Published in final edited form as:

Curr Colorectal Cancer Rep. 2017 February ; 13(1): 61–72. doi:10.1007/s11888-017-0351-z.

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

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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, a higher organ at risk sparing and enable dose escalation compared to 3DCRT. Some studies suggested 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

Introduction

Colorectal cancer (CRC) is the fourth most common cancer and the second leading cause of cancer deaths in 2016 in the United States (1). Approximately 40 000 new cases of rectal cancer will occur each year (1) with an estimated 5-year overall survival 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

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**This work was supported by the following grants: NIH R01 CA 198128 (TW). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

predicted incidence rate of colon and rectal cancer in 2030 will increase by 90% and 124% respectively in patients aged between 20 to 34 years (3).

Although advances in surgical techniques, preoperative chemoradiation therapy and imaging 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, followed by surgical resection and adjuvant chemotherapy, which was shown to decrease the risk of loco-regional recurrence (7-9). Pre-operative chemoradiation compared to post-operative chemoradiation is associated with improved local control and reduced toxicity (5). In patients with clinical T1-T2 node negative rectal cancer, postoperative chemoradiation is recommended to patients with pathological T3-T4 disease or positive lymph nodes.

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 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 (IMRT) 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 dose-limiting organs at risk are usually 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 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 radiation dose, which may improve rates of pathologic complete response, or better control of acute and long term treatment related toxicities.

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

Intensity-Modulated Radiation Therapy (IMRT) and Volumetric-Modulated Arc Therapy (VMAT)

Impact of IMRT 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% grade 3 diarrhea (5, 14). 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. 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).

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 48% vs 23% ($p=0.02$), 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 2 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).

The NRG Oncology 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 versus capecitabine and irinotecan with 3DCRT. The latter study resulted in a premature closure due to a high rate of grade 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 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 5 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 toxicity (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.

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 IMRT 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 60% of 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) since most often 5-FU or capecitabine is used. With IMRT, the HT rate varied between 0-25% (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 versus 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 5-FU or capecitabine) (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 Gy 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 reached their nadirs during the second week of RT and recovered thereafter; while hemoglobin and absolute lymphocyte cell counts declined 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 IMRT 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% (26-29, 46-49) 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 (26-28) 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 Data Base, 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 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.

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.

IMRT 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, 45-49). Target coverage including conformity and homogeneity indices and OAR sparing were superior with 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 Gy 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 55Gy in 25 fractions. The study was closed prematurely due to 6 grade 3 toxicities in 3 patients which was deemed unacceptable (47). Another phase II trial evaluated IMRT with SIB in the preoperative setting with capecitabine. No HT was found in 8 accrued patients and the pCR rate was 38% with 50% of downstaging (46).

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.

IMRT vs. VMAT

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 40Gy (18). Only one study has evaluated the impact of VMAT or arc therapy on toxicity. Richetti et al. reported a 41% down-staging 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 who may have 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 can improve sparing of OAR while insuring optimal

coverage of the target volume. In order to reduce acute and late GI toxicity, 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 8 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 3-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 3 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, RapidArc 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 2 coplanar arcs. Four weekly offline verification CT scans were performed and co-registered 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 likely has dosimetric advantages over IMRT and 3DCRT, it remains unknown if these advantages will translate into clinical benefits. Further trials are required to establish the role of PT in LARC.

Stereotactic Body Radiation Therapy (SBRT)

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 (55). Surgical resection remains the best curative option for recurrent rectal cancer (56). 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 (57-60) and survival is still poor (56). 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 Gy₃. 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 toxicity after a median follow up of 15 months (61). 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 5 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 toxicity were documented (62). 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% (63). Similar results were also reported by Dewas et al. (64).

In addition to local recurrences, SBRT has been utilized in the postoperative setting for positive or close margins for rectal cancer (65). Seven patients were treated with Cyberknife 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 (HDRB)

Contact therapy also known as the “Papillon technique” using 50kV 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 (66-69). 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 (70). 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 (71) which is not widely available in the United States. 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), previously used in the palliative setting (72, 73) 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 4 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 (74). Similarly, 483 patients underwent neoadjuvant endorectal HDRB to a dose of 26 Gy in 4 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. Currently, a phase II randomized

study is ongoing and is led 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 (75-78). Gerard et al. was the first to determine if contact therapy as a boost to EBRT could increase the pCR and the sphincter-preservation rate. 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 was no difference in morbidity, local recurrence and 2-year OS (76).

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 2 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 2 groups. After a median follow of 5.4 years, there was no difference in OS, PFS and freedom from local failure between the 2 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 (75).

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 (79).

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 (IORT)

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 (80). However, IORT was associated with a higher perioperative complication rate in several studies (81-84). 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 2 groups (85). 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 postoperative setting where increased bowel loops may present issues. Brachytherapy is a good option for palliation or increase pCR rate for non-operative management. Meanwhile, 3DCRT still is appropriate in the vast majority of cases.

Recently, an ASTRO clinical practice statement has been published on the appropriate customization of radiation therapy for stage II and III rectal cancer (86) 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 toxicity and GI toxicity, while possibility permitting dose escalation to improve clinical response rates.

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

Figure 2.
Dose color wash on axial plane demonstrating inguinal nodal coverage for rectal cancer invading the anal canal.

Table 1
Impact of IMRT on gastro-intestinal and hematologic toxicities

Authors	Trial design	Sample size (n)	Concurrent Chemotherapy agent used	IMRT dose	Grade 2 GI toxicity	Grade 3 GI toxicity	Grade 4-5 GI toxicity	Grade 2 HT	Grade 3 HT
Hong et al.	Phase II	68	Capecitabine and oxaliplatin	45Gy + 5.4 Gy boost	28%	22%	1.5%	-	-
Zhu et al.	Phase II	42	Capecitabine and oxaliplatin	44Gy in 20 fractions	28.6%	12%	0%	21%	-
Ballonoff et al.	Phase II	8	Capecitabine	45Gy/25 with SIB 55Gy/25	37.5%	0%	12.5% (1/8 patients)	0%	-
Li et al.	Phase II	63	Capecitabine	41.8Gy/22 with SIB 50.6 Gy/22	-	9.5%	0%	1.6%	-
Freedman et al.	Phase I	8	Capecitabine	45Gy/25 with SIB 55Gy/25	37.5%	12.5%	0%	25%	12.5%
Parekh et al. *	Retro-spective	48	5FU or Capecitabine	45 Gy/25 with SIB 50Gy/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. *	Retro-spective	92	Not specified	45Gy + 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. *	Retro-spective	86	5FU or capecitabine and irinotecan or capecitabine and oxaliplatin	45 Gy/ 25 + 5.4 Gy sequential boost	-	Nadir WBC grade 3-4 5% IMRT vs 0% IMRT Nadir HB grade 3-4 4% 3DCRT vs 2% IMRT			
Yang et al.	Retro-spective	120	5FU (95%) and capecitabine (5%)	45Gy/25 with SIB 50Gy/25	-	-	-	12% neutropenia 10% anemia	1% excluding lymphopenia 57% including lymphopenia
Newman et al.	Retro-spective	35	Concurrent: 5FU or capecitabine Adjuvant: oxaliplatin and 5FU or capecitabine and 5FU	50.4 Gy/28	-	-	-	-	40% during postop chemo

* Studies comparing IMRT to 3DCRT

/ NS= not significant

Table 2

Impact of IMRT on clinical outcomes

Authors	pCR rate	Tumor downstaging rate	Sphincter-preserving surgery rate	Treatment breaks rate	Post-op complication rate	Local recurrence rate	OS
Zhu et al. (49)	16%	74%	43%	-	12%	13% at 3y	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) *	20% IMRT vs 21% 3DCRT (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) *	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) *	17 vs 21% (p=1)	-	70 vs 64% (p=0.8)	0 IMRT vs 7% 3DCRT	-	-	-
Sun et al.(15) *	-	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

* Studies comparing IMRT to 3DCRT