Acute toxicity with intensity modulated radiotherapy versus 3-dimensional conformal radiotherapy during preoperative chemoradiation for locally advanced rectal cancer

Shu Y. Ng a, Kathryn L Colborn b, Lajhem Cambridge a, Carla Hajj a, T. Jonathan Yang a, Abraham J. Wu a, Karyn A. Goodman c,*

a Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York; b Division of Health Care Policy and Research, Adult and Child Consortium for Health Outcomes Research and Delivery Science; and c Department of Radiation Oncology, University of Colorado Denver School of Medicine, USA

Abstract

Background and purpose: We examined acute toxicity profiles and outcomes among rectal cancer patients treated with pre-operative chemoradiation using intensity modulated radiotherapy (IMRT) or 3-dimensional conformal radiotherapy (3DCRT) to identify predictive clinical factors associated with increased acute toxicity.

Material and methods: We retrospectively reviewed records of 301 consecutive rectal cancer patients treated with pre-operative chemotherapy and radiotherapy (median dose 5000 cGy) at our institution between 2007 and 2014.

Results: Of the 301 patients, 203 (67.4%) were treated with IMRT and 98 (32.6%) with 3DCRT. Significantly more patients experienced ≥ grade 2 diarrhea in the 3DCRT group compared to the IMRT group (22% vs 10%, p = 0.004), and those who received 3DCRT had 2.7 times greater odds of a higher diarrhea score than those on IMRT, even after adjusting for patient characteristics and chemotherapy (OR 2.71, p = 0.01). Fewer patients experienced grade 2 genitourinary toxicity in the IMRT group (6% vs 13%, 3DCRT, p = 0.04) and there was a trend toward decreased grade 2 proctitis in the IMRT group (22% vs 32% 3DCRT, p = 0.07). Patients over the age of 55 had 45% lower odds of proctitis than patients younger than 55.

Conclusion: The use of IMRT significantly reduced grade ≥2 diarrhea and GU toxicity during chemoradiation. Younger patients were more likely to report grade 2 or higher proctitis.

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Preoperative pelvic radiotherapy (RT) with concurrent 5-Fluorouracil (FU)-based chemotherapy remains the current standard of care for patients with locally advanced rectal cancer based on landmark phase III randomized trials published over a decade ago [1–3]. While the outcomes for locally advanced rectal cancer continue to improve with the introduction of more sophisticated surgical techniques, such as the total mesorectal excision (TME) [4] and with more modern chemotherapy agents [5], conventional pelvic RT is still associated with significant acute toxicities that can adversely impact a patient’s quality of life and tolerance of therapy [6,7]. While the more conformal planning approach of intensity-modulated radiotherapy (IMRT) has been introduced for the management of many other malignancies [8–11], it remains controversial for pre-operative pelvic RT for rectal cancer. In fact, although recent prospective phase II data of IMRT in combination with capecitabine and oxaliplatin failed to meet the endpoint of reduced toxicity when compared to historical data, this study did not evaluate the now-standard approach of pre-operative capecitabine and pelvic RT and therefore doesn’t fully address the benefit of IMRT when more standard chemotherapy agents are given.

A strong dose–volume relationship has been demonstrated for the small bowel irradiated and acute diarrhea during preoperative chemoradiation [12]. Dosimetric studies have shown that IMRT for rectal cancer can reduce dose to adjacent organs at risk while maintaining superior target coverage, homogeneity and conformity, making it a superior technique to 3D conformal RT (3DCRT) in the treatment of rectal cancer [13,14]. Moreover, several retrospective clinical studies have suggested that the use of IMRT does significantly decrease toxicity and also reduces treatment breaks, emergency department visits and hospitalizations [15–18]. Given the controversy surrounding the use of IMRT in preoperative...
therapy for rectal cancer, we examined acute toxicity profiles and outcomes between patients treated with IMRT and 3DCRT in a large cohort of patients and sought to identify predictive clinical factors associated with increased acute toxicity, thereby characterizing scenarios in which IMRT might be most appropriate.

Methods

After obtaining a waiver of authorization from our Institutional Review Board, we identified and retrospectively reviewed records of 318 consecutive patients with primary rectal cancer who were treated with preoperative chemoradiation between January 2007 and October 2014 at Memorial Sloan Kettering Cancer Center’s (MSKCC) main campus. All patients had biopsy-confirmed adenocarcinoma by the MSKCC Department of Pathology. Patients underwent pretreatment imaging consisting of computed tomography (CT) chest, abdomen, pelvis, rectal protocol magnetic resonance imaging (MRI), examination by a colorectal surgeon (including proctoscopy and/or endorectal ultrasound), clinical examination and routine laboratory testing. Clinical and tumor characteristics were obtained from the medical record and a prospectively maintained database.

Treatment

Radiotherapy

For patients who received induction chemotherapy, radiation therapy commenced two to three weeks after the last planned dose of chemotherapy. All patients were considered for IMRT unless the patient’s insurance coverage denied use of IMRT. All patients underwent computed tomography (CT)-based treatment planning in the prone position with intravenous contrast, a full bladder, a radio-opaque BB at the anal verge, and lower body immobilization in an Aquaplast mold. Weekly cone beam CT was performed to check setup and bladder distension. The gross tumor volume (GTV) comprised the primary tumor and enlarged regional lymph nodes and the clinical target volume (CTVA) comprised the GTV, rectum and lymph node regions, which included the mesorectum, presacral, internal iliac and superior rectal lymph nodes in keeping with the Radiation Therapy Oncology Group Anorectal Atlas [19]. We included CTVB for patients with T4 tumors invading into anterior structures and CTVB + C when there was anal canal involvement. The CTV boost comprised the GTV, adjacent mesorectum and presacral space. The initial planning target volume (PTV) was defined as a 5 mm expansion of the CTVA and the PTV boost was a 1.5 cm expansion of the CTV boost. Normal tissues contoured at the time of RT planning included the bladder, bowel, anal canal (anal verge to anorectal ring), rectum (anorectal ring to rectosigmoid flexure), femoral heads, external genitalia, and vagina in female patients. The bowel contour included small bowel and large bowel loops, excluding the rectum and anal canal, extending to 1 cm above the PTV, and did not include the mesenteric fat.

Coverage of the PTV by at least 95% of the prescribed dose was required for all plans. 3DCRT plans used 6-MV or 15-MV photos and consisted of primarily three, and in a small subset of patients four, orthogonal pelvic field beams, two lateral beams and one posterior-anterior beam for the boost fields. The PTV was treated to 45 Gy in 1.8 Gy fractions followed by a 5.4 Gy boost to a total dose of 50.4 Gy. IMRT plans consisted of five to seven equally spaced coplanar fields using 6-MV or 15-MV photons (Fig. 1). The PTV was treated to 45 Gy in 1.8 Gy fractions and the integrated PTV boost was treated to 50 Gy in 2 Gy fractions for all patients except seven who received additional 3–6 Gy boost. Dose homogeneity was assessed by volume receiving more than 5% of the prescribed dose.

Chemotherapy

For patients who received induction chemotherapy, the majority received the standard six-to-eight cycles of 5-FU, leucovorin and oxaliplatin (FOLFOX) administered every two weeks and the others received capecitabine and oxaliplatin (CapeOx). Concurrent chemotherapy was delivered either orally with capecitabine 825 mg/m² twice daily Monday through Friday, or using continuous infusional 5-FU to 225 mg/m².

Acute toxicity assessment

The treating clinician evaluated patients weekly during chemoradiation and acute toxicities were documented. The toxicity data related to pelvic radiotherapy including diarrhea, proctitis, and genitourinary (GU) symptoms, including dysuria, urinary frequency, or cystitis, and vaginal discharge were collected for the study. Acute toxicities were graded on a Lower GI toxicity form according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v3.0. Weekly toxicity grading was obtained through chart review. To ensure that patients included had a high rate of toxicity documentation, only 301 (94.7%) patients who had four or more documented toxicity assessments were included.

Statistical analysis

Differences in patient characteristics and the highest observed toxicity values were compared between the IMRT and 3DCRT groups using t-tests and Fisher’s exact tests. Multiple logistic regression models were fit to the highest observed scores for diarrhea, proctitis and GU toxicity. Toxicity scores were coded as binary by ≤ 1 or >1. Each model was fit with age, gender, clinical, distance from anal verge, BMI, type of RT (IMRT, 3DCRT) and induction chemotherapy as fixed factors. Final models only included fixed factors that were significant at p ≤ 0.05. Models were fit in R version 3.13 [20].

Results

Patient, tumor and treatment characteristics

Of the 301 patients in this study, 203 (67.4%) patients underwent IMRT and 98 (32.6%) patients underwent 3DCRT. Patient, tumor and treatment characteristics are listed in Table 1. Majority of the patients were treated for clinical stage T3 and node-positive disease. There were no significant differences in characteristics in the IMRT and 3DCRT cohorts except for induction chemotherapy, where significantly more patients treated with IMRT were also treated with induction chemotherapy (64.0% IMRT vs 31.6% 3DCRT, p < 0.0001). This is explained by the similar timeframe of the utilization of IMRT for LARC and changes to treatment policy at our
institution so that patients with LARC received neoadjuvant chemotherapy prior to chemoradiation.

**Acute toxicity**

The frequency of acute toxicity rates by treatment group is shown in Fig. 1. Significantly fewer patients experienced grade ≥2 diarrhea in the IMRT group as compared to the 3DCRT group (9.9% vs 22.4% 3DCRT, \( p = 0.004 \)). While no grade ≥3 proctitis and GU toxicity occurred in either group, significantly fewer patients experienced grade 2 GU toxicity in the IMRT group (5.9% vs 10.8% 3DCRT, \( p = 0.07 \)). There was a trend toward decreased grade 2 proctitis in the IMRT group (21.7% vs 31.6% 3DCRT, \( p = 0.07 \)). No significant differences were identified between the two groups for fatigue, dermatitis, mucositis, nausea, vomiting and vaginal discharge. Five percent of patients in both the IMRT and 3DCRT groups required treatment breaks. 1.5% of patients in the IMRT group and 2.0% of patients in the 3DCRT group did not complete chemoradiation.

**Predictive factors leading to worse toxicity**

Predictive factors including age, gender, distance from anal verge, BMI, type of RT (IMRT, 3DCRT) and induction chemotherapy were assessed for association with diarrhea, proctitis and GU toxicity (Table 2). Patients that received 3DCRT had 2.7 times greater odds of a Grade 2 or higher diarrhea score than those on IMRT, even after adjusting for patient characteristics and chemotherapy (Table 2 and \( \text{OR}_{2.71}, 95\% \text{ CI} [1.34, 5.47], p = 0.01 \)). Patients over the age of 55 had 45% lower odds of proctitis than patients younger than 55. Induction chemotherapy was associated with an 84% reduction in odds of GU toxicity overall, but patients with 3DCRT and induction chemotherapy had greatly increased odds of genitourinary symptoms (Table 2 and \( \text{OR}_{16.3}, 95\% \text{ CI} [2.6, 102] \)). This large effect size was partly due to higher GU toxicity scores being rare (only 8% grade ≥2) and 3DCRT and induction chemotherapy combinations being rare (only 10% with both).

**Discussion**

Our large retrospective study demonstrated that the use of IMRT planning for pre-operative pelvic radiotherapy for locally advanced rectal cancer significantly reduces grade ≥2 diarrhea and GU toxicity as compared to 3DCRT. Ideally, prospective trials would be better to establish the clinical impact of IMRT on toxicity.
profiles as compared to treatment with 3DCRT. However, the recently published Radiation Therapy Oncology Group (RTOG) 0822 phase II study evaluating preoperative chemoradiation with IMRT used a combination concurrent chemotherapy regimen of capecitabine and oxaliplatin [21]. Unfortunately this study was designed before the results of three large phase 3 randomized trials unequivocally demonstrated increased rates of grade 3+ diarrhea with the addition of oxaliplatin to standard pre-operative chemoradiation with concurrent capecitabine or 5-FU. The ACCORD 12/0405-PRODIGE 2, the STAR trial, and NSABP R-04 trials have now been published and given that the use of oxaliplatin with 5-FU based chemoradiation contributed to significant increased GI toxicity, this approach has been abandoned [5,22,23]. Nonetheless, the use of oxaliplatin administered concurrently with capecitabine and pelvic RT in the RTOG 0822 study may have diminished the effect of the IMRT on GI toxicity in that study, since minimizing RT dose to the small bowel would not have sufficiently offset the impact of the oxaliplatin on the development of diarrhea. Thus, we set out to evaluate the impact of IMRT on GI toxicity in the setting of standard 5-FU-based chemoradiation.

Our findings are consistent with other smaller dosimetric and clinical studies that show decreased bowel doses with IMRT and resultant reduction in GI toxicity. We have previously shown in a smaller dosimetric study at our institution that women had higher rates of developing grade ≥2 diarrhea starting at week 4 of pelvic chemoradiation for rectal cancer (24% vs 12% men, p = 0.01) and patients who were treated with 3DCRT also had higher rates of developing grade ≥2 diarrhea (22% vs 12% IMRT, p = 0.03) [18]. A higher rate of grade ≥2 proctitis was significantly associated with younger patients under 60 years of age (21% vs 9%, p = 0.02) and anal canal volume receiving ≥15 Gy (V15). A retrospective study clinical conducted by Samuelian et al. at the Mayo Clinic in Arizona showed that patients who were treated with IMRT experienced grade ≥2 diarrhea less frequently than those treated with 3DCRT (23% IMRT vs 48% 3DCRT) [17]. No significant difference was seen in proctitis and urinary toxicity between the groups. The frequency of grade ≥2 diarrhea experienced by their patients is approximately twice as high than in our patients. However, their cohort is different in that patients who received postoperative chemoradiation and those treated for recurrence were included, as compared to only those with primary tumors treated with preoperative intent in our study. Table 3 shows previous clinical studies and their results compared to our findings.

Our findings are also consistent with the study by Parekh et al. showing significantly reduced grade ≥2 diarrhea with IMRT (10% vs 43% 3DCRT, p = 0.014) [16]. While no grade 3 or higher diarrhea was seen in their IMRT patients, their small sample size may have been inadequate to capture these patients. Two patients in our IMRT group (1.0%) experienced grade 3 diarrhea and none had grade 4 toxicity, while two 3DCRT patients (2.0%) experienced grade 3 and 4 diarrhea. These small proportions experiencing higher-grade toxicity in our cohort are relatively reassuring.

Jabbour et al. showed that in 86 patients, IMRT significantly reduced all ≥3 toxicities including pain, fatigue, GI, GU and hematological symptoms. GI toxicities were not significantly reduced when analyzed independently [15]. As expected, those who received single-agent concurrent chemoradiation experienced lower rates of grade ≥3 toxicity (11%) as compared to those who received combination chemotherapy agents (i.e. including oxaliplatin) (43%, p = 0.009). Fewer hospitalizations and emergency

### Table 2

Multiple logistic regression models for diarrhea, proctitis and cystitis.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Diarrhea</th>
<th>Proctitis</th>
<th>Cystitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 55</td>
<td>OR</td>
<td>LCL</td>
<td>UCL</td>
</tr>
<tr>
<td>Female</td>
<td>0.96</td>
<td>0.48</td>
<td>1.92</td>
</tr>
<tr>
<td>Ave distance from anal verge</td>
<td>0.97</td>
<td>0.87</td>
<td>1.07</td>
</tr>
<tr>
<td>BMI</td>
<td>1</td>
<td>0.94</td>
<td>1.06</td>
</tr>
<tr>
<td>3DCRT</td>
<td>2.71</td>
<td>1.34</td>
<td>5.47</td>
</tr>
<tr>
<td>Induction Chemo</td>
<td>0.97</td>
<td>0.47</td>
<td>1.99</td>
</tr>
<tr>
<td>RT type*Induction Chemo</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

*p = not significant, therefore the interaction was excluded.
LCL = lower 95% confidence limit; UCL = upper 95% confidence limit.

### Table 3

Toxicity rates reported in published clinical studies.

<table>
<thead>
<tr>
<th>Study (year) (ref)</th>
<th>No. of patients (IMRT vs 3DCRT)</th>
<th>Concurrent chemo type</th>
<th>Toxicity</th>
<th>Grade ≥ 2 toxicity</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samuelian et al. (2012) [17]</td>
<td>92 (31 vs 61)</td>
<td>5-FU or capecitabine</td>
<td>Diarrhea</td>
<td>7 (23)</td>
<td>29 (48)</td>
</tr>
<tr>
<td>Jabbour et al. (2012) [15]</td>
<td>86 (30 vs 56)</td>
<td>5-FU or capecitabine</td>
<td>Proctitis</td>
<td>3 (10)</td>
<td>11 (18)</td>
</tr>
<tr>
<td>Parekh et al. (2013) [16]</td>
<td>48 (28 vs 20)</td>
<td>5-FU or capecitabine</td>
<td>Urinary</td>
<td>5 (16)</td>
<td>13 (21)</td>
</tr>
<tr>
<td>Hong et al. (2015) [21]</td>
<td>51 (All IMRT)</td>
<td>Capecitabine and oxaliplatin</td>
<td>Diarrhea</td>
<td>24 (47)</td>
<td>–</td>
</tr>
<tr>
<td>Hong et al. (2015) [21]</td>
<td>301 (203 vs 98)</td>
<td>5-FU or capecitabine</td>
<td>Proctitis</td>
<td>4 (8)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Urinary</td>
<td>0 (0)</td>
<td>2 (7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diarrhea</td>
<td>20 (10)</td>
<td>22 (22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Proctitis</td>
<td>44 (22)</td>
<td>31 (32)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Urinary</td>
<td>12 (6)</td>
<td>13 (13)</td>
</tr>
</tbody>
</table>

Abbreviations: Ref = reference; IMRT = intensity modulated radiotherapy; 3DCRT = 3D conformal radiotherapy; chemo = chemotherapy.

* Grade ≥ 3 toxicity reported in study.
room visits occurred in the IMRT group (2% vs 14% 3DCRT, \( p = 0.005 \)). In their study, they used a toxicity grade cutoff of grade \( \geq 3 \) while ours and other studies had used a toxicity grade cutoff of grade \( \geq 2 \). Also, the majority of the IMRT patients in their series were treated in the supine position, compared to the 3DCRT patients who were treated in the prone position.

We also sought to identify predictive clinical factors associated with increased acute toxicity and factors evaluated in the analysis included age, gender, clinical T staging, distance from anal verge, BMI, type of RT (IMRT, 3DCRT) and induction chemotherapy. Increased age was shown in our study to be associated with lower rates of proctitis, which may not be surprising as it has previously been demonstrated by anorectal manometry that age influences rectal sensory thresholds especially in females \[24,25\]. Hence, younger patients may benefit most from IMRT to reduce the incidence of proctitis.

Interestingly, patients who received induction chemotherapy had an 84% reduction in odds of developing GU toxicity overall, although those who had induction chemotherapy and were treated with pelvic radiotherapy using 3DCRT appeared to have higher odds of GU toxicity (OR16.3). This may be related to the potential for the radiosensitizing induction chemotherapy to increase the risk of bladder toxicity from the higher bladder doses delivered with 3DCRT. This suggests that there may be a rationale for using IMRT in the setting of using induction chemotherapy to minimize bladder dose and reduce the risk of GU toxicity. However, as mentioned before, it is likely because grade \( \geq 2 \) GU toxicity were rare, with only few patients having both 3DCRT and chemotherapy, that contributed to this effect. Ultimately, these findings need to be evaluated in a prospective study.

It is encouraging that pathologic CR rates in our study (19.4% IMRT vs 14.8% 3DCRT, \( p = 0.48 \)) are comparable to the aforementioned studies as well as published randomized controlled trials \[26,27\]. After a median follow-up of 34.4 months, the incidence of local recurrence in our patient cohort is also low (4.9% IMRT vs 6.1% 3DCRT, \( p = 0.78 \)).

Our study represents the largest retrospective cohort comparing acute toxicity among patients treated with pelvic RT using IMRT versus 3DCRT planning, and further supports existing evidence. Our study population was relatively homogeneous since only preoperative primary tumors treated with standard and consistent methods previously proven to be efficacious were utilized, including single-agent 5-FU based concurrent chemotherapy and prone positioning with a full bladder, which enhances the validity of our study. Factors potentially influencing severity of toxicity had not yet been explored previously, whereas our study provides some insight into clinical scenarios associated with increased toxicity, such as younger age and increased proctitis.

The findings in this study are limited by its retrospective design and the selection of patients who might benefit more from IMRT over 3DCRT, which may have dampened the true effect. While chemoradiation treatment methods in our study were standard, a significantly higher proportion of IMRT patients received induction chemotherapy, a factor that may have an independent effect on reducing the frequency of proctitis.

**Conclusion**

In our large patient cohort, the use of IMRT significantly reduced grade \( \geq 2 \) diarrhea and GU toxicity during chemoradiation with a trend toward decreased proctitis. The impact of IMRT on diarrhea and GU toxicity was not limited to any specific subgroup, however patients 55 years and younger had higher odds of experiencing worse proctitis and may benefit most from the use of IMRT to reduce this potential acute toxicity of pelvic radiotherapy.

Prospective studies with appropriate concurrent chemotherapy agents are needed to determine the best method to assess the impact of IMRT on treatment-related toxicity, however, in the absence of these prospective data, we must rely on larger retrospective analyses to guide decisions for our patients.

**Conflicts of interest statement**

None.

**References**


