuvant chemo-radiotherapy followed by Total Mesorectal Excision (TME) is considered the gold standard for treatment of Moderately Advanced Rectal Cancer (MARC). This approach is associated with excellent local control [1]. However, long term toxicity, with its adverse impact on quality of life, can affect nearly half of treated patients [2-3]. Furthermore, these side effects are not expected to improve with time [4]. Even 2 years after completion of treatment, a significant proportion of patients are not able to resume their pre-illness employment [5]. This observation has motivated many centers around the world to pursue other, less aggressive surgical approaches. The concept of organ preservation for rectal cancer was introduced by the seminal work of Dr. Habr-Gama and her colleagues from Sao Paolo [6]. At present, there are two approaches being pursued to maintain the excellent local control obtained by the standard TME while also improving long-term quality of life: full thickness transanal Local Excision (LE) and Watchful Waiting (WW). Only patients with tumors demonstrating favorable clinical response to neoadjuvant treatment are selected for either of these conservational approaches. Local excision provides the advantage of accurate assessment of the pathological response of the tumor. The local control rate of tumors in ypT0 status is excellent and is in the range of 95% [7-16]. Unfortunately, LE after neoadjuvant radiotherapy can be associated with frequent and severe complications, unlike LE when performed without radiation in early rectal cancer. This is primarily because of the adverse effects of preoperative radiation on the process of surgical wound healing [17-20]. On the other hand, the WW policy avoids any surgical

intervention in cases of Complete Clinical Response (CCR) of the treated tumors. However, because of the limitations of our clinical restaging procedures, WW can be associated with a high probability of tumor regrowth (15% to 20%) [21]. Salvage TME is usually successful in achieving excellent local control, but this requires very complex follow-up schedules and strict compliance on the part of the patient. In addition, recent reports have raised 4 concerns about the possibility of increased distant metastatic disease in patients failing the initial WW approach and developing tumor regrowth [22]. The merits of both of LE and WW approaches were recently debated [23-24]. Since 2016, our group has been enrolling patients with locally advanced rectal cancer in an IRB approved, phase II trial. We offer LE to patients with tumors in CCR status following completion of total neoadjuvant therapy. We attempted to reduce post-LE surgical complications with a slight reduction in the radiation therapy dose and field, as well as limiting the size of the resected tissue during the LE procedure. The Term Limited Local Excision (LLE) will be used in this manuscript to reference our surgical technique.

Material and Methods

Patients

Between May 2017 and October 2020, we treated 14 patients at the Van Elslander Cancer Center, Ascension St. John Hospital. The study cohort included 7 females and 7 males with a median age of 63 years (49 to 87 years). The cohort characteristics are summarized in Table 1. Two patients were staged as T2N0 and all others were staged as T3N0. At time of diagnosis, 2 patients presented with very distal tumors involving the dentate line. The distal edge of all other tumors was located between 3 cm and 8 cm from the anal verge. The craniocaudal extent of the tumors ranged from 3.8 cm to 8 cm. Five patients (36%) had complete circumferential tumor involvement of the rectal wall. There were 9 patients enrolled in our rectal cancer organ preservation phase II protocol. These patients received total neoadjuvant therapy followed by LLE. An additional 5 patients, treated at the same time period, did not participate in this protocol and received only concurrent chemoradiotherapy (without neoadjuvant chemotherapy) followed by LLE, either because they declined induction chemotherapy or by the surgeon's preference. Patients in both groups achieved CCR.

Neoadjuvant chemotherapy

Upfront neoadjuvant chemotherapy was given to patients enrolled in our prospective trial. A total of 6 cycles of FOLFOX (fluorouracil, leucovorin, oxaliplatin) were administered by infusion every 2 weeks. All 5 patients received concurrent chemo-radiotherapy with either 5 fluorouracil infusions or oral capecitabine.

Radiation therapy

Radiation therapy was initiated 3 weeks after induction chemotherapy (if given). For all 14 patients, the radiation therapy field was limited to the true pelvis with an upper border usually placed at S2 to include the primary tumor, mesorectum, and presacral and internal iliac nodes. Common iliac nodes and external iliac nodes were always excluded. The radiation therapy field was designed according to the recommendations of the International Consensus Guidelines on Clinical Target Volume Delineation in Rectal Cancer [25]. This clinical target volume is somewhat smaller than that which has previously been used in some studies of preoperative radiation, organ preservation or is currently recommended by experts, where the common iliac nodes are routinely included and the placement of the caudal border of the radiation field at the top of L5 is required [26-30]. A dose of forty-five Gy was delivered to the initial Planning Target Volume (PTV) with daily fractions of 1.8 Gy/day. Per study protocol, no boost was delivered to patients enrolled in the prospective trial when CCR Was observed after induction chemotherapy. For all other patients, a sequential boost of 5.4 Gy to 9 Gy was prescribed to a smaller PTV created by the addition of 1 cm margins to the initial gross tumor volume. Both 3-dimensional and intensity modulated techniques were used. Four patients (29%) received a radiation dose of only 45 Gy as their tumors exhibited CCR after induction chemotherapy. A boost dose of 9 Gy was delivered only in one patient, while the remaining 9 patients received a total dose of 50.4 Gy.

Assessment of tumor response

The response of tumors was assessed 1 to 2 weeks before surgery by physical examination, flexible Endoscopy, and pelvic Magnetic Resonance Imaging (MRI), using a special rectal cancer protocol and/or endoscopic ultrasound. Patients were offered LLE only if there was no clinical evidence of residual disease after neoadjuvant treatment.

Surgical resection

Surgical resections were performed either by robotic-assisted transanal minimally invasive full thickness LE 6 technique (10 patients) or by transanal conventional techniques (4 patients). The aim was to resect the residual gross abnormality apparent after neoadjuvant therapy (white scar, telangiectasia, erythema, etc.) with no or minimal mucosal margin and minimal dissection into the perirectal fat. The time interval between completion of radiation therapy and surgical resection ranged between 6 to 17 weeks with a median value of 11.5 weeks. In 12 cases, the LLE technique was used. Only 1 patient was treated off protocol, with excision of a 1 cm margin around the residual mucosal abnormality.

Results

The operation time ranged between 46 and 93 min, with a median of 60 min. Blood loss was minimal in all cases. All resected specimens were intact with no fragmentation. After neoadjuvant therapy, the largest dimension of the resected specimens in 13 patients, as measured by gross pathological examination, ranged between 3.5 cm and 1.4 cm, with a median of 2.2 cm. In 1 additional patient, the resected specimen was much larger, with a dimension of 6.8 cm. The depth of dissection ranged from 1.5 cm to 0.4 cm, with a median of 0.6 cm. After LLE, all patients were discharged either on the same or the following day of surgery except for 1 patient, who required a 48-h hospital stay. Four patients developed postoperative complications between 2 weeks to 6 weeks following LLE. In 2 patients, the LLE dissection extended to the dentate line, resulting in severe

Table 1: Summary of the patient population.

Male	7
Female	7
Age	49 to 87
T2N0	2
T3N0	12
Tumor size	3.8 cm to 8 cm
Tumor extending to dentate line	2
Circumferential tumor involvement	5
Received neoadjuvant chemo	9

Table 2: Patients that Developed Complications.

Resected Specimen Size		Dentate Line Excised	Surgical Technique	Complication	Comments
1	6.8 × 2.3 × .06	Yes	Conventional resection	Ano-cutaneous fistula	Not fully continent
2	2.5 × 1.5 × 1.4	Yes	Robotic Resection	Severe pain, hemorrhage, infection, and sepsis	Underwent completion APR
3	2 × 1.9 × 0.9	No	Robotic Resection	Rectal Bleeding	Complete resolution of symptoms
4	2 × 1.3 × 0.8	No	Robotic Resection	Fever, abdominal pain, nausea, vomiting	Complete resolution of symptoms

APR: Abdominal Perineal Resection

Table 3: Post-operative pathology and outcome.

Patients on Protocol	9	
pT0	7	Observation
pT2	1	Refused TME
pT3	1	Had complete APR
Patients off Protocol	5	
pT0	3	Observation
pT1	1	Observation
pT3	1	Refused TME

APR: Abdominal Perineal Resection; TME: Total Mesorectal Excision

complications. One patient developed a fistula requiring unroofing of the track and placement of a drainage seton; this patient has not regained full continence. The second patient developed severe pelvic pain 2 weeks after LLE, which was managed initially as an outpatient. He subsequently underwent completion abdominoperineal resection as he had YPT3 disease. This procedure was complicated by pelvic hemorrhage, infection, sepsis, and a prolonged hospital stay. In 2 of the remaining 12 patients (17%) with dissection not extending to the dentate line, only minor complications were observed. One patient was admitted for 48 h because of rectal bleeding that was resolved with conservative treatment without blood transfusion, while the other patient was admitted for 3 days because of a low-grade fever and abdominal pain, nausea, and vomiting. Symptoms resolved with a short course of antibiotics. The remaining 10 patients did not suffer from any complications. Table 2 summarizes the occurrence of complications in this series and Table 3 depicts the yp staging and post treatment disposition.

Discussion

Although the concept of organ preservation in MARC was introduced decades ago, it is not widely applied in many centers, as physicians frequently do not feel comfortable discussing this approach with their patients [31]. We hypothesized that the concept of LLE would be easier than WW to introduce to centers that have not yet adopted the idea of organ preservation, because of the ability to microscopically determine the disease status shortly after completion of therapy. The reported very low local recurrence rate after LE in multiple single-arm studies when ypT0 status is confirmed, together with the presence of level I evidence demonstrating equal control rate to that achieved by TME [32], add to the sense of security when LE is adopted as a method of organ preservation. Our LLE approach further facilitates the adoption of an organ preservation strategy as it appears to address the issue of increased severe complications rate that have frequently been cited as a problem with the classical LE approach. The reports of frequent and severe toxicity associated with the classical LE approach is likely one of the major reasons the National Comprehensive Cancer Network (NCCN) did not include LE as a recognized approach in their most recent publication, despite the fact that there is a much stronger level of evidence supporting its long-term safety in terms of tumor control than exists for WW, which was included in the recent NCCN guidelines [33]. Garcia-Aguilar et al. reported a 39% grade ≥ 3 complication rate; they determined that the high toxicity rates were unacceptable and prematurely terminated their study [17]. The most common complication in their study was perianal pain that lasted for a few months. Other noted complications included rectal bleeding, infection, and incontinence. In their study, a modest escalation of the radiation dose to 54 Gy was initially used before it was lowered to 50 Gy to 50.4 Gy. A decrease in toxicity was noticed with lowering of the radiation dose. These investigators also employed a doublet chemotherapy regimen of 5-Fluorouracil and oxaliplatin during the entire course of their trial. It also appears that LE was pursued to play a therapeutic role as the rate of negative margins was very low and the study required that all participating surgeons had to have performed at least 3 LE procedures with negative margins. The study protocol recommended the excision of 1 cm of surrounding margin of normal mucosa around the residual macroscopic abnormality. A Sao Paulo group reported frequent and severe complications with 60% of their patients experiencing wound dehiscence, as well as other complications including severe pain, rectal bleeding requiring transfusion, rectal stenosis, and recto-vaginal fistula requiring fecal diversion [18]. Arezzo et al. [20] also reported a 50% severe complication rate, the most common of which were suture dehiscence and severe pelvic pain. An enterocutaneous fistula required colostomy in one patient. The study was closed before the accrual goal because of the reported severe toxicity. This group used a short course of radiation therapy with no chemotherapy. The surgical protocol mandated resection of at least 1 cm of normal mucosa around the gross abnormality. In contrast, other authors have published favorable toxicity profiles that are similar to our findings. In a series of 425 patients who were treated by either LE alone (120 patients) or after neoadjuvant radiation (350 patients), only 10% of the patients experienced minor complications, with major complications affecting only 1.4% of the cohort [8]. Similarly, in a study of 43 patients treated by neoadjuvant therapy followed by LE, only 1 patient experienced grade III complications while five others experienced grade I or II adverse effects [9]. Our approach differs from others who aim for adequate resection of the possible residual tumor by excising the gross abnormality, which can be as big as 3 cm in some cases, with additional lateral margins of at least 1 cm. In these cases as well, the dissection can be carried out all the way to the mesorectal fascia to achieve sound oncological resection [19]. In contrast, the view of our group is similar to that of Stipa et al., who consider that LE is merely a biopsy to pathologically confirm the

impression of complete clinical response [29]. We do not rely on LE to have any therapeutic value unless the residual tumor is a limited pT1 with a negative margin of resection. We believe, therefore, that the excision should be limited to the residual gross abnormality without the need for any margin of the surrounding normal mucosa or deep resection into perirectal fat. We recommend completion TME for patients with any residual disease that is >pT1R0. We do not consider that limiting the excision to only the residual gross abnormality will risk missing any residual microscopic malignancy that may be confined to tissues outside the mucosal abnormality. Pathological studies (including unpublished data from our institution) indicate the bulk of any residual disease is present in the bowel wall directly underneath the gross mucosal abnormality [34,35]. The small dimensions of the resected tissues in our series correspond to our preference for limited excision. Our surgical approach does not take into consideration the circumferential extent or the size of the tumor at time of diagnosis as only the post-therapeutic mucosal abnormality is excised, which tends to be much smaller than the size of the cancer at initial presentation. Therefore, we can include patients with complete circumferential tumor involvement as well as large tumors in this review even though such patients would be ineligible for many organ preservation trials [8,17,32]. We cannot comment on the local tumor control rate in view of the short follow up period, the small number of patients and treatment heterogeneity in our study. However, it is worth noting that to date, none of the patients in this series has experienced local failure. Other areas of concern regarding the use of the LE approach is that, due to the formation of post-LE fibrosis, there is no opportunity to perform sphincter saving surgery when completion TME is indicated following LE, particularly if surgical complications have already occurred before completion TME is contemplated [19]. We cannot address this issue from our data as only 1 patient with initial disease encroaching the dentate line required complete abdominoperineal resection, and he would not have been a candidate for sphincter preservation even if LLE had not been performed. It is reassuring that we did not encounter any difficulties in interpreting various follow-up studies performed after completion of the entire treatment as this is also one of the issues that has been raised regarding the LE approach [19]. Our data suggest a high rate of severe complications when the surgical wound extends into the lower anal canal. Habr-Gama et al. have forwarded the theory that this finding is related to lack of tissue elasticity and different innervation in these tissues [19]. We therefore stopped offering the LLE approach to patients presenting with very low rectal tumors involving the dentate line. These patients are instead offered a WW strategy. We continue to offer total neoadjuvant therapy with possible LLE for all other patients and continue to limit the radiation dose to 45 Gy for tumors in CCR after induction chemotherapy, while other patients are treated to a total dose of 50 Gy. We no longer use the 54 Gy dose in the context of organ preservation with LLE. We do acknowledge the treatment heterogeneity in our report as it combines retrospectively and prospectively reviewed 2 groups of patients and not all patients received induction chemotherapy. However, we do not aim in this report to comment on the tumor control outcomes that can be affected by this heterogeneity, but only to report on our postoperative complication rate that would not be influenced by this variation in neoadjuvant treatment since all patients received similar courses of concurrent chemoradiotherapy.

Conclusion

The limitations of our study include its small size, and our results need to be confirmed in a larger series. However, our findings support a conclusion that managing MARC with transanal full thickness local excision after neoadjuvant therapy with CCR should be limited but not abandoned. Post-operative complications are acceptable if LLE does not extend to the dentate line, the radiation therapy field is modified as described, and the radiation dose is limited to a maximum 50.4 Gy. In contrast to WW, pathological information obtained by this procedure is of significant prognostic importance and can avoid unnecessary delay in delivering definitive treatment for patients with residual microscopic disease.

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