

## Scientific Article

# IMRT Reduces Acute Toxicity in Patients Treated With Preoperative Chemoradiation for Gastric Cancer



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## Abstract

**Purpose:** Preoperative chemoradiation is being currently evaluated in 2 randomized international trials. However, chemoradiation for gastric cancer can be associated with relatively high rates of acute toxicity. We compared rates of toxicity, toxicity-related events, and oncologic outcomes in patients treated with intensity modulated radiation therapy (IMRT) and those treated with 3-dimensional conformal radiation therapy (3DCRT).

**Methods and Materials:** We retrospectively reviewed records of 202 patients with consecutive gastric cancer treated with preoperative intent radiation therapy at our institution from 1998 to 2018. Patients with gastroesophageal junction involvement and those with metastatic disease were excluded. Eighty-two patients received 3DCRT, and 120 patients received IMRT. The median radiation dose was 45 Gy, and 99% received concurrent chemotherapy.

**Results:** There were no significant differences between the 3DCRT and IMRT groups regarding sex, race, histology, tumor location, histology, or nodal stage. The rate of grade 3 to 4 acute toxicity was significantly lower in patients treated with IMRT compared with 3DCRT (49% vs 70%,  $P = .004$ ). The composite rate of toxicity-related events (hospitalization, feeding tube use, intravenous rehydration, or radiation therapy breaks) was also significantly lower in patients treated with IMRT compared with 3DCRT (56% vs 85%,  $P < .001$ ). In addition, 68% of patients who received IMRT and 73% of patients who received 3DCRT underwent subsequent surgical resection ( $P = .245$ ). Among patients who underwent surgery, the 3-year overall survival rates were not significantly different between those treated with IMRT and 3DCRT (71% vs 69%,  $P = .786$ ). Patients receiving IMRT had a significantly higher absolute nadir lymphocyte count compared with patients receiving 3DCRT (median, 0.21 vs 0.16 K/UL;  $P = .047$ ).

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**Conclusions:** Our study suggests that IMRT might significantly reduce rates of grade 3 to 4 acute toxicity and toxicity-related events compared with 3DCRT, with no significant difference in oncologic outcomes. IMRT is an appropriate and possibly preferable radiation modality in patients treated with preoperative chemoradiation for gastric cancer.

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## Introduction

Randomized trials have shown improvements in survival from perioperative chemotherapy, postoperative chemotherapy, and postoperative chemoradiation in patients with localized gastric cancer.<sup>1-6</sup> Preoperative chemoradiation could serve as an alternative treatment approach in these patients, with potential advantages such as tumor downstaging, improved resectability, and better treatment compliance. Multiple phase 2 trials have evaluated preoperative chemoradiation for gastric cancer.<sup>7,8</sup> The promising results from these trials have led to 2 large randomized trials evaluating preoperative chemoradiation, the TOPGEAR trial and the CRITICS-II trial.<sup>9-12</sup>

Although preoperative chemoradiation offers potential advantages compared with adjuvant treatment, significant toxicities are associated with preoperative therapy. To reduce these toxicities, many institutions have begun to use intensity modulated radiation therapy (IMRT) as a way to spare organs at risk and potentially reduce acute and late toxicity. Dosimetric studies have demonstrated advantages when using IMRT compared with 3-dimensional conformal radiation therapy (3DCRT), such as significantly lower radiation doses to the liver, kidneys, and spinal cord.<sup>13-16</sup> However, there are limited clinical data evaluating IMRT for gastric cancer. In the postoperative chemoradiation setting, Minn et al reported more treatment breaks and increased creatinine levels with 3DCRT compared with IMRT, and Trip et al reported reduced late severe kidney toxicity with IMRT.<sup>17,18</sup> In contrast, Chopra et al reported no difference in acute toxicity with postoperative IMRT compared with 3DCRT.<sup>19</sup> A recent study evaluated an initial experience of 25 patients treated with preoperative IMRT and reported no significant difference in acute toxicity compared with 50 patients treated with 3DCRT.<sup>8</sup> Given the increasing global interest in preoperative chemoradiation for gastric cancer, we evaluated rates of toxicity, toxicity-related events, and oncologic outcomes in patients treated with preoperative IMRT compared with 3DCRT using a much larger cohort of patients.

## Methods and Materials

The study included patients with localized, biopsy-confirmed gastric cancer who were treated with

preoperative intent radiation therapy at our institution from 1998 to 2018. Patients with metastatic disease and those with disease arising from the gastroesophageal junction were excluded. A total of 202 consecutive patients were identified, and their medical records were reviewed. Patient characteristics are listed in Table 1. Of these patients, 82 were treated with 3DCRT and 120 were treated with IMRT. At our institution, patients were routinely treated with 3DCRT until 2004, with increasing adoption of IMRT from 2005 onward.

In both groups, the clinical tumor volume (CTV) included the gross tumor volume based on diagnostic imaging and endoscopy, a 3- to 4-cm margin along mucosal surfaces, involved lymph nodes, and elective lymphatic regions based on the site of the tumor (celiac axis, splenic hilum, porta hepatis for tumors in the proximal third of the stomach; celiac axis, splenic hilum, porta hepatis, subpyloric and pancreaticoduodenal areas for tumors in the middle third of the stomach; celiac axis, porta hepatis, subpyloric and pancreaticoduodenal areas for tumors in the distal third of the stomach). For 3DCRT, a 2- to 4-field arrangement was typically used, with a 2-cm margin from CTV to block edge. For IMRT, a 0.5- to 0.7-cm expansion was added to the CTV to form the planning target volume. Typical IMRT constraints included liver (V30 <33%, V20 <50%, and mean <30 Gy), kidney (mean <18 Gy and V20 <33% each), lungs (V20 <30%, V10 <45%, mean lung dose <20 Gy), spinal cord (Dmax <45 Gy), and heart (mean <30 Gy and V30 <30%). Chemotherapy was given before radiation, concurrently with radiation, or in both settings, with the choice of chemotherapy agent determined by the treating medical oncologist (Table 1). Patients were evaluated for surgical resection 4 to 6 weeks after the completion of chemoradiation.

Acute (occurring within 90 days after the start of radiation therapy) toxicity outcomes for patients were determined using the Common Terminology Criteria for Adverse Events version 4.0 scale during retrospective chart review. Toxicity-related events, specifically hospitalization, feeding tube use, intravenous hydration requirement, or radiation treatment breaks, were recorded. Other oncologic outcomes, including progression-free survival (PFS) and overall survival (OS), were also determined. Both OS and PFS were calculated from the first day of radiation therapy. Median follow-up from date of diagnosis was 29.5 months overall, 38.5 months in the 3DCRT group, and 28.9 months in the IMRT group.

Statistical analysis included descriptive statistics,  $\chi^2$  tests, Cox regression analysis, and Kaplan-Meier survival. SPSS software (IBM Corp, Armonk, NY) was used for statistical comparisons, and *P* values < .05 were considered statistically significant. The study was approved by our institutional review board.

### Results

The median age was 63, and 54% were male. The median radiation dose was 45 Gy (interquartile range, 45-45 Gy). In addition, 78% of patients in the 3DCRT group and 95% of patients in the IMRT group received neoadjuvant chemotherapy before RT (*P* = .001). Furthermore, 99% of patients in each group received concurrent chemotherapy. There were no significant differences between the 3DCRT and IMRT groups with respect to sex, race, histology, tumor location, tumor grade, Lauren classification, and clinical T stage or nodal status (Table 1).

### Acute toxicity

The rate of grade 3 to 4 acute toxicity was significantly lower in patients treated with IMRT compared with those treated with 3DCRT (49% vs 70%, *P* = .004; Table 2). The composite rate of toxicity-related events (hospitalization, feeding tube use, intravenous rehydration, or RT breaks) was also significantly lower in patients treated with IMRT compared with those treated with 3DCRT (56% vs 85%, *P* < .001; Table 2). The most common acute grade 3 toxicity in both the 3DCRT and IMRT groups was nausea and emesis (Table 3).

### Surgical outcomes

In the study, 73% of patients who received 3DCRT and 68% of patients who received IMRT underwent subsequent surgical resection (*P* = .245). The most common reasons for patients to not undergo surgery were progression of disease or the patient being a poor surgical candidate owing to comorbidities or treatment-related toxicities. Among patients who underwent surgical resection, the R0 rates were 95% in the 3DCRT group and 90% in the IMRT group (*P* = .286). Additionally, there was no significant difference in the pathologic complete response rate between the 3DCRT and IMRT groups (17% vs 18%, *P* = .802). There were no significant differences in the pathologic T and N stage when comparing the 3DCRT group with the IMRT group (*P* = .303 and *P* = .159, respectively, Table E4; available online at <https://doi.org/10.1016/j.adro.2019.11.003>).

**Table 1** Patient and treatment characteristics

	3DRT N = 82 (41%)	IMRT N = 120 (59%)	<i>P</i> value
Median age at diagnosis (y)	61	64	.155
Male	46 (56%)	63 (53%)	.614
White	38 (46%)	48 (40%)	.371
Tumor location			.572
Cardia	12 (15%)	10 (8%)	
Fundus	4 (5%)	6 (5%)	
Body	32 (39%)	50 (42%)	
Antrum/pylorus	34 (41%)	54 (45%)	
Histology			.425
Adenocarcinoma	47 (57%)	76 (63%)	
Adenocarcinoma with signet ring cell features	35 (43%)	42 (35%)	
Adenosquamous carcinoma	0 (0%)	1 (1%)	
Carcinoma, poorly differentiated	0 (0%)	1 (1%)	
Grade			.269
Well differentiated	0 (0%)	1 (1%)	
Moderately differentiated	13 (16%)	31 (26%)	
Poorly differentiated	62 (76%)	88 (73%)	
Lauren classification			.478
Intestinal type	3 (4%)	26 (22%)	
Diffuse	5 (6%)	25 (21%)	
Unknown	74 (90%)	69 (57%)	
Neoadjuvant chemotherapy	65 (79%)	114 (95%)	.001*
5-FU/capecitabine	22	60	
+ oxaliplatin			
5-FU/capecitabine and cisplatin/carboplatin	24	6	
Taxane based	19	46	
Other	0	2	
Concurrent chemotherapy	81 (99%)	119 (99%)	.785
5-FU/capecitabine	16	48	
5-FU/capecitabine and oxaliplatin	23	31	
Taxane based	40	36	
Other	2	4	
Surgical resection	60 (73%)	81 (68%)	.245
Patients receiving 45 Gy	94%	93%	.871
Clinical T stage			.134
T3 or below	69 (84%)	109 (91%)	
T4	13 (16%)	11 (9%)	
Clinical N status			.974
N0	35 (43%)	52 (43%)	
N+	44 (54%)	66 (55%)	
Unknown	3 (3%)	2 (2%)	

Abbreviations: 3DRT = 3-dimensional radiation therapy; 5-FU = 5-fluorouracil; IMRT = intensity modulated radiation therapy.

\* Significant *P*-value < .05.

### Lymphopenia

Patients receiving 3DCRT had a significantly lower nadir absolute lymphocyte count compared with patients receiving IMRT (median 0.16 K/UL and 0.21 K/UL,

**Table 2** Treatment-related toxicities

	3D N = 82	IMRT N = 120	Odds ratio	P value
Toxicity-related events (hospitalization, feeding tube use, IV fluid use, RT break)	70 (85%)	67 (56%)	2.68	<.001*
Grade 3-4 acute toxicity	57 (70%)	59 (49%)	2.45	.004*

Abbreviations: 3D = 3-dimensional; IMRT = intensity modulated radiation therapy; IV = intravenous; RT = radiation therapy.

\* Significant P-value <.05

**Table 3** Acute toxicity profiles

Toxicity	3DCRT (N = 82)	IMRT (N = 120)
Grade 3 toxicities	57 (70%)	59 (49%)
Esophagitis	2 (2%)	7 (6%)
Pain	5 (6%)	0 (0%)
Fatigue	4 (5%)	7 (6%)
Diarrhea	5 (6%)	6 (5%)
Dehydration	9 (11%)	4 (3%)
Nausea/emetis	32 (39%)	39 (33%)
Neutropenia	1 (1%)	0 (0%)
Malnutrition	10 (12%)	1 (1%)
Grade 4 toxicities		
GI bleed	0 (0%)	1 (1%)

Abbreviations: 3DCRT = 3-dimensional radiation therapy; GI = gastrointestinal; IMRT = intensity modulated radiation therapy.

respectively,  $P = .047$ ; Table E5, available online at <https://doi.org/10.1016/j.adro.2019.11.003>). Patients receiving 3DCRT also had a significantly lower nadir percent lymphocyte count during RT compared with patients receiving IMRT (medians of 3% and 4.5%, respectively;  $P = .002$ ). However, there were no significant differences in absolute lymphocyte counts between the groups at time points of 3, 12, and 24 months after chemoradiation.

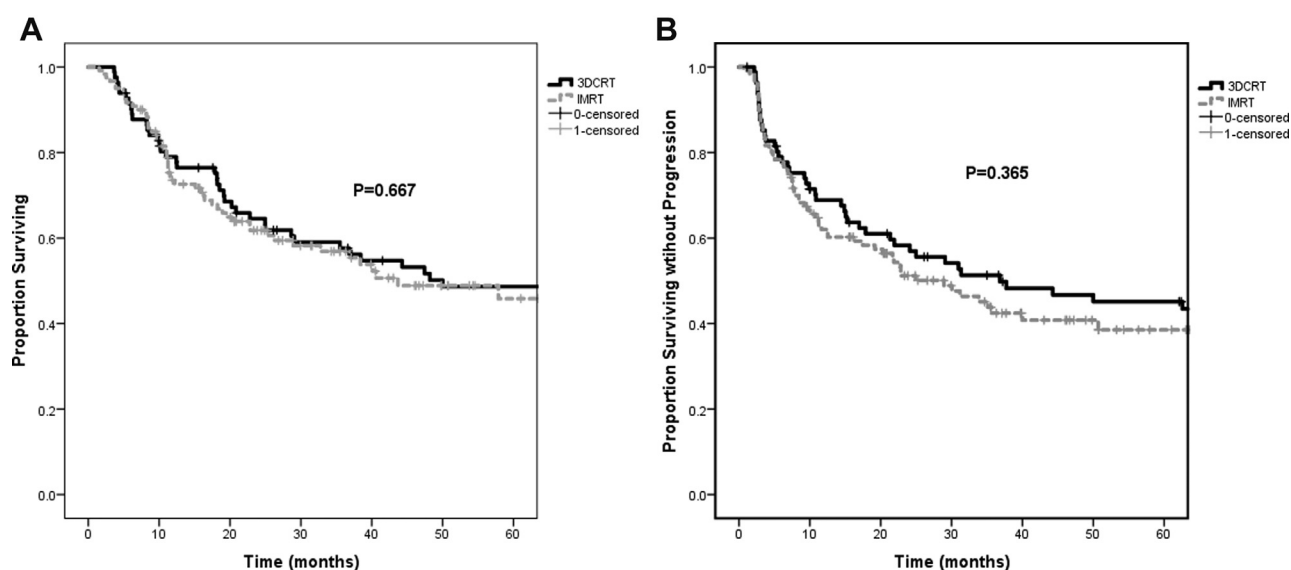
### Renal and hepatobiliary function

We evaluated changes in creatinine, albumin, total bilirubin, and alkaline phosphatase levels as markers for renal and hepatobiliary function after chemoradiation. The median change in creatinine level at 2 years after RT compared with baseline was +0.1 mg/dL in the 3DCRT

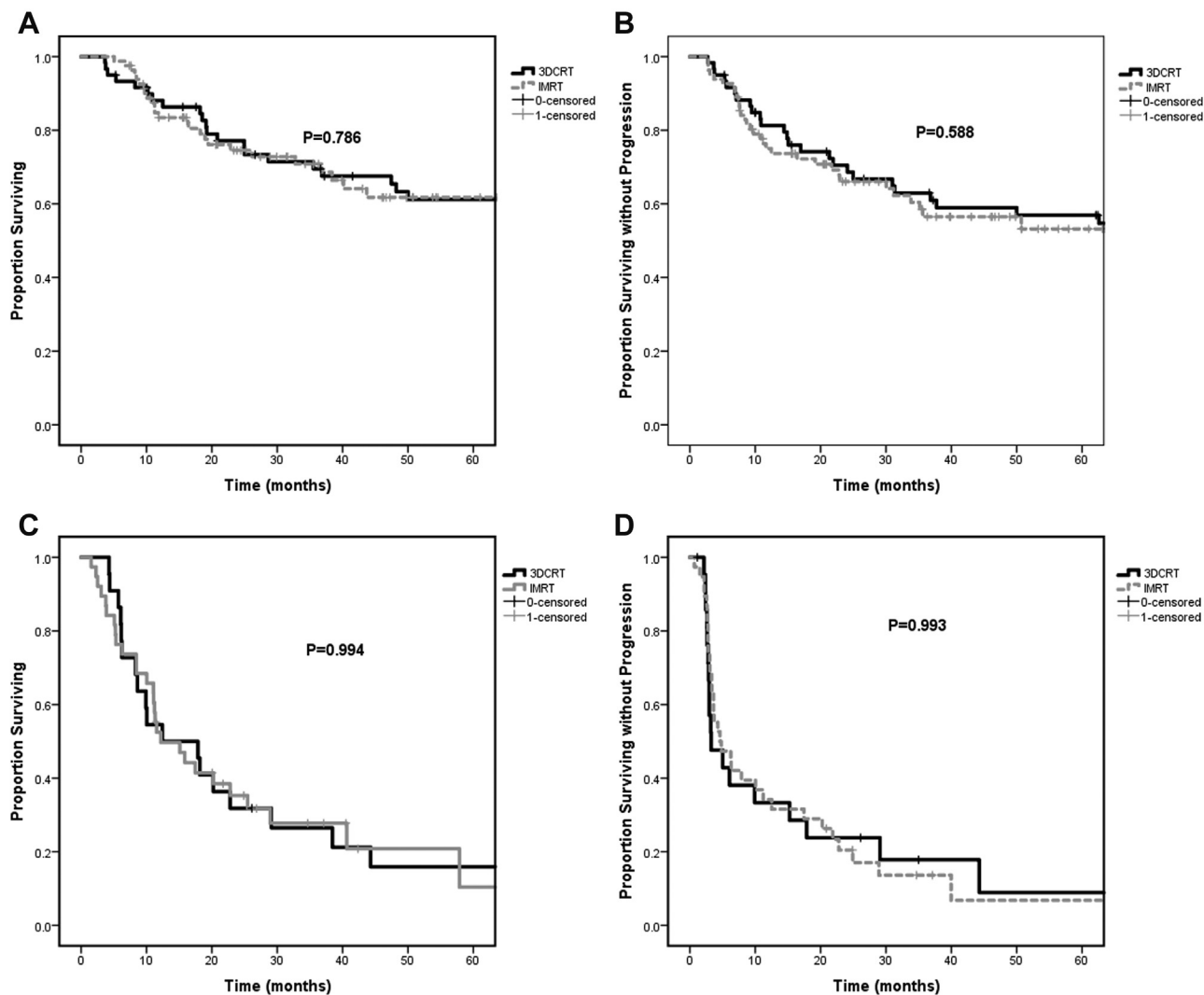
group and  $-0.01$  mg/dL in the IMRT group ( $P = .017$ ). With the exception of this change in creatinine, there were no significant differences between the 3DCRT and IMRT groups at 1 year and 2 years after chemoradiation (Table E6; available online at <https://doi.org/10.1016/j.adro.2019.11.003>).

### Survival outcomes

The 3-year OS rate was 58% for patients receiving 3DCRT and 57% for patients receiving IMRT ( $P = .667$ , Fig 1A). The median survival was 50 months for the 3DCRT group and 43.7 months for the IMRT group. The 3-year PFS rate was 51% for patients receiving 3DCRT compared with 42% for patients receiving IMRT ( $P = .365$ ; Fig 1B).



**Figure 1** (A) Overall survival for patients treated with chemoradiation, with or without surgery. (B) Progression-free survival for patients treated with chemoradiation, with or without surgery. Abbreviations: 3DCRT = 3-dimensional conformal radiation therapy; IMRT = intensity modulated radiation therapy.



**Figure 2** (A) Overall survival for patients treated with preoperative chemoradiation and surgery. (B) Progression-free survival for patients treated with preoperative chemoradiation and surgery. (C) Overall survival for patients treated with chemoradiation but no surgery. (D) Progression-free survival for patients treated with chemoradiation but no surgery. *Abbreviations:* 3DCRT = 3-dimensional conformal radiation therapy; IMRT = intensity modulated radiation therapy.

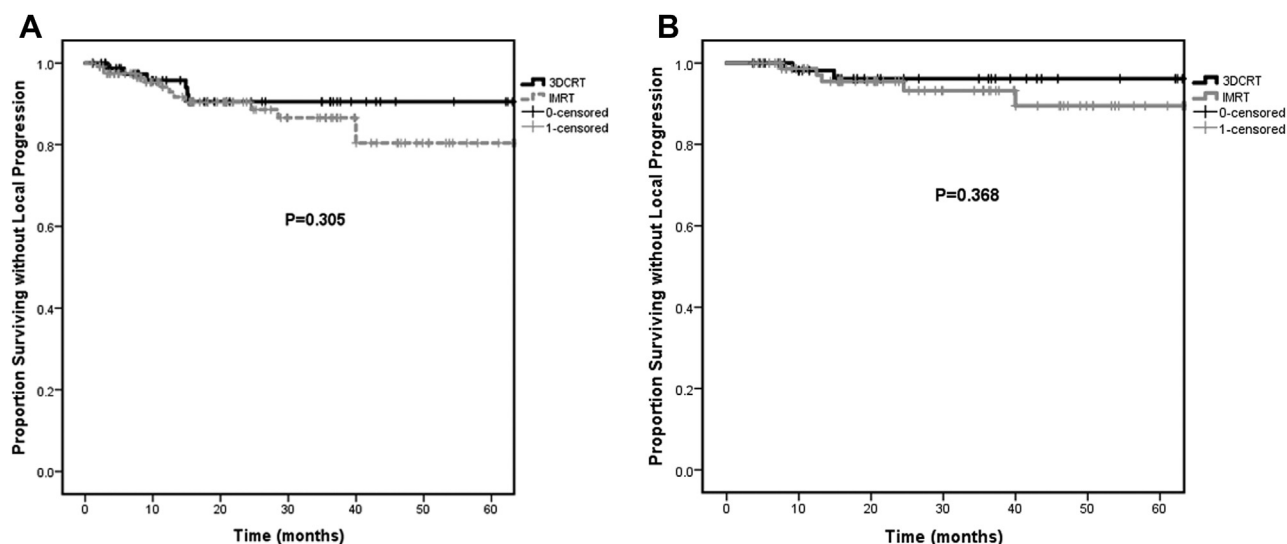
Among patients who underwent surgical resection, the 3-year OS and PFS rates were not significantly different in patients receiving 3DCRT compared with IMRT (OS: 69% vs 71%,  $P = .786$ ; PFS: 63% vs 56%,  $P = .588$ ; Fig 2A and B). Among patients who did not undergo surgical resection, the 3-year OS and PFS rates were also not significantly different in patients receiving 3DCRT compared with IMRT (OS: 26% vs 28%,  $P = .994$ ; PFS: 18% vs 14%,  $P = .993$ ; Fig 2C and D).

Three-year freedom from local progression (FFLP) rates were 90% for patients receiving 3DCRT and 87% for patients receiving IMRT ( $P = .305$ ; Fig 3A). Within the surgical cohort, 3-year FFLP rates were 96% for patients receiving 3DCRT and 93% for patients receiving IMRT ( $P = .368$ ; Fig 3B).

## Discussion

This study represents the largest analysis of clinical toxicity outcomes in patients undergoing IMRT as preoperative radiation therapy for gastric cancer. Our results suggest that preoperative IMRT appears to be associated with significantly lower grade 3 to 4 acute toxicity compared with 3DCRT techniques. This decrease in toxicity was also associated with a decrease in toxicity-related events, specifically hospitalizations, feeding tube use, intravenous fluid use, and unplanned breaks in radiation therapy. There was no significant difference in pathologic complete response rates between the IMRT and 3DCRT groups, nor was there any significant difference in OS, PFS, and FFLP rates between these groups.





**Figure 3** (A) Freedom from local progression for patients treated with chemoradiation, with or without surgery. (B) Freedom from local progression for patients treated with preoperative chemoradiation and surgery. *Abbreviations:* 3DCRT = 3-dimensional conformal radiation therapy; IMRT = intensity modulated radiation therapy.

IMRT appears to lead to reductions in acute toxicity and toxicity-related events without compromising oncologic outcomes. Given these findings, we believe that IMRT should be the preferred radiation modality for preoperative treatment of gastric cancer.

Our study does have some limitations. First, the retrospective nature of the study raises the possibility of bias or incomplete information when grading toxicity. Second, the groups of patients compared in this study were heterogeneous. In particular, patients were treated with multiple types of induction and concurrent chemotherapy, which could interact with radiation to affect toxicity. A significantly higher proportion of patients in the IMRT group received induction chemotherapy compared with the 3DCRT group; however, this would not be expected to lower toxicity rates in the IMRT group. Improvements in the management of toxicities during preoperative radiation during the period of the study could have also led to reduced toxicity in the more recent IMRT cohort, independent of the radiation therapy technique used. Additionally, the type of chemotherapy received before and concurrent with radiation therapy could have contributed to the toxicity profiles.

There is increasing interest in the use of preoperative chemoradiation for gastric cancer. Preoperative chemoradiation has many potential advantages, such as tumor downstaging, improved resectability, decreased seeding at surgery, and better treatment compliance. Two large randomized trials are currently evaluating preoperative chemoradiation: The TOPGEAR trial is comparing perioperative chemotherapy with preoperative chemoradiation, and the CRITICS-II trial is comparing preoperative chemotherapy, preoperative chemoradiation, and preoperative chemotherapy and chemoradiation.<sup>9,12</sup>

Our findings may help provide a better understanding of radiation techniques and associated toxicities in these trials. Because preoperative chemoradiation for gastric cancer is associated with relatively high rates of acute toxicity, choosing the appropriate radiation modality may influence the effectiveness of radiation compared with other treatments.

Previous studies have evaluated the effects of IMRT on toxicity in the postoperative setting. Trip et al reported lower rates of decline in left kidney function in 31 patients treated with IMRT compared with 25 treated with 3DCRT and 31 treated with AP-PA techniques (using Anterior to Posterior and Posterior to Anterior beams). Minn et al reported more treatment breaks and increased creatinine levels in 26 patients treated with 3DCRT compared with 31 treated with IMRT.<sup>17,18</sup> In contrast, Chopra et al reported no difference in acute or late toxicity between 25 patients treated with IMRT and 26 treated with 3DCRT.<sup>19</sup> The absence of a difference in acute toxicity in these studies could be due to either the smaller sample size or the postoperative setting, in which there is more small and large bowel in the treatment field. Similar to the studies by Trip et al and Minn et al, we also found higher elevations in creatinine levels in the 3DCRT group, compared with the IMRT group, at 2 years after chemoradiation. Another study reported on a cohort of 25 patients treated with preoperative IMRT, compared with 50 patients treated with preoperative 3DCRT.<sup>8</sup> The authors noted no difference in acute toxicity between the 2 groups. In contrast, we believe that our analysis has allowed us to detect a difference, owing to a much larger sample size and a more expanded definition of toxicity-associated events.

The nadir absolute lymphocyte count during radiation was significantly lower in the 3DCRT group compared

with the IMRT group; however, there were no significant differences in lymphocyte counts between the 2 groups at subsequent time points. Additional studies are needed to understand the relationship between radiation therapy and lymphopenia in patients with gastric cancer. Among the 4 molecular subtypes of gastric cancer, one is associated with DNA hypermethylation, and one is associated with PD-L1 amplification; both subtypes could be affected by immunomodulation.<sup>20</sup> Furthermore, immune checkpoint inhibitors have shown promising results for metastatic gastric cancer in multiple clinical trials.<sup>21,22</sup> Thus, understanding the relationships among radiation therapy, lymphopenia, and the immune system is particularly relevant for gastric cancer.

Perioperative chemotherapy with 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) is now being increasingly used for gastric cancer, based on results from the FLOT4 randomized trial, which showed improved OS compared with the previously used ECF/ECX (epirubicin, cisplatin, and 5-fluorouracil/capecitabine) regimens.<sup>1</sup> The survival results reported in our study for both the 3DCRT and IMRT groups compare favorably with that reported for FLOT. The 3-year OS rate was 57% for all patients in the IMRT group and 71% for patients in the IMRT group undergoing surgery, compared with 57% in the FLOT arm of the FLOT4 trial. Of note, our study excluded gastroesophageal junction patients, who typically have better prognosis, whereas the FLOT4 trial included 56% gastroesophageal junction and 44% gastric cancer patients.

Despite these limitations, we believe this study is valuable as the largest, most comprehensive comparison between IMRT and 3DCRT in the preoperative treatment for gastric cancer. This is the first study to demonstrate these clinical differences between IMRT and 3DCRT, and although it is retrospective in nature, it contributes useful information to the oncology community that would be difficult to study in a prospective manner in the United States given the rarity of the use of preoperative chemoradiation for gastric cancer.

## Conclusions

IMRT appears to decrease acute grade 3 to 4 toxicities and toxicity-related events among patients with gastric cancer undergoing preoperative chemoradiation. Our results suggest that IMRT is an appropriate and possibly preferable radiation modality for preoperative treatment of patients with gastric cancer.

## Supplementary data

Supplementary material for this article can be found at <https://doi.org/10.1016/j.adro.2019.11.003>.

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