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RADIATION THERAPY AND RADIATION THERAPY INNOVATIONS IN COLORECTAL CANCER (PP LEE AND AC RALDOW, SECTION EDITORS)

Emerging Role of Brachytherapy in the Non-operative Management of Rectal Cancer

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Abstract

Purpose of review The non-operative management of rectal cancer is an area of active research. Dose-escalated radiotherapy may improve sustained local control but toxicity is a concern. Brachytherapy is emerging as a promising boost technique that may confer dosimetric advantages over external beam radiotherapy (EBRT)–based boosts.

Recent findings Preliminary findings from two multicenter prospective randomized phase II/III trials suggest high rates of sustained 2-year local control with a combination of EBRT and either contact X-ray brachytherapy or high dose rate endorectal brachytherapy compared with an EBRT boost.

Summary Brachytherapy is a promising technique in the non-operative management of patients with rectal cancer. Further research will be needed to characterize long-term oncologic and toxicity outcomes.

Keywords Rectal cancer · Non-operative management · Brachytherapy

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed non-skin cancer in the USA and a leading cause of cancer death with 52,580 deaths expected in 2022 alone [1]. For all but the earliest staged rectal cancers, standard treatment includes total mesorectal excision. While this is a highly effective treatment [2], it can significantly impact long-term quality of life. In patients who receive low anterior resection with sphincter sparing intent, up to 50% will develop low anterior resection syndrome characterized by fecal incontinence, rectal urgency, and frequent bowel movements [3, 4]. In addition, low-lying rectal cancers require non-sphincter sparing abdominoperineal resection and consequently have permanent stomas which can be associated with post-operative complications and significant detriments in quality of life [5, 6].

Based on the potential for significant quality of life changes after surgery, especially if sphincter sparing resection is not feasible, it is clear why patients are motivated to explore non-operative management (NOM) options. Habr-Gama and colleagues were the first to publish data showing that omission of surgery in patients who achieved an excellent response to chemoradiotherapy did not have significantly compromised oncologic outcomes [7]. Multiple trials have subsequently supported the oncologic safety and feasibility of NOM paradigms [8–13]. Quality of life with NOM also appears improved across multiple domains including overall health, bowel, urinary, and sexual function compared to patients who undergo surgery [14].

Given the promising oncologic and quality of life outcomes with NOM management, there is growing interest in strategies that optimize the safety and efficacy of this treatment pathway. This review will discuss the emerging role of brachytherapy as a means of increasing the likelihood of successful NOM.

Rationale for Dose Escalation

Though clinical complete response (cCR) and local regrowth rates vary widely in the literature, standard external beam radiation therapy (EBRT) using doses of 50.4 to 54 Gy

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results in initial cCR rates of 50%, with approximately 25% local regrowth and 15% pathologic complete response rates [11, 12, 15]. There is data suggesting that cCR (and ultimately pCR) rates can be increased with escalated radiotherapy dose [16]. In a recent systematic review of NOM for rectal cancer, a dose–response relationship was identified showing increased local control with higher doses of radiation [17]. All trials included reported at least 2 years of follow-up data and enough dosimetric information to allow for estimation of tumor dose in EQD2 with alpha/beta 10 Gy. 15 trials (4 using some sort of brachytherapy boost) were ultimately analyzed, with 2-year local control ranging from 12 to 72% and primary tumor doses ranging from EQD2 40.7 to > 160 Gy. Dose–response appeared to taper off at > 100 Gy, with local control around 72% and associated with T stage. The estimated equivalent 2 Gray dose for 50% local control at 2 years was 66 Gy for cT1-2 while it was 85 Gy for T3-4 tumors.

Trying to achieve external beam doses over 60 Gy with intensity-modulated brachytherapy may be possible but is challenging given normal rectal dose limitations. The risk of CTCAE grade 2 or higher rectal toxicity including rectal bleeding significantly increases with the volume of rectum receiving 60 Gy or higher [18]. QUANTEC guidelines recommend limiting the volume of rectum receiving 65 and 70 Gy to less than 25% and 20%, respectively, in order to limit late grade 2 or higher toxicities to < 15%. Both the ongoing APHRODITE [19] and Danish Watch and Wait 3 (NCT04095299) trials, which randomize patients to 50.4 Gy EBRT or dose-escalated EBRT to 62 Gy with simultaneous integrated boost, will use IMRT. The results of these studies will be important to assess oncologic outcomes following IMRT-based dose escalation and associated acute and long-term impact on quality of life with higher than previously delivered EBRT doses.

Brachytherapy as a Boost

Endorectal brachytherapy offers an elegant solution to the challenges of EBRT dose escalation discussed thus far. Heterogenous dose deposition and steep dose fall off allow for higher tumor radiation doses with concomitant sparing of surrounding normal tissues compared to even the most conformal EBRT techniques.

The most common methods being used to perform endorectal brachytherapy include contact X-ray brachytherapy (CXB), high-dose-rate brachytherapy (HDRBT), and low-dose-rate (LDR) seeds. Most published data utilize CXB or HDRBT, therefore we will focus the remainder of the review on these methods (Table 1).

Table 1 Summary of relevant clinical studies investigating non-operative management for rectal cancer

Study	Year	Design	# Pts	Brachy method	EBRT dose	Boost dose	Complete response (cCR or pCR)	TME free survival
OPRA	2022	Phase II	324	None	45 Gy in 25 fx	5–9 Gy EBRT	74% (cCR)	59%
OPERA	2022	Phase III	148	CXB	45 Gy in 25 fx	SOC: 9 Gy in 5 fx EBRT Exp: 90 Gy in 3 fx weekly	61% (cCR) 90% (cCR)	59% 80% (3y)
HERBERT	2017	Phase I	38	HDRBT	39 Gy in 13 fx	15–24 Gy in 3 fx weekly	61% (pCR)	Not reported
MORPHEUS*	2022	Phase II/III	40	HDRBT	45 Gy in 25 fx	SOC: 9 Gy in 5 fx EBRT Exp: 30 Gy in 3 fx weekly	50% (cCR) 90% (cCR)	38.6% 76.6% (3y)

*Interim phase II analysis

CXB, contact brachytherapy;

HDRBT, high dose rate brachytherapy;

Fx, fractions;

EBRT, external beam radiation therapy;

cCR, clinical complete response (defined differently by various studies);

pCR, pathologic complete response

Contact Brachytherapy for Non-operative Management

Most of the published data supporting CXB in NOM paradigms is retrospective and originating from select high-volume centers experienced with the technique. Some of the earliest published data investigating CXB was the Lyon R96-02 randomized trial [20], which enrolled patients with locally advanced low-lying rectal cancer. Participants were treated with neoadjuvant EBRT (39 Gy in 13 fractions) and then randomized to either standard of care TME or an endorectal CXB boost 2 weeks after EBRT prior to TME. The primary endpoint was the rate of sphincter preservation. Of 88 patients randomized, 81 went on to surgery. Sphincter preservation was significantly higher in the experimental arm (76% vs 44%, $p = 0.004$). Furthermore, the addition of CXB boost led to significantly higher complete clinical response rates prior to surgery (24% vs 2%) and higher complete or near complete pathologic responses (57% vs 34%). There were no differences in grade 3 or higher toxicity, surgical complication rates, or disease free or overall survival between the two groups. This randomized trial established a proof of concept that dose escalation with CXB was feasible and may lead to significantly improved sphincter preservation.

Since this trial, Sun-Myint and colleagues reported outcomes in a retrospective cohort of 200 patients who largely had residual disease after EBRT but were unfit for or refused completion TME and instead were treated with a CXB boost [21]. CXB was delivered using a P50 machine, with up to three adaptive doses of 30 Gy every 2 weeks. Initial response assessment was determined at 6–8 weeks after CXB and follow up DRE/endoscopy was performed every 3 months with MRI and CT scans every 4–6 months after treatment. cCR was seen on initial re-staging in 144 of 200 analyzed patients (72%) with 124 (62%) of these patients sustaining a cCR allowing for organ preservation on long-term follow-up. At a median follow-up of 2.7 years, 79% of the 136 patients were alive and remained colostomy-free. One criticism of this data is the heterogeneous population which included 17 patients with early-stage tumors, which are more likely to respond to radiotherapy [22].

This same group also published their oncologic outcomes in a more narrowly defined cohort [23]. In this analysis, 83 patients were identified with cT2/3N0-2 disease who had ≤ 3 cm of residual disease after EBRT and opted for CXB rather than proceeding with surgery. At 6–8 weeks after CXB, 53 (63.8%) patients achieved initial cCR with 46 (55.4%) patients sustaining cCR through median 2.5 years of follow-up. Local regrowth occurred in 6 (11.3%) patients who all underwent successful salvage surgery. Ultimately, 83.1% of patients were disease free at time of analysis.

Building off these earlier experiences, there is now modern prospective data. A French multi-institutional prospective cohort trial enrolled patients with cT2/3 rectal cancers who were planned for NOM with a combination of CXB and EBRT [24]. Patients with tumors up to 5 cm and N1 disease with nodes < 1 cm were included. For tumors smaller than 3.5 cm, CXB (up to 3 fractions of 30–35 Gy delivered 2 weeks apart) was sequenced first followed by EBRT. For larger tumors, EBRT was sequenced first. Clinical tumor response was based on DRE, endoscopy, and MRI. 74 patients were enrolled with 53 receiving CXB first. At first response assessment on week 14, 71 (95%) patients achieved a cCR ($n = 31$) or near cCR ($n = 40$). Many near cCR patients at first response assessment converted to cCR on subsequent assessments, with 64 (86%) patients achieving a cCR at 6 months after treatment start. 13 patients with cCR or near cCR underwent local excision with 7 patients having ypT1-2 disease. Local regrowth was seen in 7 (10%) of the 71 patients with cCR or near cCR. Ultimately, 64 patients (86.4%) were alive and free from rectal tumor at time of analysis.

Efforts to compare these favorable outcomes with CXB boost to EBRT have also been undertaken. A propensity score matched analysis compared cancer-specific and distant metastasis free survival between patients treated with CXB + chemoradiation NOM and matched patients from the Accord 12 phase III trial — which treated patients with neoadjuvant chemoradiation followed by surgery [25]. 5-year cancer specific survival (82% CXB vs 89% Accord 12) and distant metastasis free survival (22% vs 15%) were not significantly different [26].

While these data were encouraging, randomized data was still lacking until recently. The OPRA randomized phase III trial was initiated in 2015 and closed to enrollment in 2020 after accruing 141 patients with cT2-3N0-1 rectal cancer up to 5 cm in diameter involving no more than 50% of luminal circumference. All patients received EBRT to 45 Gy with the control arm receiving a 9 Gy sequential EBRT boost to the tumor and the experimental arm receiving a 90 Gy in 3 fraction CXB boost. The primary endpoint of this trial was 3-year organ preservation rate. In preliminary results reported at ASCO 2022, organ preservation rate was 60% in the control arm compared to 81% in the experimental arm and for tumors < 3 cm, rates were 65% versus 91% [27••]. While these are early results and more time must be given for data maturation, this is the strongest evidence to date for the benefit of CXB boost for appropriate patients seeking NOM.

CXB as a boost with EBRT also appears to be relatively well tolerated. In the French prospective trial, grade 1–2 rectal bleeding was noted in 34% of patients which started typically 6 months post treatment and lasted for up to 2 years. 9% developed acute grade 3 acute toxicities while

11% developed late grade 3 toxicities requiring argon plasma coagulation 1–2 years after completing treatment [24]. We are still awaiting toxicity data from the OPRA trial which will provide more informed comparisons of toxicities with EBRT versus EBRT plus CXB.

In summary, CXB is a promising technique with mounting evidence supporting its role in NOM. One limitation is its limited availability with only 11 centers in Europe having P50 machines and few training opportunities for this specialized modality [28]. Interest is growing and consensus guidelines on patient selection, dose regimens, technique, and follow-up have been published to help standardize practice [29•].

HDR Brachytherapy for Non-operative Management

Endorectal HDR brachytherapy involves the use of a rectal single or multi-channel applicator to deliver high doses of conformal radiation directly to the target tumor (Fig. 1). It has been used either alone or in conjunction with EBRT prior to surgery with pooled pCR rates of 22.2% (range 18–31%) [30]. More recent work has also investigated the role of HDR-based brachytherapy boost in NOM.

In an early Danish prospective registry trial, patients with cT2-3 low rectal adenocarcinomas were treated with dose escalated EBRT (60 Gy to the primary tumor and 50 Gy to the lymph node volumes) and a 5 Gy HDRBT boost to the primary tumor during the last week of treatment [31]. Biopsies were performed every 2 weeks after the end of treatment with the final response assessment at 6 weeks post treatment. cCR was assessed on DRE and endoscopy with MRI used to assess nodal disease, but not the primary tumor. 51 patients were enrolled with 40 (78%) showing cCR. Local regrowth rate was 15.5% at 1 year and 25.9% at 2 years with median time to regrowth of 10.4 months. On long-term follow-up, 5-year local regrowth rate rose to 31% [32]. Ultimately, 58% of patients had sustained local control at 2 years without surgery. By 5 years post treatment, 49% of patients had some degree of rectal bleeding. Overall, these results showed a higher rate of clinical complete response, but similar rate of local regrowth compared to prior EBRT NOM series [7].

Further dose escalation with HDRBT was piloted by a Canadian group [33]. In contrast to the Danish approach, which delivered HDRBT during the last week of EBRT, this approach delayed the first fraction of HDRBT until 3–4 weeks after completing EBRT. This allowed for tumor regression and treatment-related proctitis to improve prior to additional therapy. As such, the tumor volume at the start of HDRBT was smaller and each subsequent fraction was planned adaptively with MRI to account for further tumor regression. Results from their prospective registry data of 92 patients treated with 40 Gy in 16 fractions of EBRT followed by 30 Gy in 3 fractions delivered weekly showed an 86.2% clinical complete response rate at 8 weeks post treatment with a local regrowth rate of 13.6% at median follow-up 1.9 years [34]. 2-year sustained local control was 71.5%. Late grade 3 bleeding requiring transfusions occurred in 12.8% of patients. With boosting smaller portions of the rectum, the higher HDRBT boost doses in this trial were both well tolerated and demonstrated improved rates of sustained local control.

Based on these promising results, the phase II/III multicenter randomized MORPEHUS trial was initiated. In this trial, patients with cT2-3abN0M0 low-mid rectal (within 10 cm of anal verge) cancers were enrolled and treated with EBRT to 45 Gy followed by either a 9 Gy EBRT boost to the primary tumor or 30 Gy in 3 weekly fractions of image-guided adaptive HDRBT. Preliminary results were published this year reporting a 50% cCR rate in the EBRT arm and 90% cCR rate in the HDRBT arm. 2-year TME-free survival was 38.6% vs 76.6% in favor of the HDRBT arm [35••]. There was a 10% rate of acute grade 3 rectal bleeding. Though the trial has yet to reach its accrual goal and longer follow-up

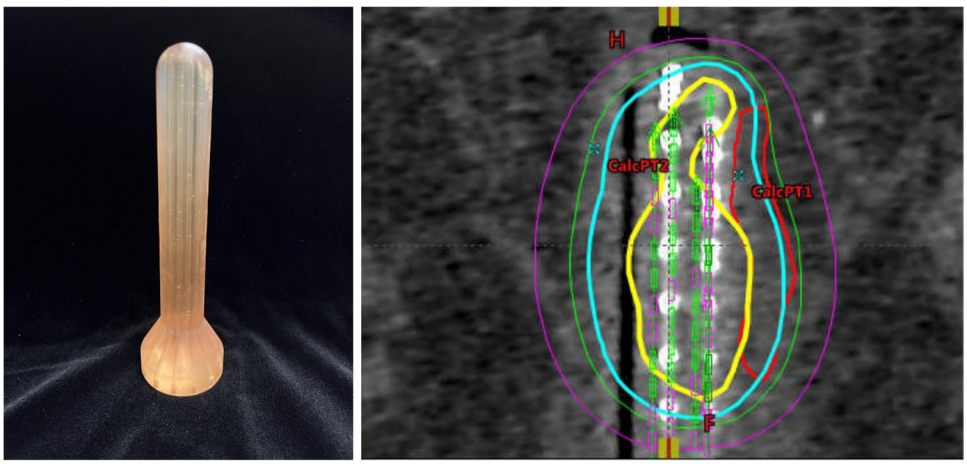

Fig. 1 Example of high dose rate endorectal brachytherapy. 3D printed multi-channel applicator (left) with dosimetry on a coronal CT slice (Red=CTV, Blue=100% isodose, Yellow=200%, Purple=50%) showing a highly conformal dose distribution (right). Images courtesy of John David, MD from University of South Florida

is needed for confirmation of sustained clinical complete response and TME-free survival, these early results are in line with the previously discussed OPRA trial and demonstrate some of the highest rates of initial clinical complete response and organ preservation to date.

These results are in contrast to two previous randomized trials (RECTAL-BOOST which added an EBRT boost of 15 Gy in 5 fractions [36] and a Danish trial which added 2 fractions of 5 Gy HDRBT [37]) that failed to show a benefit with dose escalation. This may be due to the lengthening of the time from end of treatment to response assessment allowing for additional time to achieve a cCR. However, lengthening of the time to assessment does not explain the lower regrowth rates seen with the use of CXB and HDRBT boosts. Currently, the impact of dose escalation on sustained local control is controversial. A meta-analysis found that increasing T-stage predicted for higher rates of local regrowth while dose was not associated with local regrowth rates [15]. However, of the 602 patients included in this meta-analysis, only 8% received a dose higher than 54 Gy. Logistic regression modeling suggests that response rates rise exponentially after 60 Gy [16]. It is possible that a minimum threshold dose is required to overcome the relative radioresistance of colorectal cancers and that the higher dose escalation seen in MORPHEUS and in OPRA is needed to see significant improvements in sustained long-term local control over standard EBRT.

The importance of dosimetric considerations during treatment planning can be seen by comparing toxicity outcomes between the Canadian adaptive technique against the phase I dose escalation HERBERT trial which treated 38 inoperable rectal cancer patients with 39 Gy in 13 fractions EBRT followed by 3 weekly HDRBT treatments ranging from 5 to 8 Gy [38]. Dose limiting toxicity was defined as grade 3 or higher proctitis, ultimately resulting in 7 Gy being determined as the maximum tolerable dose after DLTs were found in 3 patients treated with 8 Gy. Though acute proctitis was the dose limiting toxicity in this trial, late toxicities were significant with 40% of patients experiencing grade 3 toxicity including 6 patients (21%) reporting severe rectal bleeding. In HERBERT, dose was prescribed to up to 2 cm which could lead to up 600% prescription dose delivered to normal rectal mucosa. Predictive factors for toxicity from the HERBERT study included the prescribed D90 to the clinical target volume as well as the clinical target volume [39]. The Canadian approach modeled their prescription dose after CXB with 30 Gy prescribed to the mucosal surface, leading to 10 Gy at 1 cm depth. Additionally, a double balloon technique was used to simultaneously push the contralateral rectal wall away from the treatment field and compress the target tumor to a thickness of 1 cm or less. With central shielding used in all patients, a maximum 200% prescription dose to the mucosal surface was achieved [40]. The significantly lower rates of late toxicity with this technique (12.8% vs 40% in HERBERT) demonstrate the importance of prescribing to a limited volume and depth in order to limit the risk of rectal toxicity.

In summary, HDRBT is a more widely available modality than CXB but its adoption as a boost technique for NOM has been limited. With improvements in the technique and refinement in the dosing based on the emerging data from MORPHEUS, HDRBT promises to be a technique that will be more readily adopted.

Future Directions

There are several additional active research avenues to increase the number of candidates for NOM. The addition of multi-agent chemotherapy has been investigated in the phase II OPRA trial which randomized cT3-4N0-2 rectal cancer patients to either induction mFOLFOX6 followed by consolidation long course EBRT or induction EBRT followed by consolidation mFOLFOX6 [13]. Patients achieving cCR/ncCR were offered NOM while patients with incomplete responses had completion TME. 3-year TME free survival was 53% in the induction EBRT arm, setting a new benchmark in NOM. Multiple other ongoing trials are investigating the benefit of induction multi-agent chemotherapy such as GRECCAR12 (NCT02513278) which randomizes patients to induction mFOLFIRINOX followed by standard of care EBRT versus EBRT alone and TESS (NCT03840239) which similarly randomizes patients to induction CAPOX and EBRT versus EBRT alone. The use of less surgery with local excision instead of TME is also being investigated (TESAR, NCT02371304). Additionally, advances in genomic profiling portend the possibility of using molecular data to refine selection of patients who are best suited for NOM or who may have high risk disease which requires surgery [41]. Changes in circulating tumor DNA after neoadjuvant treatment predict for pathologic complete response and may play a role in post-treatment surveillance and detection of regrowth [42]. Finally, comparisons between different trials will be easier with recent consensus statements establishing common definitions for what constitutes a cCR, when clinical response evaluation should occur, and standardized surveillance programs [43•].

Conclusion

Though randomized data has only recently emerged, early evidence strongly suggests that endorectal brachytherapy is not only safe and feasible but effective in increasing initial clinical complete response rates leading to higher rates of organ preservation compared to EBRT alone. It is

important to note that NOM is currently still investigational with ASTRO guidelines only conditionally recommending it, preferably at high volume centers with experienced multi-disciplinary teams [44]. Ultimately, further research is needed to better identify which patients are best suited for NOM. As this treatment paradigm becomes better established, it does appear that brachytherapy will be an evidence-based treatment option for dose escalation.

Declarations

Conflict of Interest Samuel C. Zhang and Eric M. Chung each declare no potential conflicts of interest.
Katelyn M. Atkins has received personal fees from Onclive.
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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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