Radiotherapy and Oncology 121 (2016) 252–257

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Chemoradiotherapy of rectal cancer

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

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ARTICLE INFO

Article history:
Received 20 May 2016
Received in revised form 21 September 2016
Accepted 26 September 2016
Available online 14 October 2016

Keywords:
Locally advanced rectal cancer
Toxicity
Pelvic radiotherapy
Pre-operative chemoradiation
Intensity modulated radiotherapy

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.

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 conformality, 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

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http://dx.doi.org/10.1016/j.radonc.2016.09.010
0167-8140/

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 to minimize volume receiving more than 5% of the prescribed dose.

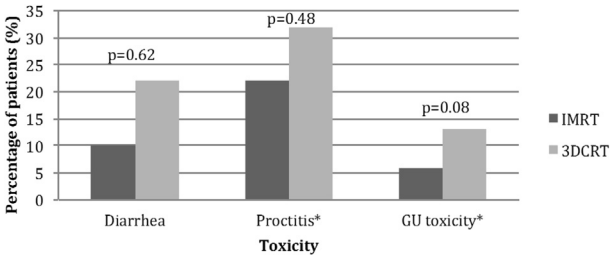

Fig. 1. Grade ⩾ 2 toxicity graded according to CTCAE v3.0. Abbreviations: IMRT = intensity modulated radiotherapy; 3DCRT = 3D conformal radiotherapy; GU = genitourinary. *No grade 3 or higher toxicity occurred in these categories.

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/m^2 twice daily Monday through Friday, or using continuous infusional 5-FU at 225 mg/m^2.

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 $\leqslant 1$ 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 $p \leqslant 0.05$. 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