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Intraoperative pelvic brachytherapy for treatment of locally advanced or recurrent colorectal cancer

R. S. Turley¹, B. G. Czito², J. C. Haney¹, D. S. Tyler^{1,3}, C. R. Mantyh^{1,4}, and J. Migaly^{1,4}

¹Department of General Surgery, Duke University Medical Center, Durham, NC, USA

²Department of Radiation Oncology, Duke University Medical Center, Durham, NC, USA

³Division of Surgical Oncology, Duke University Medical Center, Durham, NC, USA

⁴Division of Colorectal Surgery, Duke University Medical Center, Durham, NC, USA

Abstract

Background—The aim of this study was to evaluate the efficacy and morbidity of intraoperative radiation therapy (IORT) for advanced colorectal cancer.

Methods—All patients undergoing IORT for locally advanced rectal cancer from 2001–2009 were reviewed for cancer recurrence, survival and procedure-related morbidity. Cumulative event rates were estimated using the method of Kaplan and Meier.

Results—Twenty-nine patients with locally advanced (n=8) or recurrent (n=21) rectal cancers were treated with IORT and resection. Surgical interventions included low anterior resection, abdominoperineal resection, pelvic exenteration, and a variety of non-anatomic resections of pelvic recurrences. R₀ resections were achieved in 16 patients, while R₁ resections were achieved in 10, and margins were grossly positive in 3 patients. IORT was delivered to all patients over a median area of 48 (42–72) cm² at a median dose of 12 (12–15) Gy. Local and overall recurrence rates were 24% (locally advanced group) and 45% (recurrent group). Median disease-free and overall survival were 25 and 40 months respectively at a median follow-up of 26 (18–42) months. The short-term (≤ 30 days) complication rate was 45%. Eight patients developed local wound complications, 5 of which required operative intervention. Four patients developed intra-abdominal abscesses requiring drainage. Long-term (>30 days) complications were identified in 11 patients (38%) and included long-term wound complications (n=3), ureteral obstruction requiring stenting (n=1), neurogenic bladder (n=3), enteric fistulae (n=2), small bowel obstruction (n=1), and neuropathic pain (n=1).

Conclusions—Intraoperative brachytherapy is a viable IORT option during pelvic surgery for locally advanced or recurrent colorectal cancer but is associated with high postoperative morbidity. Whether intraoperative brachytherapy can improve local recurrence rates for locally advanced or recurrent colorectal cancer will require further prospective investigation.

Keywords

Intraoperative brachytherapy; Locally advanced colorectal cancer; Recurrent colorectal cancer

Corresponding Author John Migaly, M. D. DUMC 2817, Durham, NC, 27710, USA Tel. (919) 681-3977; Fax (919) 681-7934; john.migaly@duke.edu.

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Introduction

Surgical treatment of locally advanced or recurrent colorectal cancer is clinically challenging due to high rates of local recurrence and disease-specific mortality [1]. Historically, surgery alone has been associated with high rates of local recurrence and poor outcomes [2, 3]. Although preoperative external beam radiation therapy has been shown to improve locoregional control after surgery [4], many patients with locally recurrent colorectal cancer are precluded from effective postoperative external beam radiation therapy due to dose limitations imposed by previous radiation delivery or proximity of radiosensitive pelvic organs [5]. A promising alternative strategy to adjuvant, external beam therapy alone is intraoperative radiation therapy (IORT) [6]. After complete surgical resection of the tumor focus, high-dose-rate brachytherapy (HDR-IORT) can be delivered with a flexible applicator, providing complete coverage of potentially complex three-dimensional (3D) pelvic resection beds and limiting radiation exposure to radiosensitive tissues [7].

As part of a combined-modality treatment strategy including neoadjuvant chemoradiotherapy and aggressive surgical resection, HDR-IORT may improve local control and, thus, increase survival for patients with advanced colorectal malignancy. Early reports regarding the efficacy of IORT for improving disease-free and overall survival have been encouraging [5, 8, 9]. However, contemporary studies estimating perioperative complications, long-term complications, local disease control and overall survival after intraoperative brachytherapy are lacking. The primary purpose of this study is to estimate disease-free and overall survival of patients with locally-advanced (T4) or locally recurrent rectal cancer following multi-modal treatment including HDR-IORT and extensive tumor extirpation. The secondary objective of this study was to assess the tolerability of HDR-IORT by estimating short term (<30 days) and long-term (> 30 days) complications.

Materials and Methods

After obtaining approval from the Institutional Review Board, demographics, clinicopathologic data, surgical treatments, and postoperative outcomes of patients who underwent HDR-IORT and surgical resection for advanced colorectal carcinoma between 2001 and 2009 were reviewed. Most colorectal and pelvic lesions were detected preoperatively with colonoscopy, computed tomography, magnetic resonance imaging, and/or positron emission tomography. The extent of surgical resection was at the discretion of the operating surgeon with the aim of achieving negative surgical margins while preserving uninvolved pelvic organs when possible.

Preoperative Radiation

In general, radiation naïve patients with locally advanced rectal cancer (e.g. T4 primary tumor) receive 45-50.4 Gy of external beam radiation followed by surgery and IORT 8-10 weeks after their final radiation dose. Radiation is administered through a 4 field (anterior posterior, posterior anterior, opposed lateral) technique or 3 field (posterior anterior opposed lateral) technique to 45 Gy, followed by a boost to 50.4 Gy. During treatments, the patient is positioned prone on a belly board with a full bladder using 3D planning techniques. For patients who had been previously irradiated (i.e. recurrent rectal cancer), when it is felt additional radiation therapy may be possible/indicated, additional radiation therapy is administered using highly conformal techniques (either using 3D or Intensity Modulated Radiation Therapy) to a total dose of approximately 20-30 Gy, encompassing the primary disease with a small margin.

Intraoperative Radiation

HDR-IORT delivered through a flexible Harrison-Anderson-Mick (HAM) applicator was used to allow for coverage of a complex 3D pelvic resection bed as previously described [7]. Briefly, after resection was completed and the specimen was removed, a sterile HAM applicator was sutured to the resection bed and/or secured with packing (Figure 1). Lead shields were used as necessary to protect uninvolved tissues such as the bladder and ureters, and nontarget bowel was maximally retracted. The HAM applicator was then connected to the HDR remote afterloader. Once the patient was deemed hemodynamically stable by the anesthesiologist, all staff left the room and the patient was treated with brachytherapy via the remote HDR afterloader. In general, the procedure requires approximately 90 minutes of additional anesthesia time, including setup and treatment.

Data Collection

Data collected included patient demographics, tumor staging and treatment characteristics, as well as intraoperative and postoperative variables including margin status, length of stay, local and distant recurrence. Short-term (< 1 month) and long-term (>1 month) complications were identified from the medical record and included wound healing complications, intrabdominal infection, ureteral obstruction or bladder dysfunction, small bowel obstruction, enteric fistula and need for reoperation. When appropriate, data regarding previous rectal surgeries, including surgery date and type, were reviewed. Margins were ascertained based on final pathological assessment and radiation doses were obtained from radiation oncology records. Date of last follow-up or date of death of all patients was collected.

Statistical Analysis

Summary statistics were obtained using established methods and presented as either percentages for categorical values or medians with 25th-75th percentile or interquartile ranges (IQR) for continuous variables. The overall survival time was estimated from the date of surgery to the date of last follow-up. Cumulative event rates were estimated using the method of Kaplan and Meier [10]. All statistical analyses were done using commercially available software STATA® v11.1 (College Station, TX).

Results

Between 2001 and 2009, 29 patients underwent resection and HDR-IORT brachytherapy for colorectal cancer. Clinical and demographic characteristics are shown in Table 1. Eight (28%) patients were treated for locally advanced (T4) colorectal tumors, and 21 (72%) patients were treated for pelvic recurrences. Prior surgeries are summarized in Table 2 and were highly variable, ranging in complexity from transanal excision to abdominoperineal resections (APR). The median (IQR) disease-free interval for recurrent cases was 29 (17-42) months.

The majority of patients received preoperative therapy prior to surgical resection with 28/29 (97%) receiving 5-FU based chemotherapy. Given that this case series included patients with both locally advanced primary and recurrent disease, prior radiation treatments were quite heterogeneous. Twenty-eight out of twenty-nine (97%) patients received external radiation prior to surgery either for primary or recurrent disease, with a median total radiation dose of 50.4 (45-50.4) Gy. Twenty out of twenty-one (95%) patients with recurrent disease, received radiation prior to IORT as part of their primary disease treatment. One patient underwent excision of a recurrent rectosigmoid cancer followed by 43.2 Gy of adjuvant radiation. The median (IQR) time interval between the conclusion of last neoadjuvant therapy and surgery was 9 (9-12) weeks.

Six (21%) of the 29 patients were treated with low anterior resection (LAR), 5 (17%) with APR, 6 (21%) with pelvic exenterations and 12 (41%) with non-anatomic resections of pelvic recurrence. Median estimated blood loss was 500 (350-875) mL. Pathological examination of resected specimens revealed that 16/29 (55%) tumors were completely resected with negative margins on microscopic examination (R_0), 10/29 (34%) resections had microscopic tumor involvement of surgical margins (R_1), and 3/29 (10%) resections had gross residual disease (R_2). After specimen removal, all patients received HDR-IORT to a median dose of 12 (IQR: 12-15) Gy delivered to 0.5 cm depth over a median area of 48 (IQR: 42-72) cm².

Complications were tabulated and characterized based on timing (Table 3). The overall perioperative (< 30 days) complication rate was 45% (13/29), with the vast majority of these infectious in nature. These included 8 wound complications, 5 of which required operative intervention such as rotation flaps (n=2) and operative debridement (n=3). Six of the 8 wound complications involved the perineum. Four patients developed an intrabdominal infection managed by image-guided percutaneous drainage, and one patient developed aspiration pneumonia which required an extended stay in the intensive care unit. There was no perioperative mortality. The median length of hospitalization was 8 (6-11) days. Long-term (>30 days) complications were identified in 11 (38%) patients. Three (10.3%) patients required extended wound care for difficulties healing incisional wounds. Four (14%) patients developed urinary complications 30 days after surgery. Specifically, 2 patients had urinary retention and 2 had urinary incontinence. One patient developed ureteral obstruction managed initially with ureteral stenting but ultimately requiring percutaneous nephrostomy drainage, and 3 patients developed symptoms of neurogenic bladder requiring urologic consultation. One (3%) patient developed a small bowel obstruction requiring laparotomy, and 2 (7%) patients developed enteric fistulae, one enterocutaneous and one enterovaginal, both excised operatively. Finally, one patient developed long-term neuropathic pelvic pain requiring referral to a chronic pain specialist.

At a median postoperative follow-up of 26 (18-42) months, 7 (24%) patients developed local pelvic recurrence while an additional 6 (21%) developed distant metastases, resulting in an overall recurrence rate of 45%. Estimated disease-free and overall survivals are shown in Figures 2 and 3. Estimated median disease-free and overall survival were 25 and 40 months respectively.

Discussion

Achieving wide, tumor-free margins during resection of locally advanced or locally recurrent rectal cancer is often hindered or prevented by the propensity of these tumors to fixate upon or invade vital pelvic structures. Given that local recurrence can evolve into distant metastases, strategies which decrease local recurrence rates may reduce metastatic progression, and thereby improve overall patient survival [11]. One such strategy is the use of IORT, which can be delivered via different modalities, including electron beam and high-dose rate brachytherapy [12, 13]. In the present series we employed a high-dose rate iridium-192 source via a malleable applicator (HDR-IORT), a strategy intended to maximize radiation exposure to tissues at greatest risk of recurrence while minimizing exposure to neighboring radiosensitive organs due to rapid dose fall off. As compared to linear-accelerator based techniques, HDR-IORT is less limited by technical and anatomical constraints [5]. In this contemporary series using high-dose rate brachytherapy (HDR-IORT) applied via a flexible Harrison-Anderson-Mick (HAM) applicator, estimated disease-free and overall survival at 3-years was 38% and 60%, respectively.

Previous non-randomized studies have suggested IORT delivered as either an external electron beam or as brachytherapy may reduce rates of local recurrence, thereby potentially improving overall survival [5, 7, 8, 14]. Valentini et al. reported in 2009 that IORT administered using an external electron boost ranging between 10 and 15 Gy may decrease local recurrence (LR) rates after R₀ resection for primary T4M0 rectal cancer [0% LR with IORT (n=29) vs. 19% LR without IORT (n=49) at a median follow-up of 31 months] [15]. Similarly, Kusters et al reported a 5-year LR rate of 12% for patients with primary T3 or T4 rectal tumors treated with multimodality therapy including IORT delivered as an external electron beam [16]. In contrast to linear accelerator techniques, when HDR-IORT is delivered as brachytherapy via a malleable applicator there is minimal patient transport as the equipment is readily portable, thereby mitigating any potential risk imposed by transporting an anesthetized surgical patient with an open abdominal cavity. Furthermore, the malleable applicator used in the current study may be more amenable to providing a homogenous radiation dose to complex 3D structures than external beam techniques which are more geometrically limited.

More recently, a French randomized trial was conducted on patients with locally advanced rectal cancer (T3 or T4, N+, and M0) to investigate the efficacy and tolerability of IORT. In the study, all patients received 40 Gy of preoperative radiation therapy alone and were then randomized to surgery alone (n=68) or surgery with IORT (n=72). Although the study failed to show a significant improvement in local control and disease-free survival, IORT was well tolerated without a significant increase in postoperative complications. By design, however, this study excluded previously resected rectal cancer patients with local pelvic recurrences as well as patients with macroscopically positive margins after surgical excision, while including patients with T3 disease who we generally would not consider candidates for IORT, which could account for the surprising similar, low 5-year local recurrence rates (~8%) seen in both groups [17]. In stark contrast to the low LR rates in the aforementioned studies, in our study, which is comprised of patients with both locally recurrent (72%) and advanced (T4) disease (28%), there was an estimated local recurrence rate of 62% at 3 years. This recurrence rate is similar to those reported in older series and is most likely a function of our institutional bias to reserve IORT for patients with recurrent disease or T4 primary rectal tumors in whom we doubt it is possible to achieve negative surgical margins [8, 9, 14, 18]. Interestingly, none of the 3 patients in whom surgical margins were grossly positive experienced a recurrence despite a follow-up of 18-59 months. This may argue for the effectiveness of the radiotherapy.

The estimated perioperative morbidity after combined surgical resection and IORT was relatively high (45%), but, overall, consistent with the 53% morbidity rate reported by Mathis et al in 2008 [19]. Similar to other reports, the predominance of early complications (<30 days) were related to wound infections or delayed wound healing [5, 8, 9, 14, 18]. Formation of intrabdominal abscesses requiring percutaneous drainage was also common. Clearly, these complications are also encountered with extensive pelvic-rectal surgery, even in the absence of IORT. Without randomization, it is difficult to attribute these complications to radiotherapy alone. Nevertheless, the majority were successfully resolved. Furthermore, the relatively short length of hospitalization (8 days) highlights the fact that most of the complications seen in our patients were wound-related and could be managed in outpatient visits. The long-term complication rate was also relatively significant (34%), although the profile varied more. Most notably, we experienced predominance of urologic complications, most commonly bladder dysfunction and ureteral obstruction. This is consistent with a study performed at the Mayo Clinic, where 14% of patients experienced ureteral narrowing when radiation doses of at least 20 Gy were delivered via a linear accelerator [20].

There are several limitations of this study worth mentioning. First, the small sample size limits our ability to make statistical comparisons between tumor-free margins or tumor-positive margins, which have been previously correlated with recurrence and reduced survival rates [5]. Second, we could not compare survival after IORT and surgery for locally advanced (T4) and local recurrent colorectal cancers. Third, the retrospective nature of this study may underestimate the urogynecologic dysfunction or neuropathic pain complications, which have previously been reported to approach 50% and are often underreported by patients and physicians [21]. Fourth, we were unable to accurately identify second site of recurrences (local after distant recurrence or distant after local recurrence) as many patients sought further treatment for recurrence at a facility nearer to their permanent residence. Finally, the median follow-up for this study was only 26 months.

Conclusions

Despite these limitations, our study supports further investigation of HDR-IORT for patients with locally advanced or recurrent rectal cancer as this approach may be reasonably tolerated and might improve disease-free and overall survival for these patients. Although our institutional experience supports the incorporation of IORT as a possible component of an aggressive multimodal approach to treating locally advanced or recurrent colorectal malignancy, larger studies are needed to more accurately characterize its efficacy for marginally-resectable and locally recurrent colorectal cancer.

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Figure 1.
High-dose-rate brachytherapy (HDR-IORT) delivered with a flexible Harrison-Anderson-Mick (HAM) applicator

Figure 2.
Disease-free survival

Figure 3.
Overall survival

Table 1

Patient Demographics

Age (IQR)	58 (54-68)
Sex (%)	
Male	12 (41)
Female	17 (59)
ASA physical classification, (%)	
2	12 (41)
3	17 (59)
Comorbidities, (%)	
Diabetes mellitus	3 (10)
Hypertension	5 (17)
Congestive heart failure	1 (3)
History of stroke	1 (3)
Chronic obstructive pulmonary disease	1 (3)
History of DVT	2 (7)
Coronary artery disease	2 (7)
Chronic renal insufficiency	1 (3)
Heart transplant	1 (3)
BMI (IQR)	25.6 (21.5-29.4)

IQR- Interquartile range (25%-75%), ASA – American Society of Anesthesiologists, DVT – Deep venous thrombosis, BMI-Body mass index

Table 2**Previous Colorectal Surgical History and Preoperative Treatments**

<i>Previous surgery (%)</i>	
No previous surgery (T4)	8 (28)
Low anterior resection	13 (45)
Abdominoperineal resection	2 (7)
Transanal excision	2 (7)
Segmental colonresection	4 (14)
<i>Preoperative treatments (%)</i>	
5-FU based neoadjuvant chemotherapy	28 (97)
External beam radiation	28 (97)
Median Radiation Dose (Gy) (IQR)	50.4 (45-50.4)

Gy- Gray, IQR- Interquartile Range (25%-75%),

Table 3**Complications**

<i>Perioperative complications (< 30 days) (%)</i>	
Any complication	13 (45)
Mortality	0 (0)
Wound complications	8 (28)
Intraabdominal abscesses	4 (14)
Aspiration Pneumonia	1 (3)
Anastamotic leak	1 (3)
<i>Long-term complications (> 30 days) (%)</i>	
Any perioperative complication	11 (38)
Wound complications requiring long-term care	3 (10)
Neurogenic bladder dysfunction	4 (14)
Ureteral stricture	1 (3)
Enterocutaneous fistula	1 (3)
Enterovaginal fistula	1 (3)
Small bowel obstruction	1 (3)
Chronic pelvic pain	1 (3)