Curr Colorectal Cancer Rep (2017) 13:61–72
DOI 10.1007/s11888-017-0351-z

The Impact of Novel Radiation Treatment Techniques on Toxicity and Clinical Outcomes in Rectal Cancer

Lara Hathout[1] · **Terence Williams**[2] · **Salma K. Jabbour**[1]

Published online: 10 March 2017

Abstract
Purpose of Review Three-dimensional conformal radiation therapy (3DCRT) has been the standard technique in the treatment of rectal cancer. The use of new radiation treatment technologies such as intensity-modulated radiation therapy (IMRT), proton therapy (PT), stereotactic body radiation therapy (SBRT), and brachytherapy (BT) has been increasing over the past 10 years. This review will highlight the advantages and drawbacks of these techniques.
Recent Findings IMRT, PT, SBRT, and BT achieve a higher target coverage conformity and a higher organ at risk sparing and enable dose escalation compared to 3DCRT. Some studies suggest a reduction in gastrointestinal and hematologic toxicities and an increase in the complete pathologic response rate; however, the clinical benefit of these techniques remains controversial.
Summary The results of these new techniques seem encouraging despite conclusive data. Further trials are required to establish their role in rectal cancer.

Keywords Novel technologies · IMRT · Proton therapy · SBRT · Rectal cancer

This article is part of the Topical Collection on *Radiation Therapy and Radiation Therapy Innovations in Colorectal Cancer*

✉ Salma K. Jabbour
jabbousk@cinj.rutgers.edu

[1] Department of Radiation Oncology, Rutgers Cancer Institute of New Jersey, Rutgers Robert Wood Johnson Medical School, Rutgers, The State University of New Jersey, New Brunswick, NJ 08901, USA

[2] The Ohio State University, James Cance Hospital, Columbus OH 43210, USA

Introduction

Colorectal cancer (CRC) is the fourth most common cancer and the second leading cause of cancer deaths in 2016 in the USA [1]. Approximately 40, 000 new cases of rectal cancer will occur each year [1] with an estimated 5-year overall survival rate of 65% [2]. Despite the improvement of the overall incidence and survival rates due to screening and early detection, the incidence of colorectal cancer in patients younger than 50 years has been increasing without a corresponding increase in patients older than 50 years of age. The predicted incidence rate of colon and rectal cancer in 2030 will increase by 90 and 124% in patients between 20 and 34 years of age [3].

Although advances in surgical techniques [4], preoperative chemoradiation therapy [5] and imaging [6] have improved local control and overall survival outcomes; these increases in the incidence of rectal cancer emphasize the need for therapies that improve local response rates while reducing possible long-term effects of therapy.

Neoadjuvant long-course chemoradiation is the gold standard for locally advanced rectal cancer (T3-T4 or lymph node positive), followed by surgical resection and adjuvant chemotherapy, which was shown to decrease the risk of loco-regional recurrence [7–9]. Preoperative chemoradiation compared to postoperative chemoradiation was associated with improved local control and reduced toxicity [5]. Postoperative chemoradiation is recommended to patients with pathological T3-T4 disease or lymph node positive rectal cancer [10, 11]. For patients with T1-T2 node negative rectal cancer managed with local excision who have high- risk features, postoperative chemoradiation is also recommended.

Historically, radiation has been delivered using three-dimensional conformal radiation therapy (3DCRT) in a three- or four-field dose delivery technique with excellent target coverage and a well-documented, well-tolerated toxicity profile. With

the advent of new technologies, many studies have evaluated the benefits of these technologies in rectal cancer. Intensity modulated radiation therapy is a highly conformal treatment; the radiation beam intensity is modulated to achieve an elevated radiation dose intensity near the tumor and a decreased dose intensity near the neighboring normal tissues which may result in a lower rate of complications. In rectal cancer, the two main dose-limiting organs at risk are the small bowel and the bone marrow. Grade ≥3 toxicity is less than 10% when <195 cc of small bowel receives a dose of 45 Gy or higher [12]. For rectal cancer, since the prescription is most often 50.4 Gy, it is hence important to limit the dose to the small bowel. As for the bone marrow, it has been shown that hematologic toxicity is increased with increasing pelvic bone marrow volume irradiated [13]. As the technologies have evolved to more accurately deliver dose, we have the potential to increase dose, which may improve rates of pathologic complete response or better control acute and long-term treatment related toxicities.

This review summarizes the latest radiation techniques highlighting their advantages and drawbacks.

Intensity-Modulated Radiation Therapy and Volumetric-Modulated Arc Therapy

Impact of Intensity-Modulated Radiation Therapy on Gastrointestinal Toxicity

Gastrointestinal (GI) toxicity, with the primary toxicity of diarrhea, occurs as the most common cause of morbidity during preoperative chemoradiation for locally advanced rectal cancer (LARC) at a rate of 12–36% for grade ≥3 diarrhea [5, 14]. Intensity-modulated radiation therapy (IMRT) has the ability to deliver a high tumor target conformity while reducing the dose to the organs at risk (OAR) which could result in greater sparing of the small bowel and decreased GI toxicity (Fig. 1). The utilization of IMRT as an alternative to 3DCRT has significantly increased over the last few years from 24% in 2006 to 50% in 2013. Female gender was an independent factor associated with IMRT use possibly explained by the large volume of small bowel in the pelvis among female patients who have undergone hysterectomy [15]. Several retrospective dosimetric studies have compared 3DCRT to IMRT in patients treated with preoperative chemoradiation [16–21]. IMRT significantly improved the OAR sparing while preserving excellent planning target volume coverage and conformity compared to 3DCRT [17–21].

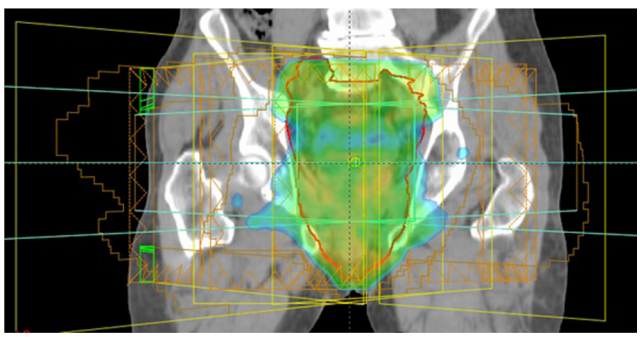

Fig. 1 IMRT fields for rectal cancer invading the anal canal, coronal CT simulation scan

A dose-volume relationship has been established between the absolute volumes of irradiated small bowel at the 15 Gy dose level (V15) and grade 3 acute toxicities in patients treated with preoperative chemoradiation for rectal cancer [22–25]. IMRT was associated with a reduction in the volume of small bowel irradiated at levels ranging from 15 to 50 Gy [16–21]. While some studies reported a reduction in the small bowel V15 with IMRT [17, 18, 20, 21], others did not find a difference compared to 3DCRT [19]. As for the homogeneity index, some studies suggested that achieving high target dose conformity with IMRT could be at the expense of more dose inhomogeneity [16–18], while others reported an improvement in target dose homogeneity with IMRT [19–21]. The latter could be explained by the various definitions of homogeneity index used throughout the different studies.

Regarding the clinical toxicity profile, the reduction of GI toxicity with IMRT is controversial (Table 1). A retrospective review from the Mayo Clinic Arizona compared IMRT to 3DCRT in 92 patients with rectal cancer treated with preoperative or postoperative radiotherapy. Overall grade ≥2 GI toxicity and grade ≥ 2 diarrhea were significantly reduced with IMRT compared to 3DCRT; 32 vs 62% ($p = 0.006$) and 23 vs 48% ($p = 0.02$), respectively, but only physician-reported outcomes were employed [26•]. Another study by Parekh et al. described similar findings in a retrospective review of 48 patients. Reduced grade ≥2 overall GI toxicity and grade ≥2 diarrhea were observed in patients treated with IMRT compared to 3DCRT; 30 vs 61% ($p = 0.036$) and 10 vs 43% ($p = 0.014$), respectively [27]. Acute non-gastrointestinal toxicity was comparable between the two groups in both retrospective studies [26•, 27]. A multi-institutional retrospective study compared the toxicity profile of IMRT vs 3DCRT in preoperative chemoradiation therapy for LARC. Although IMRT significantly reduced all grade ≥3 toxicities, the rate of grade ≥3 GI toxicity was similar between the IMRT and 3DCRT groups. Multi-agent chemotherapy was associated with increased toxicity compared to single agent chemotherapy [28•].

Recently, the NRG Oncology Radiation Therapy Oncology Group (RTOG) 0822 trial evaluated the rate of GI toxicity in patients treated with neoadjuvant chemoradiation with concurrent capecitabine/oxaliplatin (CAPOX) for LARC [29••]. This study was based on the RTOG 0247 phase II randomized trial comparing capecitabine and oxaliplatin with 3DCRT vs capecitabine and irinotecan with 3DCRT. The latter study resulted in a premature closure due to a high rate of grades 3 and 4 GI toxicity in both arms [30]; consequently, IMRT was used in RTOG 0822 to mitigate the rate of GI toxicity. A total of 68

Table 1 Impact of IMRT on gastrointestinal and hematologic toxicities

	Trial design	Sample size (*n*)	Concurrent Chemotherapy agent used	IMRT dose	Grade 2 GI toxicity	Grade 3 GI toxicity	Grades 4–5 GI toxicity	Grade 2 HT	Grade ≥3 HT
Hong et al.	Phase II	68	Capecitabine and oxaliplatin	45 + 5.4 Gy boost	28%	22%	1.5%	–	–
Zhu et al.	Phase II	42	Capecitabine and oxaliplatin	44 Gy in 20 fractions	28.6%	12%	0%	21%	–
Ballonoff et al.	Phase II	8	Capecitabine	45 Gy/25 with SIB 55 Gy/25	37.5%	0%	12.5% (one eight patients)	0%	–
Li et al.	Phase II	63	Capecitabine	41.8 Gy/22 with SIB 50.6 Gy/22	–	9.5%	0%	1.6%	–
Freedman et al.	Phase I	8	Capecitabine	45 Gy/25 with SIB 55 Gy/25	37.5%	12.5%	0%	25%	12.5%
Parekh et al.[a]	Retrospective	48	5FU or Capecitabine	45 Gy/25 with SIB 50 Gy/25	20% IMRT vs 50% 3DCRT $p = 0.036$	11% IMRT vs 11% 3DCRT $p = 1$	0%	Grade ≥2 10% IMRT vs 28.5% 3DCRT $p = 0.16$	
Samuelian et al.[a]	Retrospective	92	Not specified	45 + 5.4–9 Gy sequential boost	29% IMRT vs 52% 3DCRT $p = 0.006$	3% IMRT vs 10% 3DCRT $p = 0.42$	0%	21.3% IMRT vs 39% 3DCRT p = NS	3.2 vs 5% p = NS
Jabbour et al. [a]	Retrospective	86	5FU or capecitabine and irinotecan or capecitabine and oxaliplatin	45 Gy/25 + 5.4 Gy sequential boost	–	Nadir WBC grades 3–4 5% 3DCRT vs 0% IMRT Nadir HB grades 3–4 4% 3DCRT vs 2% IMRT			
Yang et al.	Retrospective	120	5FU (95%) and capecitabine (5%)	45 Gy/25 with SIB 50 Gy/25	–	–	–	12% neutropenia 10% anemia	1% excluding lymphopenia 57% including lymphopenia
Newman et al.	Retrospective	35	Concurrent: 5FU or capecitabine Adjuvant: oxaliplatin and 5FU or capecitabine and 5FU	50.4 Gy/28	–	–	–	–	40% during postop chemo

NS not significant

[a] Studies comparing IMRT to 3DCRT

patients were evaluable. Pelvic radiation to a dose of 45 Gy was delivered with IMRT followed by a 3DCRT boost to the gross disease to 50.4 Gy. Grade ≥2 GI toxicity and grade ≥3 diarrhea were reported in 50 and 17.6% of patients, respectively [29••]. Although real-time quality assurance was performed in all patients with only five unacceptable variations, the grade ≥2 GI toxicity was significantly higher than the target rate of 28% and the reported rate of 40% in RTOG 0247 [30]. In addition, the small bowel V15 was not associated with grade 3 or more GI toxicity [29••]. These results could be explained by the lack of small bowel dosimetric constraints; only 23 patients met the dosimetric constraint of small bowel V15 < 150 cc suggested by Baglan et al., and only 17 patients met the small bowel V15 < 120 cc [22] suggested by Robertson et al. [24]. Moreover, oxaliplatin is known to cause upper and lower GI toxicities [31, 32] which could have contributed to the high rate of toxicity in the RTOG 0822 trial. Three randomized trials have investigated the role of oxaliplatin in preoperative chemoradiotherapy for LARC [33–35]. The addition of oxaliplatin to 5FU or capecitabine failed to improve the pathologic complete response rate (pCR), sphincter-sparing surgery rate, and overall survival (OS); however, it significantly increased the overall toxicity and GI toxicity, particularly diarrhea. However, one prospective randomized study did demonstrate an improvement in progression-free survival [36].

In summary, IMRT seems to reduce the volume of small bowel irradiated; however, it remains unclear whether these dosimetric advantages translate into a lower rate of acute GI toxicity compared to 3DCRT.

Impact of Intensity-Modulated Radiation Therapy on hematologic toxicity

About 40% of the active bone marrow is comprised within the pelvis [37], and radiation therapy (RT) can injure radiosensitive bone marrow cells resulting in acute myelosuppression [38]. In anal canal carcinoma studies, IMRT enabled pelvic bone marrow sparing [39] which resulted in lower rates of hematologic toxicities [40, 41] where the use of concurrent standard of care mitomycin-C contributes to myelosuppression with rate of 60% for grade 3 hematologic toxicity with/without IMRT. In contrast, the baseline rate of hematologic toxicity (HT) grade ≥3 in preoperative 3DCRT chemoradiation was 6–10% in LARC [5, 14, 42]. With IMRT, the HT rate varied between 0 and 25% (Table 1). Three retrospective studies have evaluated the rates of HT among patients treated with IMRT compared to those treated with 3DCRT. Jabbour et al. reported a significantly reduced rate of grade ≥3 HT vs grade ≤ 2 HT with IMRT in patients treated with preoperative chemoradiotherapy [28•].Newman et al. quantified bone marrow suppression during postoperative chemotherapy in patients previously treated with preoperative chemoradiotherapy (with 5FU or capecitabine) for rectal cancer [43•]. During postoperative chemotherapy with oxaliplatin and 5FU, HT grade ≥3 occurred in 40% of patients which is consistent with the results reported by Hong et al. in a phase 2 trial [44]. The pelvic bone marrow contours were divided into ilium, lower pelvis, and lumbosacrum regions. Increased pelvic mean dose, lower pelvis mean dose, increased pelvic bone marrow V25-40, and increased lower pelvis V25 and V40 were significantly associated with HT grade ≥3 during postoperative chemotherapy. Moreover, mean dose exceeding 36.6 and 32.6 Gy to the pelvis and lower pelvis mean dose, respectively, correlated with HT grade ≥3.

In addition, it has been suggested by Yang et al. that different hematologic cell types reach their nadir at different time points during pelvic radiotherapy. The white blood cells (WBC), absolute neutrophil count (ANC), and platelet cells reach their nadirs during the second week of RT and recover thereafter, while hemoglobin and absolute lymphocyte cell counts decline in a continuous fashion during pelvic RT. The use of 3DCRT compared to IMRT was associated with a lower WBC ratio and ANC cell count. When analyzing the dosimetric variables, coxal (ilium, ischium, and pubis) bone marrow V45 and sacral bone marrow V45 were significantly correlated with a lower WBC and ANC ratio at nadir, respectively [45] but the sacrum is difficult to spare in a standard rectal field in which the mesorectum and presacrum require radiation coverage.

Bone marrow sparing could be achieved with IMRT; however, more studies are needed to establish the bone marrow dose-volume constraints for patients treated preoperatively with chemoradiotherapy in LARC. Understanding the relative contributions of bone marrow function at different time points of therapy for rectal cancer will be important to continue to study.

Impact of Intensity-Modulated Radiation Therapy on Survival and Clinical Outcomes

Regarding the benefit of IMRT on clinical outcomes, the pathologic complete response (pCR) and sphincter-preservation rates vary between 0 and 38% [26•, 27, 28•, 29••, 46, 47, 48•, 49•] and 43 and 82% [15, 26•, 27, 29••, 46, 48•, 49•], respectively (Table 2). When compared to 3DCRT, IMRT did not result in improved pCR [26•, 27, 28•] or tumor downstaging rates [15, 28•]. The improvement of the sphincter preservation rate with IMRT is controversial. On one hand, two retrospective studies did not report any difference between IMRT and 3DCRT [26•, 27]. On the other hand, a nationwide analysis, recently published, reported a higher risk of positive margins and a higher rate of sphincter loss surgery with IMRT compared to 3DCRT. Indeed, using the National Cancer Database, 7386 rectal cancer patients of whom 45% received IMRT and 55% received 3DCRT were analyzed; the primary endpoint was OS. IMRT did not improve the perioperative and clinical outcomes; however, it was associated with

Table 2 Impact of IMRT on clinical outcomes

	pCR rate	Tumor downstaging rate	Sphincter-preserving surgery rate	Treatment breaks rate	Postop complication rate	Local recurrence rate	OS
Zhu et al. [49•]	16%	74%	43%	–	12%	13% at 3 years	66% at 3 years
Freedman et al. [47]	0%	–	–	–	–	–	–
Ballonoff et al.[46]	38%	63%	66%	12.5%	–	0 at 26 months	–
Li et al.[48•]	31%	79%	66%	–	7%	6% at 2 years	96% at 2 years
Hong et al.[29••]	15%	–	79%	–	–	7%	83% at 4 years
Jabbour et al.[28•] [a]	20% IMRT vs 21% ($p = 0.55$)	60% IMRT vs 50% 3DCRT ($p = 0.25$)	–	0% IMRT vs 20% 3DCRT *($p = 0.0002$)*	–	7% in both groups ($p = 0.65$)	–
Samuelian et al.[26•][a]	19% IMRT vs 28% 3DCRT ($p = 0.7$)	–	82% IMRT vs 84% 3DCRT ($p = 0.8$)	6.5% IMRT vs 16.4% 3DCRT ($p = 0.3$)	Any: 47% IMRT vs 43% 3DCRT ($p = 0.8$) Confined to the pelvis: 5.4% IMRT vs 15% 3DCRT ($p = 0.41$)	–	–
Parekh et al. [27][a]	17 vs 21% ($p = 1$)	–	70 vs 64% ($p = 0.8$)	0% IMRT vs 7% 3DCRT	–	–	–
Sun et al.[15][a]	–	55% IMRT vs 57% 3DCRT ($p = 0.09$)	65% IMRT vs 72% 3DCRT *($p < 0.001$)*	–	Unplanned postoperative readmission 6% IMRT vs 8% 3DCRT *($p = 0.02$)* 30-day postoperative mortality 0.8 vs 0.6% ($p = 0.36$)	–	64 IMRT vs 64% 3DCRT at 8 years

[a] Studies comparing IMRT to 3DCRT

worse R0 resection suggesting that IMRT might be deleterious in LARC [15]. This study may be difficult to interpret since it is unclear if IMRT was used in situations where patients had larger or lower lying tumor volumes or required inguinal lymph node irradiation (Fig. 2).

As for the postoperative mortality and complication rate, no differences between IMRT and 3DCRT were found [15, 26•]. But, there were fewer hospitalizations, emergency visits [28•], and treatment breaks with IMRT [27, 28•].

Given the lack of convincing data about the clinical benefits of IMRT, additional studies should be conducted on this topic. Given the focus on intensification of chemotherapy or addition of novel radiosensitizers to improve pCR rates, the use of IMRT to better spare toxicity may fall into favor.

Intensity-Modulated Radiation Therapy for Simultaneous Integrated Boost

In some of the studies cited previously, IMRT has also been used to deliver a simultaneous integrated boost (SIB) for LARC [17, 19, 21, 27, 45–47, 48•, 49•]. Target coverage including conformity and homogeneity indices and OAR sparing was superior with volumetric-modulated arc therapy (VMAT) and IMRT compared to 3DCRT [17, 21]. A single-arm prospective study assessed the toxicity, postoperative complications, and pCR rate of concomitant boost IMRT and capecitabine in patients with LARC [48•]. A total of 63 patients were enrolled of whom five did not undergo surgery. The dose delivered to the pelvis and the simultaneous boost dose to the gross disease were 41.8 and 50.6 Gy, respectively, with 10 MV photons in 22 fractions. Grade 3 diarrhea occurred in 9.5% of patients while no grade 4 toxicity was reported. Of the 58 patients who underwent surgery, pCR was 31%, postoperative complications occurred in 7%, and the sphincter preservation rate was 66% [48•]. Freedman et al. conducted a phase I dose escalation study to determine the safety of SIB IMRT. A total of 8 patients were treated with preoperative hypofractionated chemoradiotherapy with IMRT to a total dose of 55 Gy in 25 fractions. The study was closed prematurely due to six grade 3 toxicities in three patients which were deemed unacceptable [47]. Another phase II trial evaluated IMRT with SIB in the preoperative setting with capecitabine. No HT was found in eight accrued patients, and the pCR rate was 38% with 50% of downstaging [46].

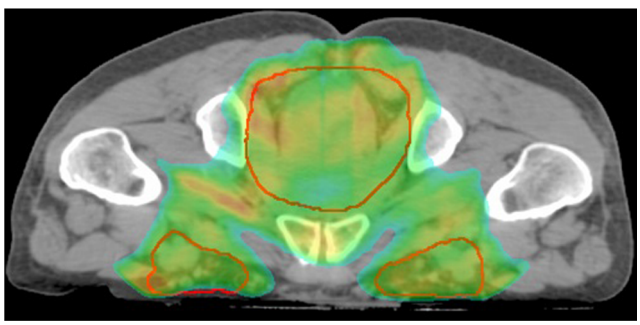

Fig. 2 Dose color wash on axial CT simulation scan demonstrating inguinal nodal coverage for rectal cancer invading the anal canal

A recent prospective observational trial examined the role of watchful waiting in patients with distal rectal tumors (T2-T3, N0-1) managed with high-dose radiotherapy with concurrent chemotherapy alone. A total of 51 patients were treated with IMRT to 50 Gy in 30 fractions to the pelvis with SIB to the tumor to 60 Gy with concurrent Tegafur-Uracil followed by a 5-Gy brachytherapy boost to the tumor. Complete clinical response was observed in 40 patients who were allocated to observation, the rest underwent surgery. After a median follow-up of 24 months, local recurrence at 1 year in the observation group was 15.5% [50••].

In conclusion, the toxicity profile of SIB-IMRT is not established yet; more data and longer follow-up are needed.

Intensity-Modulated Radiation Therapy vs Volumetric-Modulated Arc Therapy

VMAT has been compared to IMRT or 3DCRT in a few retrospective dosimetric studies [17, 18, 21, 51]. The conformity index was improved with VMAT compared to 3DCRT. Two studies reported a worse or similar homogeneity index with VMAT compared to 3DCRT [17, 18, 51] while Zhao et al. described a better homogeneity index with VMAT compared to 3DCRT, and it was similar between VMAT and IMRT [21]. The small bowel V15 was significantly reduced with VMAT compared to 3DCRT [17, 21], and there was a 65% reduction in the small bowel volume irradiated to 40 Gy [18]. Only one study has evaluated the impact of VMAT or arc therapy on toxicity. Richetti et al. reported a 41% downstaging rate with arc therapy, and acute toxicity was comparable in both groups [51].

Overall, the results of VMAT are encouraging; however, these studies are retrospective with a small number of patients. In order to evaluate the impact of VMAT on dosimetric and clinical outcomes, further investigations are required.

In conclusion, the role of IMRT in neoadjuvant chemoradiation for LARC remains controversial. IMRT may be advantageous for patients with T4 tumors where external iliac coverage is needed, low lying tumors invading the anal canal in which coverage of the inguinal lymph node basins is necessary, and for patients treated postoperatively with a large volume of small bowel at risk.

Proton Therapy

Compared to photons, protons are charged particles with a relatively large mass which deliver most of their dose in the last few millimeters of the particle's range. This phenomenon called the Bragg Peak improves the OAR sparing while

insuring optimal coverage of the target volume. In order to reduce acute and late GI toxicities, a few studies have evaluated the role of proton therapy (PT) in rectal cancer.

Colaco et al. compared 3DCRT, IMRT, and PT dosimetric plans in eight patients to assess the potential benefit of PT over IMRT and 3DCRT. Patients were simulated in the prone position with a full bladder. Target volumes and treatment plan goals were similar to the RTOG 0822 trial. A three-field approach was used for the proton plans similar to 3DCRT but with a heavier weighting on the posterior field compared to the lateral fields. Target coverage was similar between the three plans; PT, however, significantly reduced the pelvic bone marrow exposure compared to IMRT and 3DCRT. As for the small bowel, the superiority of PT over IMRT was limited to the V10 and V20 levels and there was no difference in reducing the dose to the bladder [52]. Another dosimetric study by Wolff et al. compared 3DCRT, IMRT, VMAT, and PT in 25 patients with LARC. Dose reduction to the OAR, target volume coverage, and conformity index were significantly better with PT [53].

A recent study from the University of Pennsylvania investigated whether Proton Pencil Beam Scanning (PBS) can result in dosimetric advantages relative to interfraction uncertainties over VMAT. Ten patients with LARC were immobilized with indexed knee and foot lock and simulated in the supine position. Two clinical PBS plans were generated on the planning CT, a single posterior PBS field and parallel-opposed PBS fields. The VMAT plans were generated on the planning CT using two coplanar arcs. Four weekly offline verification CT scans were performed and coregistered with the planning CT to assess robustness relative to anatomic changes. A greater OAR sparing was observed in the PBS plans however the clinical target coverage was similar among all plans [54•].

Although PT has dosimetric advantages over IMRT and 3DCRT, it remains unknown if these advantages will translate into clinical benefits. Due to the properties of PT, it can be of use in the reirradiation setting to spare normal organs that received prior radiation [55]. Further trials are required to establish the role of PT in LARC.

Stereotactic Body Radiation Therapy

Despite the low rate of local recurrence in LARC after preoperative chemoradiation and total mesorectal excision (TME) [5], local recurrence remains problematic with significant morbidity from severe pain, bleeding, and poor quality of life [56]. Surgical resection remains the best curative option for recurrent rectal cancer [57]. Nevertheless, the postoperative complication rate is substantially high and varies from 15 to 68% such as pelvic collections, intestinal obstruction, wound infection/breakdown, and deep venous thrombosis [58–61], and survival is still poor with these events [57]. Other alternatives to surgery include external beam radiotherapy (EBRT) and stereotactic body radiotherapy (SBRT). SBRT is a safer option in the context of reirradiation compared to EBRT since target conformity and normal structures avoidance are excellent. Abusaris et al. evaluated 27 patients treated with SBRT after EBRT for recurrent cancer in the abdomen and pelvic region to a median SBRT dose of 90 Gy_3. A symptomatic response was observed in 96% of patients, and the 2-year local control was 53% with a low rate of acute and late toxicities after a median follow-up of 15 months [62]. Another series of 18 patients previously irradiated were treated with Cyberknife SBRT for pelvic recurrences from colorectal cancer to a median dose of 25 Gy in five fractions. After a median follow-up of 38 months, the overall median survival and 3-year local control rate after SBRT were 40 months and 86%, respectively. One grade 3 and one grade 4 toxicities were documented [63]. A similar study also evaluated the efficacy and safety of Cyberknife SBRT in the management of presacral recurrences from rectal cancers. No grade 3 or 4 toxicities were documented and the 2-year local control rate was 68% [64]. Similar results were also reported by Dewas et al. [65].

In addition to local recurrences, SBRT has been utilized in the postoperative setting for positive or close margins for rectal cancer [66]. Seven patients were treated with SBRT to a median dose of 25 Gy in 5 fractions after surgery and preoperative chemoradiation to a median dose of 50.4 Gy. After a median follow-up of 23.5 months, the 2-year local control and overall survival were 100% and 71%, respectively with no grade 3 or more toxicity.

While SBRT seems to be a safe and efficient treatment option for recurrent rectal cancer and for positive margins in patients previously treated with neoadjuvant chemoradiation, further prospective trials need to be done to adequately evaluate this treatment approach.

Contact Therapy and High-Dose Rate Brachytherapy

Contact therapy also known as the “Papillon technique” using 50 kVp energy has been widely used for the treatment of early stage rectal cancer as a definitive therapy or in the postoperative setting with excellent local control and cure rates [67–70]. The main advantage of contact therapy is the sharp dose fall off with depth: 100% at 0 mm, 44% at 5 mm, 23% at 100 mm, and 9% at 20 mm [71]. Despite the effectiveness and low toxicity profile of this technique, its use has been declining. First, it necessitates a specialized proctoscope that allows an X-ray tube to be passed through it and placed in direct contact with the tumor [72] which is not widely available in the USA. Second, the treatment is delivered with the patient in the knee-chest position which could be challenging in the western population due to body habitus. Lastly, the expertise in contact

therapy is limited throughout the country. On the other hand, the use of high-dose rate endocavitary brachytherapy (HDRB), used in the past in the palliative setting [73, 74], has gained popularity. Te Vuong pioneered the use of HDRB in North America; a phase I/II trial assessed the efficacy of endorectal HDRB in the preoperative setting. Operable stage T2 to early T4 tumors were included, a dose of 26 Gy in four consecutive fractions was delivered and surgery was performed 4 to 8 weeks later. Brachytherapy did not cause a higher rate of surgical complications. Postoperative EBRT with concurrent chemotherapy was delivered to patients with evidence of positive lymph nodes. A complete pathological response was obtained in 32% of patients and 36% had only residual microfoci of carcinoma. The main toxicity was grade 2 proctitis and occasional grade 3 dermatitis for very distal tumors [75]. Similarly, 483 patients underwent neoadjuvant endorectal HDRB to a dose of 26 Gy in four fractions for T3 and low T2 with positive circumferential radial margin. The pCR rate was 27% and the rate of positive nodes was 31%. After a median follow-up of 5 years, the actuarial local recurrence rate, DFS, and OS were 5, 66, and 73%, respectively [76]. Currently, a phase II randomized study is ongoing lead by John Hopkins group evaluating the effectiveness of endorectal HDRB compared to the standard neoadjuvant chemoradiation. The primary endpoint is pCR and the secondary endpoints are toxicity, local recurrence, progression-free survival (PFS), OS, and distant metastases (NCT02017704). This study will provide the community with more solid data.

Brachytherapy has also been used as a boost to long-course neoadjuvant chemoradiation in order to achieve dose escalation in several studies [77••, 78–80]. Gerard et al. was the first to determine whether contact therapy as a boost to EBRT could increase the pCR and the sphincter preservation rates. A total of 88 patients were randomized to either EBRT or EBRT and a HDRB boost (25 Gy). The addition of HDRB significantly improved the complete clinical response (evaluated by digital rectal exam and proctoscopy), the pCR, and the sphincter preservation rates. Nevertheless, there were no differences in morbidity, local recurrence, and 2-year OS [78].

Another study by Appelt et al. prospectively randomized 221 patients with LARC to either long-course chemoradiation with oral Tegafur-Uracil and leucovorin alone or chemoradiation with a brachytherapy boost. Both arms received EBRT to a total dose of 50.4 Gy in 28 fractions. Brachytherapy was delivered in two fractions on weeks 4 and 6 using a rigid single-channel endorectal applicator to a total dose of 20 Gy prescribed at 1 cm from the applicator surface. Patients who could not comply with brachytherapy were treated with EBRT boost of 6–12 Gy in 2 Gy per fraction. The primary endpoint was tumor response at the time of surgery. The rate of major tumor regression was significantly higher in the brachytherapy group (41 vs 28%); however, there was no difference in the number of R0 resections between the two groups. After a median follow-up of 5.4 years, there was no difference in OS, PFS, and freedom from local failure between the two groups. The authors concluded that despite an improvement in pCR, the addition of endorectal brachytherapy did not translate into an improvement in OS, PFS, and locoregional control [77••].

The role of brachytherapy in inoperable patients or as a palliative approach has been investigated by Hoskin et al. in a retrospective review. Fifty patients were treated with brachytherapy as sole treatment or as a boost to EBRT for either inoperable rectal tumors or as palliation. Local tumor response was achieved in 21 of the 25 assessable patients with 14 complete responses. Median survival for patients treated with definitive EBRT and brachytherapy boost was 25 months and 7 months for patients treated with a palliative intent. Of the 28 patients presenting with rectal bleeding at presentation, 57% achieved a complete clinical resolution, with a median response duration of 10 months [81].

Endorectal brachytherapy has been shown to be effective in patients with inoperable tumors and in the palliative setting. When used as a boost, it seems to improve the pCR but did not impact the recurrence rate and OS. More randomized studies are needed to shed more light on the benefit of brachytherapy in rectal cancer.

Intraoperative Radiation Therapy

Intraoperative radiation therapy (IORT) can be safely delivered after surgical resection providing excellent coverage to the pelvic resection bed while minimizing the dose to the normal tissues in patients with LARC. Harrison et al. reported their experience with the Harrison-Andersen-Mick applicator (HAM); the local control rates at 2 years for primary or recurrent disease were 81 and 63%, respectively. In patients with negative margins, the local control rates reached 92 and 82% for primary disease and recurrent disease, respectively [82]. However, IORT was associated with a higher perioperative complication rate in several studies [83–86]. Klink et al. evaluated retrospectively 162 patients with LARC of whom 52 received IORT, and the remainder were treated with resection alone. The authors did not find any difference in the perioperative complication rates between the two groups [87]. Prospective randomized trials are needed to properly evaluate the benefit and toxicity of IORT in patients with locally advanced or recurrent rectal cancer.

Conclusions

The management of LARC with radiotherapy is evolving with the advent of new technologies. IMRT, PT, and SBRT have been shown to provide dosimetric advantages compared to

3DCRT, although these advantages did not translate into improved clinical outcomes. The use of IMRT may be required in the setting of chemotherapy intensification or in the post-operative setting where increased bowel loops may be present. Brachytherapy is a good option for palliation or to increase pCR rates for non-operative management. Meanwhile, 3DCRT is still appropriate in the vast majority of cases.

Recently, an ASTRO clinical practice statement has been published on the appropriate customization of radiation therapy for stages II and III rectal cancer [88••], although newer studies have since emerged. Nevertheless, these guidelines can help the clinician decide on the best treatment approach depending on the size of the tumor, the location, and the fractionation scheme.

Further studies are required to establish the role of these new technologies in LARC, which may help to decrease bone marrow and GI toxicities, while possibly permitting dose escalation to improve clinical response rates.

Acknowledgments This work was supported by the following grants: NIH R01 CA198128 (TW). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Compliance with Ethical Standards

Conflict of Interest Lara Hathout and Salma K. Jabbour declare that they have no conflict of interest.

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.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66(1):7–30.
2. Surveillance E, End Results (SEER). 18 registries National Cancer Institute. 2015.
3. Bailey CE, Hu CY, You YN, Bednarski BK, Rodriguez-Bigas MA, Skibber JM, et al. Increasing disparities in the age-related incidences of colon and rectal cancers in the United States, 1975-2010. JAMA Surg. 2015;150(1):17–22.
4. Havenga K, Enker WE, Norstein J, Moriya Y, Heald RJ, van Houwelingen HC, et al. Improved survival and local control after total mesorectal excision or D3 lymphadenectomy in the treatment of primary rectal cancer: an international analysis of 1411 patients. Eur J Surg Oncol. 1999;25(4):368–74.
5. Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004;351(17):1731–40.
6. Battersby NJ, How P, Moran B, Stelzner S, West NP, Branagan G, et al. Prospective validation of a low rectal cancer magnetic resonance imaging staging system and development of a local recurrence risk stratification model: the MERCURY II study. Ann Surg. 2016;263(4):751–60.
7. Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. N Engl J Med. 1997;336(14):980-7.
8. Folkesson J, Birgisson H, Pahlman L, Cedermark B, Glimelius B, Gunnarsson U. Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. J Clin Oncol. 2005;23(24):5644–50.
9. McCarthy K, Pearson K, Fulton R, Hewitt J. Pre-operative chemoradiation for non-metastatic locally advanced rectal cancer. Cochrane Database Syst Rev. 2012;12:CD008368.
10. NIH consensus conference. Adjuvant therapy for patients with colon and rectal cancer. JAMA. 1990;264(11):1444–50.
11. Krook JE, Moertel CG, Gunderson LL, Wieand HS, Collins RT, Beart RW, et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. N Engl J Med. 1991;324(11):709–15.
12. Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constine LS, Eisbruch A, et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys. 2010;76(3 Suppl):S10–9.
13. Rose BS, Aydogan B, Liang Y, Yeginer M, Hasselle MD, Dandekar V, et al. Normal tissue complication probability modeling of acute hematologic toxicity in cervical cancer patients treated with chemoradiotherapy. Int J Radiat Oncol Biol Phys. 2011;79(3):800–7.
14. Roh MS, Colangelo LH, O'Connell MJ, Yothers G, Deutsch M, Allegra CJ, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. J Clin Oncol. 2009;27(31):5124–30.
15. Sun Z, Adam MA, Kim J, Czito B, Mantyh C, Migaly J. Intensity-modulated radiation therapy is not associated with perioperative or survival benefit over 3D-conformal radiotherapy for rectal cancer. J Gastrointest Surg. 2016;21:106–11.
16. Arbea L, Ramos LI, Martinez-Monge R, Moreno M, Aristu J. Intensity-modulated radiation therapy (IMRT) vs. 3D conformal radiotherapy (3DCRT) in locally advanced rectal cancer (LARC): dosimetric comparison and clinical implications. Radiat Oncol. 2010;5:17.
17. Cilla S, Caravatta L, Picardi V, Sabatino D, Macchia G, Digesu C, et al. Volumetric modulated arc therapy with simultaneous integrated boost for locally advanced rectal cancer. Clin Oncol (R Coll Radiol). 2012;24(4):261–8.
18. Duthoy W, De Gersem W, Vergote K, Boterberg T, Derie C, Smeets P, et al. Clinical implementation of intensity-modulated arc therapy (IMAT) for rectal cancer. Int J Radiat Oncol Biol Phys. 2004;60(3):794–806.
19. Guerrero Urbano MT, Henrys AJ, Adams EJ, Norman AR, Bedford JL, Harrington KJ, et al. Intensity-modulated radiotherapy in patients with locally advanced rectal cancer reduces volume of bowel treated to high dose levels. Int J Radiat Oncol Biol Phys. 2006;65(3):907–16.
20. Mok H, Crane CH, Palmer MB, Briere TM, Beddar S, Delclos ME, et al. Intensity modulated radiation therapy (IMRT): differences in target volumes and improvement in clinically relevant doses to small bowel in rectal carcinoma. Radiat Oncol. 2011;6:63.
21. Zhao J, Hu W, Cai G, Wang J, Xie J, Peng J, et al. Dosimetric comparisons of VMAT, IMRT and 3DCRT for locally advanced rectal cancer with simultaneous integrated boost. Oncotarget. 2016;7(5):6345–51.
22. Baglan KL, Frazier RC, Yan D, Huang RR, Martinez AA, Robertson JM. The dose-volume relationship of acute small bowel toxicity from concurrent 5-FU-based chemotherapy and radiation

therapy for rectal cancer. Int J Radiat Oncol Biol Phys. 2002;52(1): 176–83.
23. Robertson JM, Lockman D, Yan D, Wallace M. The dose-volume relationship of small bowel irradiation and acute grade 3 diarrhea during chemoradiotherapy for rectal cancer. Int J Radiat Oncol Biol Phys. 2008;70(2):413–8.
24. Robertson JM, Sohn M, Yan D. Predicting grade 3 acute diarrhea during radiation therapy for rectal cancer using a cutoff-dose logistic regression normal tissue complication probability model. Int J Radiat Oncol Biol Phys. 2010;77(1):66–72.
25. Tho LM, Glegg M, Paterson J, Yap C, MacLeod A, McCabe M, et al. Acute small bowel toxicity and preoperative chemoradiotherapy for rectal cancer: investigating dose-volume relationships and role for inverse planning. Int J Radiat Oncol Biol Phys. 2006;66(2): 505–13.
26.• Samuelian JM, Callister MD, Ashman JB, Young-Fadok TM, Borad MJ, Gunderson LL. Reduced acute bowel toxicity in patients treated with intensity-modulated radiotherapy for rectal cancer. Int J Radiat Oncol Biol Phys. 2012;82(5):1981–7. **Retrospective analysis of 92 patients of whom 66% were treated with 3DCRT and 34% with IMRT. IMRT was associated with a lower rate of GI toxicity**.
27. Parekh A, Truong MT, Pashtan I, Qureshi MM, Martin NE, Nawaz O, et al. Acute gastrointestinal toxicity and tumor response with preoperative intensity modulated radiation therapy for rectal cancer. Gastrointest Cancer Res. 2013;6(5-6):137–43.
28.• Jabbour SK, Patel S, Herman JM, Wild A, Nagda SN, Altoos T, et al. Intensity-modulated radiation therapy for rectal carcinoma can reduce treatment breaks and emergency department visits. Int J Surg Oncol. 2012;2012:891067. **A retrospective review of 86 patients treated with IMRT (n=30) and 3DCRT (n=56). They were fewer hospitalizations, treatment breaks and grade ≥ 3 toxicities in the IMRT arm**.
29.•• Hong TS, Moughan J, Garofalo MC, Bendell J, Berger AC, Oldenburg NB, et al. NRG Oncology Radiation Therapy Oncology Group 0822: a phase 2 study of preoperative chemoradiation therapy using intensity modulated radiation therapy in combination with capecitabine and oxaliplatin for patients with locally advanced rectal cancer. Int J Radiat Oncol Biol Phys. 2015;93(1): 29–36. **Largest prospective trial evaluating the rate of GI toxicity of neoadjuvant chemoradiation with capecitabine, oxaliplatin, and IMRT in patients with locally advanced rectal cancer. Acute grade 2 to 5 GI toxicity was the primary outcome. IMRT failed to reduce acute GI toxicity**.
30. Wong SJ, Winter K, Meropol NJ, Anne PR, Kachnic L, Rashid A, et al. Radiation Therapy Oncology Group 0247: a randomized phase II study of neoadjuvant capecitabine and irinotecan or capecitabine and oxaliplatin with concurrent radiotherapy for patients with locally advanced rectal cancer. Int J Radiat Oncol Biol Phys. 2012;82(4):1367–75.
31. Becouarn Y, Ychou M, Ducreux M, Borel C, Bertheault-Cvitkovic F, Seitz JF, et al. Phase II trial of oxaliplatin as first-line chemotherapy in metastatic colorectal cancer patients. Digestive Group of French Federation of Cancer Centers. J Clin Oncol. 1998;16(8): 2739–44.
32. Diaz-Rubio E, Sastre J, Zaniboni A, Labianca R, Cortes-Funes H, de Braud F, et al. Oxaliplatin as single agent in previously untreated colorectal carcinoma patients: a phase II multicentric study. Ann Oncol. 1998;9(1):105–8.
33. Aschele C, Cionini L, Lonardi S, Pinto C, Cordio S, Rosati G, et al. Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. J Clin Oncol. 2011;29(20):2773–80.
34. Gerard JP, Azria D, Gourgou-Bourgade S, Martel-Laffay I, Hennequin C, Etienne PL, et al. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. J Clin Oncol. 2010;28(10):1638–44.
35. O'Connell MJ, Colangelo LH, Beart RW, Petrelli NJ, Allegra CJ, Sharif S, et al. Capecitabine and oxaliplatin in the preoperative multimodality treatment of rectal cancer: surgical end points from National Surgical Adjuvant Breast and Bowel Project trial R-04. J Clin Oncol. 2014;32(18):1927–34.
36. Rodel C, Graeven U, Fietkau R, Hohenberger W, Hothorn T, Arnold D, et al. Oxaliplatin added to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy of locally advanced rectal cancer (the German CAO/ARO/AIO-04 study): final results of the multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2015;16(8):979–89.
37. Ellis RE. The distribution of active bone marrow in the adult. Phys Med Biol. 1961;5:255–8.
38. Mauch P, Constine L, Greenberger J, Knospe W, Sullivan J, Liesveld JL, et al. Hematopoietic stem cell compartment: acute and late effects of radiation therapy and chemotherapy. Int J Radiat Oncol Biol Phys. 1995;31(5):1319–39.
39. Mell LK, Schomas DA, Salama JK, Devisetty K, Aydogan B, Miller RC, et al. Association between bone marrow dosimetric parameters and acute hematologic toxicity in anal cancer patients treated with concurrent chemotherapy and intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys. 2008;70(5):1431–7.
40. Bazan JG, Hara W, Hsu A, Kunz PA, Ford J, Fisher GA, et al. Intensity-modulated radiation therapy versus conventional radiation therapy for squamous cell carcinoma of the anal canal. Cancer. 2011;117(15):3342–51.
41. Salama JK, Mell LK, Schomas DA, Miller RC, Devisetty K, Jani AB, et al. Concurrent chemotherapy and intensity-modulated radiation therapy for anal canal cancer patients: a multicenter experience. J Clin Oncol. 2007;25(29):4581–6.
42. Bazan JG, Luxton G, Kozak MM, Anderson EM, Hancock SL, Kapp DS, et al. Impact of chemotherapy on normal tissue complication probability models of acute hematologic toxicity in patients receiving pelvic intensity modulated radiation therapy. Int J Radiat Oncol Biol Phys. 2013;87(5):983–91.
43.• Newman NB, Sidhu MK, Baby R, Moss RA, Nissenblatt MJ, Chen T, et al. Long-term bone marrow suppression during postoperative chemotherapy in rectal cancer patients after preoperative chemoradiation therapy. Int J Radiat Oncol Biol Phys. 2016;94(5):1052–60. **Retrospective analysis of 35 patients treated with preoperative chemoradiation followed by adjuvant chemotherapy for locally advanced rectal cancer. The primary endpoint was to quantify bone marrow suppression during postoperative chemotherapy resulting from preoperative chemoradiation. Sparing of the bone marrow during preoperative radiation therapy can reduce hematologic toxicity and aid tolerance of adjuvant chemotherapy**.
44. Hong YS, Nam BH, Kim KP, Kim JE, Park SJ, Park YS, et al. Oxaliplatin, fluorouracil, and leucovorin versus fluorouracil and leucovorin as adjuvant chemotherapy for locally advanced rectal cancer after preoperative chemoradiotherapy (ADORE): an open-label, multicentre, phase 2, randomised controlled trial. Lancet Oncol. 2014;15(11):1245–53.
45. Yang TJ, Oh JH, Apte A, Son CH, Deasy JO, Goodman KA. Clinical and dosimetric predictors of acute hematologic toxicity in rectal cancer patients undergoing chemoradiotherapy. Radiother Oncol. 2014;113(1):29–34.
46. Ballonoff A, Kavanagh B, McCarter M, Kane M, Pearlman N, Nash R, et al. Preoperative capecitabine and accelerated intensity-modulated radiotherapy in locally advanced rectal cancer: a phase II trial. Am J Clin Oncol. 2008;31(3):264–70.
47. Freedman GM, Meropol NJ, Sigurdson ER, Hoffman J, Callahan E, Price R, et al. Phase I trial of preoperative hypofractionated intensity-modulated radiotherapy with incorporated boost and oral

capecitabine in locally advanced rectal cancer. Int J Radiat Oncol Biol Phys. 2007;67(5):1389–93.

48.• Li JL, Ji JF, Cai Y, Li XF, Li YH, Wu H, et al. Preoperative concomitant boost intensity-modulated radiotherapy with oral capecitabine in locally advanced mid-low rectal cancer: a phase II trial. Radiother Oncol. 2012;102(1):4–9. **A phase II study of 63 patients treated with IMRT with simultaneous integrated boost with concurrent capecitabine evaluating the toxicity, postoperative complications, and pathological complete response (pCR). IMRT with concurrent boost can achieve a high pCR rate and a low toxicity profile**.

49.• Zhu J, Gu W, Lian P, Sheng W, Cai G, Shi D, et al. A phase II trial of neoadjuvant IMRT-based chemoradiotherapy followed by one cycle of capecitabine for stage II/III rectal adenocarcinoma. Radiat Oncol. 2013;8:130. **A phase II trial of 42 patients treated with IMRT and concurrent oxaliplatin and capecitabine revealed good treatment outcomes with mild toxicities and acceptable surgical complications**.

50.•• Appelt AL, Ploen J, Harling H, Jensen FS, Jensen LH, Jorgensen JC, et al. High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study. Lancet Oncol. 2015;16(8):919–27. **Prospective observational study examining the efficacy of high-dose chemoradiotherapy and brachytherapy boost in patients with distal rectal cancer followed by watchful waiting in clinical complete responders**.

51. Richetti A, Fogliata A, Clivio A, Nicolini G, Pesce G, Salati E, et al. Neo-adjuvant chemo-radiation of rectal cancer with volumetric modulated arc therapy: summary of technical and dosimetric features and early clinical experience. Radiat Oncol. 2010;5:14.

52. Colaco RJ, Nichols RC, Huh S, Getman N, Ho MW, Li Z, et al. Protons offer reduced bone marrow, small bowel, and urinary bladder exposure for patients receiving neoadjuvant radiotherapy for resectable rectal cancer. J Gastrointest Oncol. 2014;5(1):3–8.

53. Wolff HA, Wagner DM, Conradi LC, Hennies S, Ghadimi M, Hess CF, et al. Irradiation with protons for the individualized treatment of patients with locally advanced rectal cancer: a planning study with clinical implications. Radiother Oncol. 2012;102(1):30–7.

54.• Blanco Kiely JP, White BM. Robust proton pencil beam scanning treatment planning for rectal cancer radiation therapy. Int J Radiat Oncol Biol Phys. 2016;95(1):208–15. **Proton Pencil Beam Scanning was compared to VMAT to evaluate the potential to offer advantages relative to interfraction uncertainties and dose volume histograms. It was found to be as robust as VMAT**.

55. Vuong T, Devic S. High-dose-rate pre-operative endorectal brachytherapy for patients with rectal cancer. J Contemp Brachytherapy. 2015;7(2):183–188.

56. Camilleri-Brennan J, Steele RJ. The impact of recurrent rectal cancer on quality of life. Eur J Surg Oncol. 2001;27(4):349–53.

57. Nielsen MB, Laurberg S, Holm T. Current management of locally recurrent rectal cancer. Colorectal Dis. 2011;13(7):732–42.

58. Asoglu O, Karanlik H, Muslumanoglu M, Igci A, Emek E, Ozmen V, et al. Prognostic and predictive factors after surgical treatment for locally recurrent rectal cancer: a single institute experience. Eur J Surg Oncol. 2007;33(10):1199–206.

59. Heriot AG, Byrne CM, Lee P, Dobbs B, Tilney H, Solomon MJ, et al. Extended radical resection: the choice for locally recurrent rectal cancer. Dis Colon Rectum. 2008;51(3):284–91.

60. Vermaas M, Ferenschild FT, Nuyttens JJ, Marinelli AW, Wiggers T, van der Sijp JR, et al. Preoperative radiotherapy improves outcome in recurrent rectal cancer. Dis Colon Rectum. 2005;48(5):918–28.

61. Wells BJ, Stotland P, Ko MA, Al-Sukhni W, Wunder J, Ferguson P, et al. Results of an aggressive approach to resection of locally recurrent rectal cancer. Ann Surg Oncol. 2007;14(2):390–5.

62. Abusaris H, Hoogeman M, Nuyttens JJ. Re-irradiation: outcome, cumulative dose and toxicity in patients retreated with stereotactic radiotherapy in the abdominal or pelvic region. Technol Cancer Res Treat. 2012;11(6):591–7.

63. Dagoglu N, Mahadevan A, Nedea E, Poylin V, Nagle D. Stereotactic body radiotherapy (SBRT) reirradiation for pelvic recurrence from colorectal cancer. J Surg Oncol. 2015;111(4):478–82.

64. Defoe SG, Bernard ME, Rwigema JC, Heron DE, Ozhasoglu C, Burton S. Stereotactic body radiotherapy for the treatment of presacral recurrences from rectal cancers. J Cancer Res Ther. 2011;7(4):408–11.

65. Dewas S, Bibault JE, Mirabel X, Nickers P, Castelain B, Lacornerie T, et al. Robotic image-guided reirradiation of lateral pelvic recurrences: preliminary results. Radiat Oncol. 2011;6:77.

66. Dagoglu N, Nedea E, Poylin V, Nagle D, Mahadevan A. Post operative stereotactic radiosurgery for positive or close margins after preoperative chemoradiation and surgery for rectal cancer. J Gastrointest Oncol. 2016;7(3):315–20.

67. Hull TL, Lavery IC, Saxton JP. Endocavitary irradiation. An option in select patients with rectal cancer. Dis Colon Rectum. 1994;37(12):1266–70.

68. Kovalic JJ. Endocavitary irradiation for rectal cancer and villous adenomas. Int J Radiat Oncol Biol Phys. 1988;14(2):261–4.

69. Papillon J. Intracavitary irradiation of early rectal cancer for cure. A series of 186 cases. Cancer. 1975;36(2):696–701.

70. Christoforidis D, McNally MP, Jarosek SL, Madoff RD, Finne CO. Endocavitary contact radiation therapy for ultrasonographically staged T1 N0 and T2 N0 rectal cancer. Br J Surg. 2009;96(4):430–6.

71. Gerard JP, Romestaing P, Ardiet JM, Mornex F. Sphincter preservation in rectal cancer. Endocavitary radiation therapy. Semin Radiat Oncol. 1998;8(1):13–23.

72. Geisler DP. Local treatment for rectal cancer. Clin Colon Rectal Surg. 2007;20(3):182–9.

73. Kaufman N, Nori D, Shank B, Linares L, Harrison L, Fass D, et al. Remote afterloading intraluminal brachytherapy in the treatment of rectal, rectosigmoid, and anal cancer: a feasibility study. Int J Radiat Oncol Biol Phys. 1989;17(3):663–8.

74. Evans MD, Podgorsak EB. Rectal and oesophageal treatment by the Selectron High Dose Rate afterloader. Med Dosim. 1988;13(2):79–81.

75. Vuong T, Belliveau PJ, Michel RP, Moftah BA, Parent J, Trudel JL, et al. Conformal preoperative endorectal brachytherapy treatment for locally advanced rectal cancer: early results of a phase I/II study. Dis Colon Rectum. 2002;45(11):1486–93. discussion 93-5.

76. Plastaras JP, Berman AT, Freedman GM. Special cases for proton beam radiotherapy: re-irradiation, lymphoma, and breast cancer. J Seminoncol. 2014. doi:10.1053/j.seminoncol.2014.10.001.

77.•• Appelt AL, Vogelius IR, Ploen J, Rafaelsen SR, Lindebjerg J, Havelund BM, et al. Long-term results of a randomized trial in locally advanced rectal cancer: no benefit from adding a brachytherapy boost. Int J Radiat Oncol Biol Phys. 2014;90(1):110–8. **Largest study evaluating the benefit from a brachytherapy boost addition to long-course neoadjuvant chemoradiation. Despite an increased rate of pathologic tumor response after surgery, the addition of a brachytherapy boost did not impact late outcome**.

78. Gerard JP, Chapet O, Nemoz C, Hartweig J, Romestaing P, Coquard R, et al. Improved sphincter preservation in low rectal cancer with high-dose preoperative radiotherapy: the lyon R96-02 randomized trial. J Clin Oncol. 2004;22(12):2404–9.

79. Jakobsen A, Mortensen JP, Bisgaard C, Lindebjerg J, Hansen JW, Rafaelsen SR. Preoperative chemoradiation of locally advanced T3 rectal cancer combined with an endorectal boost. Int J Radiat Oncol Biol Phys. 2006;64(2):461–5.

80. Sun Myint A, Lee CD, Snee AJ, Perkins K, Jelley FE, Wong H. High dose rate brachytherapy as a boost after preoperative

chemoradiotherapy for more advanced rectal tumours: the Clatterbridge experience. Clin Oncol (R Coll Radiol). 2007;19(9):711–9.

81. Hoskin PJ, de Canha SM, Bownes P, Bryant L, Glynne JR. High dose rate afterloading intraluminal brachytherapy for advanced inoperable rectal carcinoma. Radiother Oncol. 2004;73(2):195–8.
82. Harrison LB, Minsky BD, Enker WE, Mychalczak B, Guillem J, Paty PB, et al. High dose rate intraoperative radiation therapy (HDR-IORT) as part of the management strategy for locally advanced primary and recurrent rectal cancer. Int J Radiat Oncol Biol Phys. 1998;42(2):325–30.
83. Diaz-Gonzalez JA, Calvo FA, Cortes J, Garcia-Sabrido JL, Gomez-Espi M, Del Valle E, et al. Prognostic factors for disease-free survival in patients with T3-4 or N+ rectal cancer treated with preoperative chemoradiation therapy, surgery, and intraoperative irradiation. Int J Radiat Oncol Biol Phys. 2006;64(4):1122–8.
84. Kienle P, Abend F, Dueck M, Abel U, Treiber M, Riedl S. Influence of intraoperative and postoperative radiotherapy on functional outcome in patients undergoing standard and deep anterior resection for rectal cancer. Dis Colon Rectum. 2006;49(5):557–67.
85. Krempien R, Roeder F, Oertel S, Roebel M, Weitz J, Hensley FW, et al. Long-term results of intraoperative presacral electron boost radiotherapy (IOERT) in combination with total mesorectal excision (TME) and chemoradiation in patients with locally advanced rectal cancer. Int J Radiat Oncol Biol Phys. 2006;66(4):1143–51.
86. Turley RS, Czito BG, Haney JC, Tyler DS, Mantyh CR, Migaly J. Intraoperative pelvic brachytherapy for treatment of locally advanced or recurrent colorectal cancer. Tech Coloproctol. 2013;17(1):95–100.
87. Klink CD, Binnebosel M, Holy R, Neumann UP, Junge K. Influence of intraoperative radiotherapy (IORT) on perioperative outcome after surgical resection of rectal cancer. World J Surg. 2014;38(4):992–6.
88.•• Goodman KA, Patton CE, Fisher GA, Hoffe SE, Haddock MG, Parikh PJ, et al. Appropriate customization of radiation therapy for stage II and III rectal cancer: executive summary of an ASTRO clinical practice statement using the RAND/UCLA appropriateness method. Pract Radiat Oncol. 2016;6(3):166–75. **An ASTRO practice clinical statement has been recently published addressing the appropriate customization of radiation therapy in different clinical scenarios**.