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The Role of Intensity-Modulated Radiotherapy to Optimize Outcomes in Locally Advanced Rectal Cancer

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Abstract Intensity-modulated radiation therapy (IMRT) as neoadjuvant treatment of locally advanced rectal cancer (LARC) patients has been explored by some authors since 2006. Dosimetrical analyses and clinical outcomes have been published in recent years. Although there are encouraging dosimetrical results, there are no solid clinical data supporting the routine use of IMRT for preoperative treatment of LARC patients. In this article, we analyze the published dosimetrical and clinical data and current evidence for the use of IMRT in LARC patients. We hypothesize the role of IMRT to treat rectal cancer patients in the current technological age. The small bowel dose reduction that could lead to a reduction in GI toxicity and encourage higher rates of compliance, the potential dose escalation to the target volume, and the integration with higher doses of chemotherapy and its potential implications to optimize clinical outcomes in terms of toxicity and efficacy are discussed.

Keywords Locally advanced rectal cancer · Intensity-modulated radiation therapy · Gastrointestinal toxicity · Capecitabine · Oxaliplatin

Introduction

Preoperative chemoradiotherapy (CHRT) followed by total mesorectal excision (TME) is the recommended standard therapy for patients with locally advanced rectal cancer (LARC). Compared to postoperative CHRT in LARC, preoperative CHRT produces significantly lower local recurrence rates, less acute and chronic toxicity, and an increased rate of sphincter preservation [1]. Tridimensional conformal radiotherapy (3DCRT) with conventional protracted fractionation (45–50 Gy in daily fractions of 1.8–2 Gy during weeks 5 and 6) with concurrent fluoropyrimidin-based chemotherapy followed by surgery at 4 to 8 weeks is the recommended standard treatment [1, 2•]. The efficacy of this multimodality approach is acceptable with an increase in local control rates. However, two main issues concern oncologist: (1) the acute grade 3/4 gastrointestinal (GI) toxicity observed in 12–25 % of patients, which could compromise treatment compliance and (2) the high rate of distant metastasis, ranging from 19–36 % [3, 4, 5•].

The relationship between small bowel (SB) radiation dose and grade 3 diarrhea is well-known, and the SB V15 (the absolute volume of SB receiving at least 15 Gy) has been suggested as a reliable cutoff during dose plan evaluation [6, 7].

The development of novel and sophisticated irradiation techniques as intensity-modulated radiation therapy (IMRT) represents a spectacular progress in planning and delivering external beam radiation therapy. IMRT generates highly conformal and irregularly shaped dose distribution while reducing dose to adjacent normal tissue structures. IMRT has demonstrated dosimetric superiority over 3DCRT in the majority of tumor sites, including pelvic tumors where the irradiated bowel can be significantly reduced [8]. Developments in radiation therapy planning have also improved the information regarding three-dimensional dose distribution in the patient and increasingly sophisticated radiation techniques using image-guided RT (IGRT) are allowing a more accurate dose delivery. The accurate assessment of target volume delineation using IGRT to eventually minimize normal tissue toxicity has been

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identified as a priority for the future landscape of rectal cancer management [9].

On the other hand, a higher rate of tumor regression in the surgical specimen has been associated with increased disease-free survival and overall survival after preoperative CHRT in rectal cancer [10–12]. Although concomitant 5-fluorouracil (5-FU) is the standard chemotherapy (CHT) schedule and no other agents administered preoperatively have been shown to affect patients' outcomes, the use of more active and effective concomitant chemotherapeutics agents along with radiotherapy with an adequate toxicity profile could have the potential to improve pathological responses.

From these premises, IMRT as neoadjuvant treatment of LARC patients has been explored by some authors since 2006. Dosimetrical analyses and clinical outcomes have been published in recent years, although no long-term data are available. In this article, we analyze the dosimetric studies, published clinical data, and current evidence for the use of IMRT in LARC patients and its potential implications to optimize clinical outcomes in terms of toxicity and efficacy.

Dosimetrical Studies

The initial studies in LARC patients using IMRT were designed to compare dosimetrical differences between IMRT and tridimensional standard plans. Table 1 shows the data of the different dosimetric studies published. All studies concluded that IMRT adequately encompassed target volumes and achieved a significant reduction in high doses to SB.

Guerrero et al. showed that the bowel volume irradiated to 45 and 50 Gy (V45 and V50, respectively) was significantly reduced with IMRT compared to that seen with 3DCRT while maintaining target coverage [13]. Tho et al. performed additional IMRT planning in eight LARC patients and demonstrated that the median dose to the SB was reduced by 5.1 Gy (p=0.008); they also generated a mathematical model to predict the occurrence of acute diarrhea at V5 (volume of SB that receives 5 Gy) and V15 (volume of SB that receives 15 Gy) dose levels. They did not observe any statistically significant increase in planning target volume (PTV) dose inhomogeneity [7].

Callister et al. showed that IMRT plans were associated with a 19 % decrease in the mean dose delivered to SB and a 16 % reduction in the V30 and V45 compared to levels seen with 3DCRT planning [14].

More recent studies describe a significant reduction in V15 and V40 with IMRT plans compared with 3DCRT [15–17]. The homogeneity and conformity indexes that describe the dose distribution and the adaptation of the isodose to the tumor volume while limiting irradiation of healthy tissues were significantly improved with IMRT compared to those in 3DCRT in the most dosimetrical analyses performed in these studies. Only Arbea et al. reported an increased heterogeneity across the target volume with IMRT plans [15].

These results suggested that pelvic IMRT could potentially enhance the therapeutic ratio by reducing SB doses without reducing target coverage (Fig. 1). This potential to reduce the toxicity profile of IMRT in LARC patients allowed the design of protocols exploring whether a clinical benefit was also observed.

Clinical Studies

A limited number of studies have been publishing combining preoperative CHT and IMRT in LARC patients. Table 2 details the results in terms of GI toxicity and compliance rates in the phase II trials that have used CHT-IMRT in LARC patients. Pathological response rates are also shown. All the studies combined IMRT with capecitabine or capecitabine and oxaliplatin (CAPOX).

Ballonoff et al. published a phase II, single institution trial in which LARC patients were treated with preoperative IMRT (45 Gy in 1.8 Gy fractions to the PTV with an accelerated integrated boost of 55 Gy to the gross tumor volume (GTV) in 2.2 Gy fractions) and concurrent capecitabine (825 mg/m^2 BID, 5 days/week × 5 weeks), followed by TME 6 weeks later [18]. The small number of patients makes it difficult to draw definite conclusions about treatment tolerance; toxicity was high, and one of the eight patients included in the study had grade 4 diarrhea, although no other patient had grade 3 or higher toxicity. Compliance rates of RT and CHT were both 100 %.

A longer prospective phase II study was conducted by Engels et al.; this study included 108 LARC patients treated with IMRT using helical tomotherapy with a dose of 46 Gy in 23 fractions to the PTV and a simultaneous integrated boost of 55.2 Gy to the GTV without chemotherapy [19]. Only one instance of grade 3 or higher GI toxicity was reported. Grade 2 GI toxicity was 14 %, and the compliance rate for radiation therapy was 100 %.

Simultaneously, Arbea et al. carried out a prospective study of preoperative CAPOX-IMRT in rectal cancer with 47.5 Gy of hypofractionated (large dose per fraction) IMRT (2,375 Gy/fx) prescribed to the PTV [20]. A total of 100 patients with LARC were analyzed; no grade 4 toxicity was reported. Grade 3 diarrhea was observed in 13 patients (9 %), and grade 1–2 rectitis was the most frequent toxicity observed in 74 % of the patients. The compliance rate for RT was 98 %, and the compliance rate for chemotherapy was 80 %. Eighty-eight percent of patients completed concomitant CHT, with only transient interruptions of capecitabine or minimal dose reductions of CAPOX.

The Radiation Therapy Oncology Group (RTOG) has completed a phase II trial (RTOG 0822) of preoperative IMRT

Table 1 Dosimetrical studies with IMRT in rectal cancer

Author	Number of patients	Dosimetric parameter	Effect in small bowel
Guerrero-Urbano et al. [13]	5	V45	64 % reduction
Tho et al. [7]	8	Median dose	5.1 Gy reduction
Callister et al. [14]	10	Mean dose	29 % reduction
		V45, V30	16 % reduction
Engels et al. [16]	11	V15	32 % reduction
Arbea [15]	15	V40	50 % reduction
Mok [17]	5	Mean dose	6.6 Gy reduction
		V15	12 % reduction

with CAPOX for T3–T4 rectal cancer [21•]. Patients were treated with pelvic IMRT with a dose of 45 Gy to the PTV in 25 fractions, followed by a boost with an additional 5.4 Gy to the GTV. Preliminary results have been reported and suggest a reduction in grade 2 or greater toxicities, but toxicity data analysis is currently being performed to identify optimal IMRT planning criteria for future studies.

A more recent study included 78 patients treated with 50 Gy of IMRT to the pelvis and a concomitant boost of 5 Gy in 25 fractions to the primary tumor, with concurrent oxaliplatin (50 mg/m^2 day 1 weekly) and capecitabine (625 mg/m^2 bid days 1–5 weekly) [22]. The incidence of G3 diarrhea was 10.4 %, and the compliance rates for RT and CHT were 100 % and 61 %, respectively.

Finally, Hernando-Requejo et al. published the results of a prospective pilot study of personalized chemotherapy and escalated-dose radiotherapy with an integrated boost IMRT technique [23]. The planned dose to the PTV encompassing the tumor, mesorectum, and pelvic lymph nodes was 46 Gy in 23 fractions, and the boost at a dose of 57.5 Gy in 23 fractions included the macroscopic primary tumor and enlarged lymph nodes. The patients underwent surgery 6–8 weeks later. Seventy-four patients were included, and grade 3 or acute CHRT-related toxicity was 17.6 % with GI toxicity in four patients (5.4 %). The compliance rates for RT and CHT were 100 and 98 %, respectively.

Discussion

Clinical and dosimetric data described above show that IMRT achieves a more conformal dose distribution while decreasing the high dose of radiation in the SB, without detrimentally affecting tumor coverage. IMRT in rectal cancer decreased

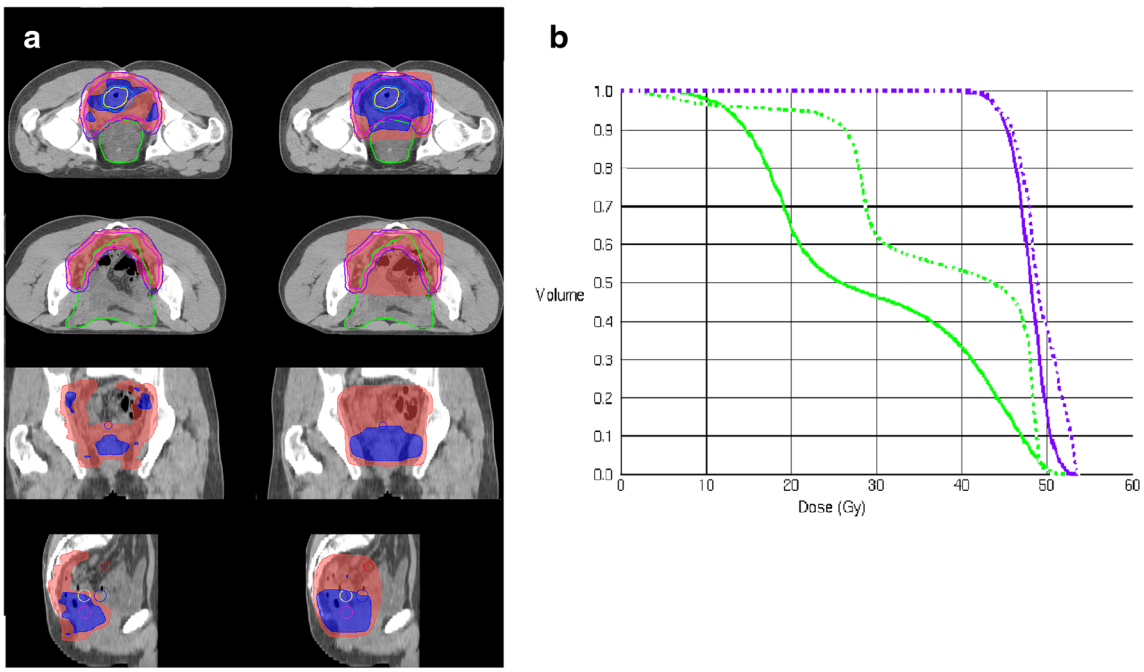

Fig. 1 **a** Differences between 45 Gy and 50 Gy dose distribution (*red* and *blue* colours respectively) in LARC patient planned with IMRT (*left*) and 3DCRT (*right*). **b** Dose volume histogram of 3DCRT plan (*dash line*) compared with IMRT plan (*solid line*). *Green*: Small bowel. *Purple*: PTV

Table 2 Clinical studies with IMRT in rectal cancer

Author year	No. of patients	Study	Dose prescription	GI toxicity	Compliance	pCR (%)
Ballonoff et al. [18]	8	Phase II IMRT CAPECITABINE	55 Gy GTV (2.2 Gy/fx) 45 Gy PTV (1.8 Gy/fx)	≥G3 15.5 %	RT 100 % CHT 100 %	38
Engels et al. [19]	108	Phase II IMRT	55.2 Gy GTV (2.4 Gy/fx) 46 Gy PTV (2 Gy/fx)	≥G3 1 % G2 14 %	RT 100 %	8
Arbea et al. [20]	100	Phase II IMRT CAPOX	47.5 Gy PTV (2.37 Gy/fx)	G3 9 % NO G4	RT 98 CHT 80 %	13
RTOG [21]	79	Phase II IMRT CAPOX	47 Gy Boost 5.4 Gy (1.8 Gy/fx)	G3 22 % G4 1 %	-	15
Zhu et al. [22]	78	Phase II IMRT CAPOX	50 Gy PTV Concomitant boost 55 Gy 25 fx	G3 10.4 %	RT 100 % CHT 61 %	23.7
Hernando-Requejo [23]	74	Prospective dose escalation IMRT CAPECITABINE	46 Gy PTV Concomitant boost 57.5 Gy 23fx	G3 9.5 % No G4	RT 100 % CHT 98 %	30.6

IMRT intensity-modulated radiation therapy, *GTV* gross tumor volume, *CTV* clinical tumor volume, *PTV* planning target volume, *fx* fraction, *CAPOX* capecitabine-oxaliplatin, *pCR* complete pathological response

GI toxicity, with a rate of grade III diarrhea lower than expected with 3DCRT. These data should be taken with caution because these results come from phase II trials, and a lack of statistically significant evidence is obvious.

From a dosimetric point of view, we should note two considerations. First, in regard to target dose homogeneity, IMRT planning results in a trade-off between the coverage of the target and the avoidance of adjacent healthy structures. It has been suggested that the reduction in dose homogeneity within the target is the price to pay for a better conformity (a recognized circumstance related to the greater number of treatment beams). Although not all the studies demonstrated a decrease in target heterogeneity, it is recommended that clinicians continue to be aware that prescription to a single point is usually unsatisfactory for IMRT and that prescription should be given to the PTV as a whole [24].

The second issue concerns target volume definition for adequate IMRT planning and the inter- and intra-fractional movement of the target and OAR. The IMRT technique creates sharp dose gradients, which are less forgiving with respect to misalignment and motion. Appropriate delineation of target volumes and organs at risk is critical due to the high degree of conformity achieved with IMRT, and the use of RTOG guidelines for contouring the elective clinical target volume is suggested to assure optimal target delineation [25]. With respect to intra-fractional motion, the use of more sophisticated therapy techniques such as IGRT or volumetric-modulated arc therapy (VMAT) may overcome the potential inaccuracies of IMRT. Adaptive radiation therapy strategies have been introduced to reduce PTV margin and to adapt different dose distributions to daily changes in the PTV [26].

Although there are encouraging dosimetrical results, there are no randomized phase III trials and there are no solid clinical data supporting the routine use of IMRT for preoperative treatment of LARC patients. We should emphasize some interesting clinical findings that could potentially give to IMRT a role in optimizing outcomes in LARC treatment. First, in considering outcome in terms of acute toxicity, the vast majority of the phase II trials discussed above use IMRT combined with CAPOX as the treatment cornerstone for patients with LARC. Recent studies in LARC have focused on neoadjuvant therapies based on adding oxaliplatin to conventional capecitabine-based radiotherapy. Oxaliplatin has shown no clear benefit in terms of pathological response and a worse toxicity profile with higher rates of GI toxicity [3, 27]. In the phase III trial ACCORD 12/0405-Prodige 2, full-dose radiotherapy was given only to 87 % of patients in the CAPOX 50 group. A definitive discontinuation of CHT was observed in 8.8 % of patients, and dose modification of the CHT regimen was performed in 59 % of patients. The overall rate of grades 3 to 4 toxicity was 25.4 %, and grade 3 diarrhea was observed in 12.6 % of patients. In the STAR-01 randomized phase III trial, compliance with fluorouracil administration was reduced among patients treated with oxaliplatin compared to compliance among patients treated with radiation and 5-FU alone. As a result, a lower proportion received at least 80 % of the planned cumulative dose of fluoropyrimidine, and only the 84 % received the full dose of radiotherapy [28]. Nonetheless, the treatment compliance differed from that in the phase II

trials in which IMRT was selected as radiation therapy. The RT compliance observed in the phase II trials was 98–100 %, with grade 3 toxicity rates of 9–22 %. Judging from these results, we should await definitive data from the phase II 0820 RTOG trial designed to elucidate whether the acute GI toxicity seen in RTOG 0247 could be reduced using inverse-planning IMRT optimized to limit dose to small bowel [21•].

In regard to outcome in terms of efficacy defined as pathological response rate, data is lacking and far from robust. Taking into account the pCR rate described in phase II trials which used IMRT, including those in which it was combined with CAPOX, we find similar data regarding pathological response (pCR 10–30 %). When compared to standard radiotherapy approaches, IMRT seemed to be as active, at least in terms of response rates when standard doses were prescribed [3, 28, 29]. IMRT may offer the use of simultaneous boost and the possibility of applying hypofractionated radiation schedules while using conventional fractioning into the pelvis. The use of accelerated radiotherapy has the potential benefit of shortening treatment time by reducing the number of fractions and increasing the fraction size. This approach may lead a lower chance of tumor repopulation, which ultimately may improve the rate of pCR [30]. The role of escalating the dose of preoperative RT is being studied, and solid data are scarce [31]. At least one study has reported an increase in rectal tumor response with no detrimental effect on treatment toxicity and early clinical outcome through the use of 3DCRT 39 Gy in 13 fractions with boost (85 Gy in three fractions) using endocavitary contact x-ray [32]. Using this approach, it may be possible to use IMRT in the design of GTV dose escalation studies to increase response rates (pCR) and optimize outcomes in LARC patients, without detrimentally affecting acute toxicity.

There are scarce clinical data available regarding hypofractionated radiation using IMRT in LARC patients. The only available data is drawn from studies of feasibility with an acceptable acute toxicity profile when moderate hypofractionated dose (2.2–2.5 Gy/fx) is prescribed combined with different CHT regimens [19, 20, 23]. A Korean group testing the use of a small field boost using pelvic radiation therapy (43.2 Gy in 24 fractions plus a concomitant boost of 7.2 Gy in 12 fractions delivered to the pelvis and tumor) reported an 11.6 % pCR rate [33, 34]. More recently, the pCR reported from experience using a concomitant IMRT boost of 57.5 Gy in 23 fractions with simultaneous CAPO was 30.6 % with a T and N downstaging of 76.38 and 47.2 %, respectively [23]. Yeo et al. have reported the use of higher hypofractionated IMRT treatment with concomitant CHT in a prospective phase 2 multicenter trial designed to investigate the efficacy and safety of preoperative short-course IMRT (25 Gy in five fractions) with concurrent 5FU-based CHT followed by delayed surgery for LARC patients [35]. They concluded that despite the use of an advanced RT technique, a considerable percentage of patients experienced severe toxicities.

Taking into account all this clinical considerations, IMRT may play an important role in the treatment of patients with LARC in the future. Can we design an IMRT-protocol to integrate more active chemotherapy with a good compliance rate? Can we design a protocol based on dose escalation to treat either nodes outside the mesorectum or tumor threatening the circumferential margin? Can we achieve a complete clinical response and avoid surgery altogether? Probable are achievable challenges.

Finally, in considering the potential role of IMRT treatment in LARC patients, late morbidity and second tumors must be taken into account. Hypofractionated IMRT has the potential to significantly increase normal tissue fibrosis not removed at surgery. Recent analysis of late toxicity in LARC patients treated with hypofractionated IMRT has shown absolute incidence of grade 3 late GI and urinary toxicities of 9 and 4 %, respectively, with a 13 % rate of any grade 3 late toxicity at a median follow-up of 54 months [36]. In this trial, patients received a dose of 46 Gy in daily fractions of 2 Gy to the primary tumor, the mesorectum, and the draining lymph nodes; 57 patients of the boost group received a simultaneous integrated boost of 0.4 Gy per day up to a total dose of 55.2 Gy to the primary tumor. These toxicity results are comparable to the reported rate of grade 3 toxicity of 9 % from the German CAO/ARO/AIO-94 phase III trial, where preoperative RT consisted of 50.4 Gy in 28 fractions of 3DCRT 2.

Lastly, the probability of an increase in the 10-year incidence of second tumors in patients treated with IMRT is a concern because of the larger volume of normal tissue exposed to lower doses compared with 3DCRT techniques. Some have estimated the probable increase to range from 1 to 1.75 % compared to that seen in patients treated with 3CDRT [37]. However, clinical evidence regarding this issue has been increasing in recent years, and current data show that there has not been an increase in second cancers after IMRT. In a retrospective study of 240 women with breast cancer who either received three-dimensional conventional RT or IMRT, there was no significant difference in the incidence of second tumors between the two groups at a median follow-up time of 6.3 years [38]. Additionally, a long-term follow-up study of 561 prostate cancer patients treated with high-dose IMRT found that none had developed second tumor at a median time of 7 years [39]. There is no data available in the context of LARC.

Conclusion

Although there is no solid clinical data that supporting the routine use of IMRT for preoperative treatment of LARC patients, IMRT is a feasible radiation approach to prescribe in

selected patients, mainly if the dosimetric distribution in the small bowel and V15 or SB are not at tolerable limits. Also, it would be interesting to study if neoadjuvant IMRT for LARC patients could be included in protocols in order to investigate whether or not applying IMRT in combination with CAPOX would increase GI acute toxicity and whether its use would allow an optimal chemotherapy dose density schedule with a higher compliance rates and a higher pCR rate. Additionally, it would be also interesting to elucidate if hypofractioned radiotherapy to the GTV and an increase in the biological dose applied to the tumor in combination with CHT may also produce a higher response rate without an impact on acute and late toxicity events.

In summary, whether IMRT can be used to improve outcomes for LARC patients though its ease of combination with different CHT agents or because of its potential to deliver higher RT doses to the GTV without worsening the toxicity profile still merits further investigation.

Compliance with Ethics Guidelines

Conflict of Interest The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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