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Intensity-modulated radiotherapy reduces gastrointestinal toxicity in locally advanced pancreas cancer

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Abstract

Purpose—We compared gastrointestinal (GI) and hematologic toxicity in patients with locally advanced pancreas cancer (LAPC) undergoing definitive chemoradiation using intensity modulated radiotherapy (IMRT) or 3D conformal radiotherapy (3D-CRT) planning.

Methods and Materials—We retrospectively studied 205 patients with LAPC undergoing IMRT (n=134) and 3D-CRT (n=71) between 05/03 and 03/12. Patient, tumor, and treatment characteristics and acute GI/hematology toxicity according to Common Terminology Criteria for Adverse Events v3.0 were recorded. Multivariable logistic regression models were used to test association between acute grade 2+ GI and hematologic toxicity outcomes and predictors. Propensity score analysis for grade 2+ GI toxicity was performed to reduce bias for confounding variables: age, gender, radiation dose, field size, and chemotherapy type.

Results—Median follow-up time for survivors was 22 months, similar between groups. Median RT dose was significantly higher for IMRT vs. 3D-CRT (5600 cGy vs 5040 cGy, $P<.001$); concurrent chemotherapy was mainly gemcitabine (56%) or 5-fluorouracil (5-FU, 38%). Grade 2+ GI toxicity occurred in 34% (n=24) of 3D-CRT compared with 16% (n=21) of IMRT patients. Using propensity-score analysis, 3D-CRT had significantly higher grade 2+ GI toxicity (odds ratio, 1.26 [95% CI, 1.08-1.45], $P=.001$). Grade 2+ hematologic toxicity was similar between

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*Denotes equal contribution of the 2 first authors.

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IMRT and 3D-CRT groups but was significantly greater in recipients of concurrent gemcitabine over 5-FU (62% vs 29%, $P<.0001$).

Conclusions—IMRT is associated with significant lower grade 2+ GI toxicity versus 3D-CRT for patients undergoing definitive chemoradiotherapy for LAPC. Since IMRT is better tolerated at higher doses and may allow further dose escalation, potentially improving local control for this aggressive disease. Further prospective studies of dose-escalated chemoradiation using IMRT are warranted.

Introduction

Locally advanced pancreatic cancer (LAPC) remains an oncologic challenge, as definitive surgical resection is not an option and outcomes with chemotherapy with or without radiotherapy are poor¹. Despite conflicting results among studies assessing chemoradiation in LAPC, the recently reported Phase III randomized trial, LAP07, demonstrated a benefit in local tumor control and a prolonged time to second-line therapy with chemoradiation after gemcitabine versus gemcitabine alone,² providing preliminary evidence for potentially improving quality of life with chemoradiation in the management of LAPC. However, administering radiation to the pancreas is limited by the proximity of highly radiosensitive critical structures, including the liver, stomach, small bowel, kidneys, and spinal cord. Intensity-modulated radiotherapy (IMRT) has allowed for lower dose and toxicity to the liver and kidneys.^{3, 4} Clinically, IMRT has been shown to reduce acute toxicity in other gastrointestinal (GI) cancers.^{5, 6} A recent systematic review of toxicity after IMRT and 3D conformal radiotherapy (3D-CRT) for pancreatic cancer found that the predominant treatment-related toxicities—nausea, vomiting, diarrhea, and late GI toxicity—were significantly reduced in patients treated with IMRT.⁷

Nonetheless, IMRT planning in pancreatic cancer is still being investigated. The goal of this study was to assess IMRT versus 3D-CRT on GI and hematologic toxicities in the setting of definitive chemoradiation for LAPC patients. Given the lack of prospective randomized data, we retrospectively reviewed our large, single-institution experience and performed a propensity-score analysis to adjust for potential imbalances in known risk factors, to evaluate the effect of the radiotherapy planning technique.

Methods and materials

Patient population and data collection and analysis

A waiver of authorization was obtained from the Institutional Review Board, and clinical data of all LAPC patients treated with definitive chemoradiation from May 2003 to March 2012 at our institution were retrospectively reviewed. All patients had tissue diagnoses of pancreatic adenocarcinoma, confirmed by cytologic or pathologic review at our institution. Locally advanced unresectable disease was defined as superior mesenteric artery or celiac axis encasement >180 degrees, unreconstructible superior mesenteric vein/portal occlusion, or aortic invasion, per National Comprehensive Cancer Network Practice Guidelines in Oncology v.2.2015. Patient, tumor, and treatment characteristics were obtained from the medical record and a database of pancreatic cancer patients treated with radiotherapy. Of the

205 patients, 54% were male and the median age at diagnosis was 63 years (range, 57-71 years). Seventy-nine percent of tumors were located in the head/neck of the pancreas and 21% in the body/tail. Patient, tumor, and treatment characteristics are summarized in Table 1. Radiation records were obtained for all patients, and target volumes and radiation field sizes were recorded when available. The planning target volume (PTV) was available for only 130 (63%) patients. As a surrogate measure, radiotherapy field size was calculated for each plan using the greatest field length multiplied by the greatest field width for each plan.

All patients were monitored weekly during chemoradiation for acute GI toxicities including nausea, vomiting, diarrhea, and abdominal pain. Weekly complete blood work with differentials included hemoglobin (g/dL), platelets count (K/ μ L), white blood cell count (K/ μ L), absolute neutrophil count (K/ μ L), and absolute lymphocyte count (K/ μ L). All toxicities were scored according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 on standardized toxicity assessment forms during weekly routine on-treatment clinic visits. We also reviewed the charts of the patients for instances of hospital admissions.

Chemotherapy

A total of 156 (76%) patients received induction chemotherapy, administered for 1-12 months prior to radiation. Standard induction chemotherapy consisted of weekly intravenously administered gemcitabine, or gemcitabine-based regimens. A few patients received FOLFIRINOX (folinic acid, fluorouracil [5-FU], irinotecan, and oxaliplatin), FOLFOX (folinic acid, fluorouracil, and oxaliplatin), or combinations of the chemotherapy agents listed above. Table 1 outlines the chemotherapy induction regimens.

All patients received concurrent radiosensitizing chemotherapy during radiotherapy. Most patients (56%) received gemcitabine-based chemotherapy, with infusional 5-FU or capecitabine in 77 patients (38%) and flavopiridol in 13 patients (6%) (Table 1). Chemotherapy dose or administration techniques were modified or held at the discretion of the treating physician. We analyzed four combinations of concurrent therapy: gemcitabine vs gemcitabine + 5-FU/capecitabine or erlotinib vs 5-FU/capecitabine vs flavopiridol.

Radiation-therapy planning

All patients underwent computed tomography (CT)-guided simulation with intravenous and oral contrast media. Radiation-therapy planning was performed using 3D-CRT planning techniques in 71 (35%) patients, and IMRT planning techniques in 134 (65%) patients treated starting in 2007, when the institutional policy changed to initiate IMRT planning for pancreatic cancer. For the 3D-CRT plans, a 4-field box beam arrangement was used with anterior-posterior, posterior-anterior, and right and left lateral beams. Treatment volumes were constructed according to the same guidelines used to construct the 3D fields used in RTOG 97-04. The field borders were based on bony anatomy to cover the gross tumor volume (GTV) and clinical target volume (CTV), typically extending from approximately T11 to L2. The treatment field was based on the location of the GTV with at least a 2 cm margin, and the draining lymph node regions, including the celiac, peripancreatic, pancreatoduodenal, portahepatic, and para-aortic lymph node basins. For IMRT plans, the GTV included radiographically apparent gross tumor and suspicious/enlarged lymph nodes

on CT simulation. The CTV included the same draining lymph node basins described for the 3D-CRT fields. A PTV was generated to account for daily setup error and internal respiration-related tumor motion. For 3D-CRT plans, the prescription dose was 5040 cGy in 28 daily fractions to the entire field using 15 MV photons. A dose-volume histogram (DVH) was constructed to evaluate the dose to the kidneys and liver based on the planning CT scan. IMRT treatment planning was performed using custom in-house software. 5040 cGy was prescribed to the PTV in 28 daily fractions. A simultaneous integrated boost was delivered to gross disease for a total of 5600 cGy. An IMRT plan was optimized to minimize the PTV receiving <98% or >102% of the prescription dose. The standard beam arrangement involved five gantry angles (Fig 1). Treatment was delivered using dynamic multileaf collimation and 15 MV photon beams. DVHs were constructed for doses to the target volumes, kidneys, liver, bowel, stomach, and spinal cord.

Statistical analysis

Frequency distributions for patient characteristics by toxicity outcomes (grade 2 GI and hematologic toxicity) and Fisher's exact test and the Wilcoxon rank sum test were used to examine covariate differences between outcomes. Multivariable logistic regression models were used to test the association between acute grade 2+ GI and hematologic toxicity outcomes and predictors. Hosmer and Lemeshow goodness-of-fit statistic was used to assess the model fit. To confirm the results and mimic randomized trials due to potential bias of comparing acute grade 2+ GI toxicity between 3D-CRT and IMRT, a propensity-score analysis was performed to account for potential confounding variables, including age, gender, radiation dose, radiotherapy field size, and concurrent chemotherapy type. The propensity score is particularly advantageous in non-randomized comparisons as, unlike traditional regression methods, it can account for an unlimited number of variables that might have influenced outcome (covariates) into a single scalar value. We used a logistic regression model with complex survey design to examine the effect of radiation on grade 2 GI toxicity, adjusting for propensity score. The statistical packages SAS (9.1) and R (2.3.1) were used to generate the test statistics and build the regression model.

Results

Median follow-up from the start of radiation treatment to the end of last follow-up among survivors was 22 months (range, 0.6-49.2 months). Median overall survival (OS) for all patients was 15.3 months (95% CI, 13.2-17.3 months) with no significant difference between the 3D-CRT and IMRT groups. Median dose for all patients was 5040 cGy (range, 1980-5600 cGy), with a significantly higher median dose for IMRT than 3D-CRT (5600 cGy vs 5040 cGy, $P<.001$). More patients received induction therapy in the IMRT group and a greater proportion received concurrent gemcitabine versus 5-FU based therapy in the IMRT group. Median treatment time was 28 days. Nineteen patients required treatment breaks, 9 in the 3D-CRT group (13%; average, 7.8 days) and 10 in the IMRT group (7%; average, 6.8 days). To assess the effect of field size, we compared the treatment area defined as the greatest width multiplied by the greatest length of radiation-treatment fields. There was no significant difference between the median treatment area for IMRT (median, 174 cm³; range, 84-273 cm³) and 3D-CRT (median 187 cm³; range, 80-323 cm³).

Acute GI toxicity

An overview of the reported acute GI and hematologic toxicities and their grades is shown in Table 2. Of the 205 patients treated with either 3D-CRT or IMRT, 45 (22%) experienced grade 2+ GI toxicity. Acute grade 2+ GI and hematologic toxicity by age, tumor location, and RT type are detailed in Table 3. On univariate analysis, only type of RT planning was significantly associated with acute Grade 2+ GI toxicity with 24 (34%) 3D-CRT patients experiencing grade 2+ GI toxicity and only 21 (16%) IMRT patients developing grade 2+ GI toxicity.

A multivariate logistic regression model of grade 2+ GI acute toxicity is shown in Table 4. Patients who received 3D-CRT, compared with IMRT, had significantly higher incidence of grade 2+ GI acute toxicity (odds ratio, 3.3 [95% CI, 1.2-9.4], $P=.02$). Propensity-score analysis (Table 5) showed a statistically significant increase in grade 2+ GI toxicity among patients treated with 3D-CRT (odds ratio, 1.26 [95% CI, 1.08-1.45], $P=.0025$). Other treatment factors including age at diagnosis, gender, radiation dose, receipt of induction chemotherapy, the type of concurrent chemotherapy used, and the radiotherapy field size, did not significantly impact GI toxicity.

Acute hematologic toxicity

A total of 139 patients (68%) experienced grade 2+ hematologic toxicity. Fifty-six percent received a gemcitabine-based chemotherapy (gemcitabine vs gemcitabine + 5-FU/capecitabine vs gemcitabine + erlotinib), 38% received 5-FU/capecitabine chemotherapy, and 6% received flavopiridol. Grade 2+ hematologic toxicity did not significantly differ between the 3D-CRT and IMRT groups but was significantly higher for concurrent gemcitabine versus concurrent 5-FU (62% vs 29%, $P<.0001$). Interestingly, women experienced less grade 2+ hematologic toxicity than men (65% vs 35%, $P=.02$).

Hospitalizations

There were a total of 33 instances of hospital admissions during treatment and 30 admissions within 30 days of completion of therapy. The most common reasons for hospital admissions during treatment included GI toxicity, primarily nausea and vomiting ($n=16$), infection ($n=8$), and cholangitis ($n=5$). Hospitalization after treatment and up to 30 days after treatment were caused by infection ($n=11$), GI toxicity, primarily diarrhea or small bowel obstruction ($n=8$), and cholangitis (2). Eighteen percent of the patients treated with 3D-CRT were hospitalized during treatment, and 14% were hospitalized after treatment and up to 30 days post-treatment. Similarly, 14% of the patients treated with IMRT were hospitalized during radiation and 15% were hospitalized within 30 days after treatment ended. Few events in either group were directly attributed to radiation, and most were multifactorial in etiology.

Discussion

In this large retrospective analysis of LAPC undergoing definitive chemoradiation, radiotherapy using IMRT planning was associated with significantly reduced acute grade 2+ GI toxicity versus 3D-CRT planning, despite the higher radiation dose. Even after adjusting

for group imbalances using the propensity-score analysis, the difference was still significant. Sixteen percent of IMRT patients experienced grade 2+ GI toxicity, compared with 34% of 3D-CRT patients, a 50% reduction in acute GI toxicity for IMRT. This result may be attributed to the ability to decrease radiation to dose-limiting structures with IMRT planning, while delivering high-dose radiation to the tumor volume. We could not compare PTV size between IMRT and 3D-CRT groups, as these were not recorded for all 3D-CRT patients; however, the treatment area was used as a surrogate for treated volume and was not a confounder in the propensity-score analysis. A multivariate logistic regression model showed that the treatment area/fields size did not predict grade 2+ GI toxicity for 3D-CRT vs IMRT.

Other single-institution studies have reported on the ability of IMRT to reduce GI toxicity by decreasing the radiation delivered to critical structures in the abdomen. Abelson et al found that among 47 patients treated adjuvantly or definitively with IMRT, 4% developed grade 3+ acute toxicity and 4% developed grade 3+ late toxicity.⁷ Milano et al demonstrated that IMRT plans significantly reduced radiation dose to the kidney and small bowel compared with 3D-CRT plans, among patients with pancreatic or bile duct cancers.⁶ Ben-Josef et al published a series of 15 patients who received concurrent capecitabine and IMRT, in which one patient developed grade 3 toxicity and none developed grade 4,⁸ and more recently published a prospective study demonstrating the feasibility and safety of IMRT (55 Gy) with concurrent full-dose gemcitabine in patients with LAPC (15). They found encouraging two-year rates of freedom from local progression and overall survival. Yovino et al studied 46 patients treated at two institutions with concurrent chemoradiation with IMRT for resected pancreatic/ampullary cancer. There was a significant reduction in acute upper and lower GI toxicity compared with previously reported rates of 3D-CRT toxicity.⁹

Hematologic toxicity can also limit the ability to administer chemoradiation. Concurrent chemotherapy significantly affected the incidence of hematologic toxicity in our patient sample, with gemcitabine-based chemotherapy causing increased toxicity, compared with 5-FU-based chemotherapy. However, the type of concurrent chemotherapy did not significantly worsen GI toxicity in our analysis. This finding is consistent with the previously mentioned studies, and with a study conducted by Huang et al, which found no significant difference in levels of acute grade 2+ GI toxicities between gemcitabine-based versus 5-FU-based chemoradiation treatment.¹⁰ On the other hand, in the SCALOP Phase II trial, the rates of grade 3+ hematologic and GI toxicities were both higher with concurrent gemcitabine than capecitabine.¹¹ The Eastern Cooperative Oncology Group (ECOG) trial E4201 found 79% of patients experienced various types of grade 3 and 4 toxicities when treated with gemcitabine and concurrent radiotherapy.¹² An important limitation of our study is that data were collected through a retrospective chart review, which may have introduced bias by underestimating or overestimating acute toxicity rates. However, severe toxicities would have required additional medical care and/or treatment breaks, which would have been clearly documented. In addition, the hospitalizations during chemoradiation and within 30 days after completion of therapy were assessed and demonstrated that the majority of hospitalizations were not related to radiotherapy, and were more commonly related to infection or tumor-related issues such as cholangitis from compression of the common bile duct. Another limitation of this study is that IMRT was administered as part of an

institutional change in practice beginning in 2007, rather than in a prospective controlled manner. However, all treatment plans were developed and conducted at one institution, limiting the bias introduced by multi-institutional plans. Finally, the inclusion of elective nodes in definitive radiotherapy fields for LAPC has become debatable; with the use of stereotactic body radiotherapy and or more dose-escalated hypofractionated approaches, the regional nodes are omitted from the field. Although this is not standard for conventionally fractionated radiotherapy, either in the definitive or adjuvant setting for pancreas cancer since the risk of positive nodes in surgical series exceeds 65%,¹³ the use of smaller fields excluding the elective nodes would also have the potential to reduce acute toxicity.

While the role of definitive chemoradiation for the treatment of LAPC remains controversial, the recent data from the Phase III randomized LAP07 trial demonstrated a local control benefit for chemoradiation after 4 months of gemcitabine versus 6 months of gemcitabine alone.² Local progression of disease in the abdomen is highly morbid and associated with GI obstructive symptoms and pain. There is ongoing research on the benefits of increased dose radiotherapy, administered through IMRT vs 3D-CRT, with concurrent chemotherapy for LAPC. The RTOG 1201 study is a Phase III randomized trial intended to evaluate dose-intensified chemoradiation using IMRT to deliver a higher dose (6300 cGy) to the primary tumor compared with the standard dose (5040c Gy) using 3D-CRT.¹⁴

In the absence of other options for managing local disease, delivery of effective radiotherapy while minimizing the acute toxicity remains critical. Prior prospective studies evaluating radiotherapy for LAPC have used 3D-CRT or older planning techniques, and thus the potential benefits of radiotherapy on outcomes may have been impacted by higher rates of acute toxicity.¹⁵ Nonetheless, further prospective studies, such as RTOG 1201, are necessary to evaluate the benefits of dose-escalated chemoradiation using IMRT combined with more aggressive chemotherapy regimens with the hope of eventually improving outcomes for this devastating disease.

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Figure 1.

Intensity-modulated radiation therapy standard beam arrangement involving five gantry angles, shown in axial (top) and coronal views (bottom).

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Table 1
Patient, tumor, and treatment characteristics

Characteristic	3D-CRT N=71 n (%)	IMRT N=134 n (%)	Total n	P value
Gender				.977
Male	38 (54)	72 (54)	110	
Female	33 (46)	62 (46)	95	
Tumor location				.129
Head/neck	60 (85)	101 (75)	161	
Body/tail	11 (15)	33 (25)	44	
Induction chemotherapy*				<.01
Gemcitabine alone	15 (21)	34 (25)	49	
Gemcitabine + 5-FU/cape	1 (1)	11 (8)	12	
Gemcitabine +	6 (8)	50 (38)	56	
oxaliplatin/cisplatin	0 (0)	12 (9)	12	
Gemcitabine + docetaxel ± cape	41 (58)	8 (6)	49	
None	8 (11)	19 (14)	27	
Other [§]				
Concurrent chemotherapy*				<.001
5-FU/cape	30 (42)	47 (46)	77	
Gemcitabine-based	30 (42)	85 (63)	115	
chemotherapy [†]	11 (16)	2 (1)	13	
Flavopiridol/none				
Treatment breaks	11 (13)	10 (7)	21	.186
Mean break duration (days)	7.8	6.8		
Treatment stopped early	6 (8.4)	7 (5.2)	13	
Mean radiotherapy dose delivered (Gy)	3485	3663		
Total radiotherapy dose (Gy)	5040 (1980-5600)	5600 (1980-5600)	5040 (1980-5600)	<.001
Field size X*Y (cm²)				
Median	187	174	183	.086
Range	80-323	84-273	80-323	

n, number of patients; 5-FU, 5-fluorouracil; cape, capecitabine; 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiation therapy.

* Chemotherapy doses: Induction: gemcitabine (1000 mg/m^2); gemcitabine plus capecitabine (1000 mg , oral, bid), gemcitabine plus docetaxel (30 mg/m^2), cisplatin (30 mg/m^2), oxaliplatin (80 mg/m^2), or erlotinib (100 mg); FOLFIRINOX (folinic acid, fluorouracil [5-FU], irinotecan, and oxaliplatin; 400 mg/m^2 , 1600 mg/m^2 , 180 mg/m^2 , 85 mg/m^2), FOLFOX (folinic acid, fluorouracil, and oxaliplatin; 400 mg/m^2 , 1600 mg/m^2 , 85 mg/m^2). Concurrent: gemcitabine alone (40 mg/m^2 twice weekly), gemcitabine plus infusional 5-FU (range, $150\text{--}500 \text{ mg/m}^2$) or capecitabine (1000 mg), or gemcitabine plus erlotinib (100 mg); infusional 5-FU (225 mg/m^2 continuous venous infusion) or capecitabine ($825\text{--}1000 \text{ mg/m}^2$ twice daily); flavopiridol (40 mg/m^2).

§ Other includes capecitabine ($n=1$), FOLFOX ($n=1$), FOLFIRINOX ($n=10$), erlotinib ($n=1$), gemcitabine + erlotinib ($n=9$), or variations of the induction chemotherapies listed in the table ($n=4$).

† Gemcitabine-based chemotherapy includes gemcitabine $\pm$ fluorouracil or capecitabine ($n=100$) and gemcitabine + erlotinib ($n=15$).

Table 2
Acute Toxicities by Grade

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	56	12	5	0
3DCRT (% of group)	18 (25%)	7 (9.9%)	2 (2.8%)	0 (0%)
IMRT (% of group)	38 (28%)	5 (3.7%)	3 (2.2%)	0 (0%)
Nausea	110	28	3	0
3DCRT	34 (48%)	13 (18%)	0 (0%)	0 (0%)
IMRT	76 (58%)	15 (11%)	3 (2.2%)	0 (0%)
Vomiting	53	8	0	1
3DCRT	12 (17%)	5 (7%)	0 (0%)	0 (0%)
IMRT	41 (31%)	3 (2.2%)	0 (0%)	1 (0.7%)
Fatigue	87	60	5	1
3DCRT	21 (30%)	9 (13%)	1 (1.4%)	1 (1.4%)
IMRT	66 (49%)	51 (38%)	4 (3.0%)	0 (0%)
Dermatitis	21	0	0	0
3DCRT	8 (11%)	0 (0%)	0 (0%)	0 (0%)
IMRT	13 (9.7%)	0 (0%)	0 (0%)	0 (0%)
Dyspnea	2	0	0	0
3DCRT	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
IMRT	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)
Anemia	84	63	21	4
3DCRT	27 (38%)	22 (31%)	7 (9.9%)	1 (1.4%)
IMRT	57 (43%)	41 (31%)	14 (10%)	3 (2.2%)
Leukopenia	39	81	45	5
3DCRT	8 (11%)	33 (46%)	16 (23%)	4 (5.6%)
IMRT	31 (23%)	48 (36%)	29 (22%)	1 (0.7%)
Neutropenia	1	9	4	1
3DCRT	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
IMRT	0 (0%)	9 (6.7%)	4 (3.0%)	1 (0.7%)
Thrombocytopenia	103	37	27	5
3DCRT	32 (45%)	17 (24%)	9 (13%)	0 (0%)

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
IMRT	71 (52%)	20 (15%)	18 (13%)	5 (3.7%)

3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiation therapy.

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Table 3

Association between patient's characteristics and outcomes

Characteristics	Gastrointestinal acute toxicity grade 2+				Hematologic toxicity grade 2+			
	Total	Yes (N=45)	No (N=160)	P value	Yes (N=139)	No (N=66)	P value	P value
Age at diagnosis [years; median (IQR)]	63 (57-71)	61 (54-70)	64 (58-71)	0.16	63 (55-70)	64 (58-72)	0.25	
Gender				0.10				0.02
Male	110 (53.66)	22 (48.89)	88 (55)		67 (48.2)	43 (65.15)		
Tumor location				0.31				0.36
Body/tail	44 (21.46)	7 (15.56)	37 (23.13)		27 (19.42)	17 (25.76)		
Head/neck	161 (78.54)	38 (84.44)	123 (76.88)		112 (80.58)	49 (74.24)		
Type of radiotherapy				0.004				0.43
3D-CRT	71 (34.63)	24 (53.33)	47 (29.38)		51 (36.69)	20 (30.3)		
IMRT	134 (65.37)	21 (46.67)	113 (70.63)		88 (63.31)	46 (69.7)		
Total dose (cGy)				0.09				0.65
>5040	96 (46.83)	16 (35.56)	80 (50)		67 (48.2)	29 (43.94)		
Induction chemotherapy				0.11				0.38
Yes	156 (76.1)	30 (66.6)	1126 (78.7)		103 (74.1)	53 (80.3)		
Concurrent chemotherapy				0.312				<.0001
None/flavopiridol	13 (6.3%)	4 (8.9%)	9 (5.6%)		6 (4.3%)	7 (10.6%)		
Fluorouracil or capecitabine	77 (37.6%)	13 (28.89%)	64 (40.00)		36 (25.9%)	41 (62.1%)		
Gemcitabine-based chemotherapy*	115 (56.1%)	28 (62.2%)	87 (54.3%)		97 (69.8 %)	18 (27.2%)		
Field size (X*Y; median (range))	178.3 (80-323)	179 (106-323)	178 (80-289)	0.221	175 (80-323)	187 (84-270)		.196

3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiation therapy; IQR, interquartile range.

* Gemcitabine-based chemotherapy includes gemcitabine ± fluorouracil or capecitabine (n=100) and gemcitabine + erlotinib (n=15).

Table 4
Multivariate logistic regression model of grade 2+ acute gastrointestinal toxicity

	Odds Ratio (95%CI)	P value
3D-CRT vs IMRT	5.0 (1.5-17.1)	<.01
Age at diagnosis	0.9 (0.95-1.02)	.621
Male vs female	0.7 (0.33-1.45)	.339
>5040 cGy vs <5040 cGy	1.8 (0.53-6.13)	.340
Concurrent chemotherapy		.318
Gemcitabine-based chemotherapy agent (N=115)	1.00 (reference)	
Fluorouracil or capecitabine (n=77)	0.53 (0.23-1.21)	
None/flavopiridol (n=13)	0.82 (0.20-3.42)	
Field size	1.01 (0.99-1.01)	.190

3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiation therapy.

Table 5
Propensity score analysis of grade 2+ acute gastrointestinal toxicity*

	Odds ratio (95%CI)	P value
3D-CRT vs IMRT	1.34 (1.06-1.70)	.014

3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiation therapy.

* Age at diagnosis, gender, dosage, and concurrent chemotherapy (gemcitabine-based chemotherapy agent (N=115) vs flavopiridol - and no chemo vs Fluorouracil or Capecitabine) and field size (X*Y) were used to generate PS