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Scientific Article

Dose escalation with an IMRT technique in 15 to 28 fractions is better tolerated than standard doses of 3DCRT for LAPC

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Abstract

Purpose: To review acute and late toxicities after chemoradiation for locally advanced pancreatic ductal adenocarcinoma in patients who were treated with escalated dose radiation (EDR).

Methods and materials: Maximum Common Terminology Criteria for Adverse Events Version 4.0 acute toxicities (AT) during radiation and within 60 days after radiation were recorded for both acute gastrointestinal toxicity and overall toxicity (OT). Late toxicities were also recorded. EDR was generally delivered with daily image guidance and breath-hold techniques using intensity modulated radiation therapy (IMRT) planning. These were compared with patients who received standard dose radiation (SDR) delivered as 50.4 Gy in 28 fractions using 3-dimensional chemoradiation therapy planning.

Results: A total of 59 of 154 patients (39%) received EDR with biologically equivalent doses >70 Gy. The most frequent schedules were 63 Gy in 28 fractions (19 of 154 patients), 67.5 Gy in 15 fractions (10 of 154 patients), and 70 Gy in 28 fractions (15 of 154 patients). No grade 4 or grade 5 OT or late toxicities were reported. Rates of grade 3 acute gastrointestinal toxicity were

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significantly lower in patients who received EDR compared with SDR (1% vs 14%; $P < .001$). Similarly, rates of grade 3 OT were also lower for EDR compared with SDR (4% vs 16%; $P = .004$). The proportion of patients who experienced no AT was higher in the EDR group than the SDR group (36% vs 15%; $P = .001$). For EDR patients treated with IMRT, a lower risk of AT was associated with a later treatment year ($P = .007$), nonpancreatic head tumor location ($P = .01$), breath-hold ($P = .002$), 4-dimensional computed tomography ($P = .003$), computed tomography on rails ($P = .002$), and lower stomach V40 ($P = .03$). With a median time of 12 months (range, 1-79 months) from the start of radiation therapy to the last known follow-up in the EDR group, 51 of 59 patients (86%) had no late toxicity. Six of 59 EDR patients (10%) had either strictures or gastrointestinal bleeding that required intervention. No significant predictors of late toxicity were identified.

Conclusion: Overall acute and late toxicity rates were low with EDR using an IMRT technique with image guidance and respiratory gating.

Introduction

Pancreatic cancer remains the fourth leading cause of cancer-related death in the United States, with a 5-year overall survival of approximately 5%,[1] despite improvements in systemic chemotherapy and advances in radiation and surgical techniques. Locally advanced pancreatic cancer (LAPC) is particularly difficult to treat because it exhibits only a modest response to chemotherapy[2] and is by definition unresectable. A high proportion of patients with LAPC experience local progression and/or die with a significant burden of local disease and may experience a significant amount of morbidity and mortality from local progression.[3-5] This pattern of adverse events in LAPC suggests that local control may be critical to reducing the symptomatic burden of this disease. Recent data have suggested that although modest doses of chemoradiation do not improve survival compared with chemotherapy alone, local control is significantly improved.[6,7]

Standard radiation therapy has failed to produce an overall survival benefit in the population of patients with LAPC but may provide modest local control and increase time off systemic chemotherapy.[6,7] Standard dose radiation (SDR) for pancreatic cancer is often limited to 50.4 Gy in 28 fractions because the dose is constrained by radiosensitive organs in close proximity to the pancreas, including the duodenum, jejunum, and stomach. Radiation dose escalation through more conformal treatment techniques, such as intensity modulated radiation therapy (IMRT), stereotactic body radiation therapy (SBRT), or proton therapy, has overcome this threshold to improve local control and overall survival in other tumor sites, including cholangiocarcinoma,[8] prostate,[9] and head and neck cancers.[10]

At MD Anderson Cancer Center, biologically equivalent doses (BEDs) up to twice as high as SDR have been delivered using IMRT in an attempt to improve local control.[8,11] The results of this technique were recently reported by Krishnan et al[11] and provided preliminary evidence that radiation dose escalation during consolidative chemoradiation therapy improves both overall survival and locoregional recurrence-free survival in carefully selected patients. Previous studies demonstrated lower toxicity with an IMRT technique for pancreatic ductal adenocarcinoma (PDAC) over a 3-dimensional conformal technique using equivalent dose and fractionation schemes.[12-15] In this study, we report both acute and late toxicity using an IMRT technique with dose escalation.

Methods and materials

Patient selection

Institutional review board approval was obtained. We retrospectively reviewed the records of all patients with LAPC treated with definitive-intent standard or escalated dose radiation (EDR) at MD Anderson Cancer Center between 2006 and 2016. Patients who were treated for a first malignancy and received the standard 4 to 6 months of standard regimen (ie, 5-fluorouracil-, gemcitabine-, or cetuximab-based) induction chemotherapy followed by standard regimen chemoradiation were included. The definition of locally advanced was based on a surgeon's review of computed tomography (CT) images. Generally, this was based on a >180 degree encasement of the superior mesenteric artery, celiac axis, or occlusion of the superior mesenteric vein and/or portal venous confluence. Patients who received BED >70 Gy were considered for EDR.

Demographic, treatment, and tumor characteristics were recorded. Treatment plans were obtained and reviewed to collect dosimetric parameters. The Common Terminology Criteria for Adverse Events Version

4.0 (CTCAE v4.0) were used to define toxicity on the basis of physician documentation during radiation on treatment visits, treatment summaries, and first follow-up visits with any provider. These toxicity data were collected for both acute gastrointestinal toxicity (during treatment and within 60 days), acute overall toxicity, and late toxicity (>60 days from treatment end). Late toxicities requiring intervention or not requiring intervention were both recorded. For the analysis of predictors of toxicity in the dose-escalated group, patients who received standard induction chemotherapy followed by concurrent chemoradiation were selected to provide a homogeneous population. These were compared with a cohort of patients who received SDR. All patients who were treated with SDR were treated with 50.4 Gy in 28 fractions using a 3-field technique without breath-hold or respiratory gating.

Treatment technique

All patients received pretreatment imaging, including a pancreatic protocol CT scan of the abdomen and pelvis with intravenous and oral contrast. CT simulation planning was performed with the patient in the supine position using a vacuum lock cradle for immobilization with a wing board and the arms above the head. The standard technique for treating patients in the most recent era with EDR included a 4-dimensional CT simulation under natural breathing conditions to estimate the extent of target motion and inspirational breath-hold (BHCT) with and without contrast to mitigate the motion. The 4-dimensional CT was performed with Philips' pneumatic bellows (Philips Healthcare, Amsterdam, the Netherlands) and the BHCT were acquired using Varian's real-time position management system (Varian Inc., Palo Alto, CA).

If the patient could hold his or her breath reliably within 5 mm of the gating window, a BHCT scan was used for the primary planning image set and patients were treated under breath-hold. If the patient could not hold his or her breath consistently, the average images derived from a 4-dimensional CT scan were used for treatment planning and the patient was treated under normal breathing conditions. The majority of patients in the modern era were treated under breath-hold with the tumor motion confined to within 5 mm during delivery of radiation. A phase contrast CT scan was performed with multiple breath-hold scans taken at 30-second intervals from the start of the contrast infusion. Patients were generally asked to remain nil per os for 3 hours prior to simulation and treatment.

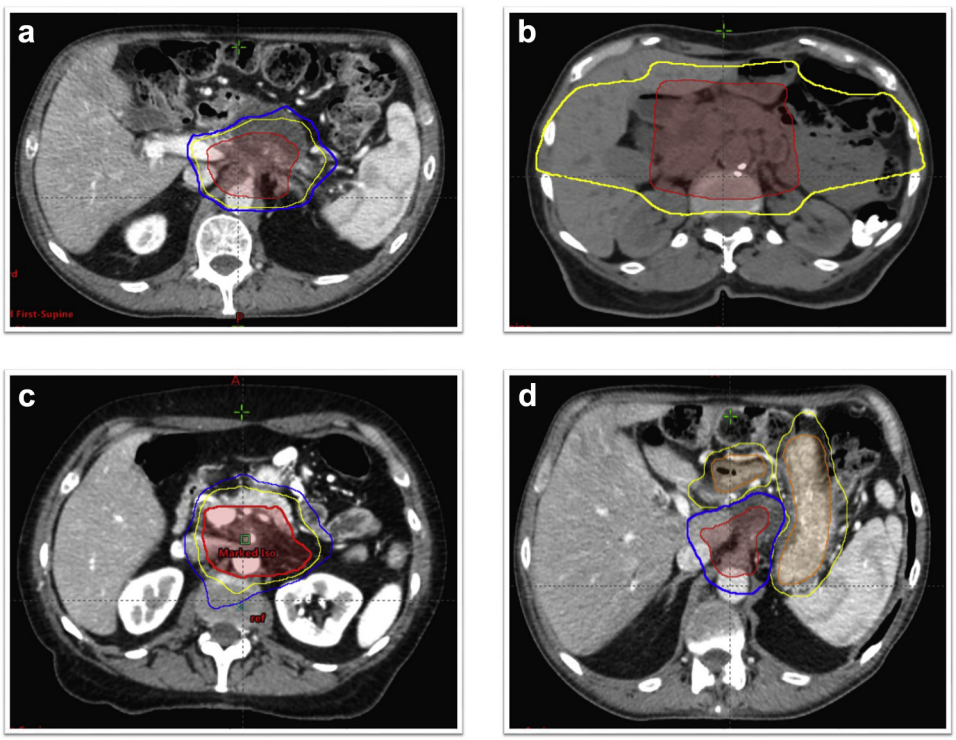

Figure 1 Representative treatment plans for (a) Patient treated on Radiation Therapy Oncology Group (RTOG) 1201 protocol for escalated dose pancreatic radiation to a dose of 63Gy in 28 fractions (red line indicates 63Gy isodose line, yellow indicates 55Gy and blue indicates 45Gy), b) patient treated with standard four field technique and dose (red correlates to 50.4Gy isodose line and yellow correlates to 30Gy isodose line), c) Patient treated to 67.5 in 15 fractions (Red line correlates to 67.5Gy isodose line, Yellow line indicates 50Gy and Blue line indicates 45Gy), and d) demonstrates treatment planning technique utilizing PRV for duodenum and stomach to shape dose. Stomach and duodenum are contoured in orange, with 0.5cm expansion for PRV. The blue line correlates with 50Gy line and red line correlates to 63Gy line (15 fractions).

Table 1 Patient and treatment characteristics for all patients who received induction chemotherapy followed by escalated dose chemoradiation (n = 59)

Variable	SDR N (%)	EDR N (%)	SDR Median (IQR)	EDR Median (IQR)	*P*-value[a]
Radiation Dose[b]			50.4 Gy (0)	63.6 (7)	
Fractions[b]			28 (0)	28 (3)	
Year Treated			2010 (3)	2012 (5)	**< .001**[c]
2005-2008	0 (0)	10 (17)			
2009-2012	84 (88)	26 (44)			
2013-2016	12 (13)	23 (39)			
Surgery					**< .001**
No	68 (71)	50 (91)			
Yes	28 (28)	5 (9)			
T Stage					**< .001**
T4	51 (53)	41 (70)			
T3	45 (47)	13 (22)			
T2	0 (0)	4 (7)			
Missing		1 (2)			
N Stage					0.39
N1	73 (76)	16 (27)			
N0	23 (24)	42 (71)			
Tumor Max Dimension (cm)			3.3 (1.3)	3.7 (2.18)	
Tumor Location					**< .001**
Body	14 (15)	23 (39)			
Head	64 (67)	19 (32)			
Neck	12 (13)	12 (20)			
Tail	6 (6)	5 (9)			
Concurrent Chemotherapy					0.34
5-FU–based	61 (64)	43 (73)			
Gemcitabine-based	22 (5)	12 (20)			
Cetuximab/Other	12 (13)	4 (7)			
Breath-Hold[b]					
No		36 (61)			
Yes		23 (39)			
CT on Rails[b]					
No		35 (59)			
Yes		24 (41)			
4-Dimensional CT[b]					
No		30 (51)			
Yes		29 (49)			
Imaging During Treatment[b]					
CT on Rails		24 (41)			
DKV Only		18 (31)			
Weekly Cone Beam CT (+DKV)		7 (12)			
Weekly kV Only		7 (12)			
Daily cone beam CT Only		3 (5)			
Highest CTCAE Acute GI Toxicity					**< .001**
0	24 (25)	34 (58)			
1	46 (48)	18 (31)			
2	12 (13)	7 (12)			
3	13 (14)	0 (0)			
Highest CTCAE Acute Overall Toxicity					**.002**
0	22 (37)	22 (37)			
1	49 (52)	26 (44)			
2	17 (18)	9 (15)			
3	15 (16)	2 (3)			
Any Late Toxicity					
No		51 (86)			
Yes		8 (14)			

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Table 1 (*continued*)

Variable	SDR N (%)	EDR N (%)	SDR Median (IQR)	EDR Median (IQR)	*P*-value[a]
Any Acute Toxicity					
No	24 (25)	22 (37)			
Yes	71 (75)	37 (63)			
Duodenal V40 (cm^3)[b]				19.25 (36.2)	
Duodenal V50 (cm^3)[b]				10.07 (25.53)	
Duodenal V55 (cm^3)[b]				0.1 (1.95)	
Duodenal V60 (cm^3)[b]				0 (0)	
Duodenal Max Dose (Gy)[b]				58.34 (8.86)	
Duodenal Mean Dose (Gy)[b]				32.12 (20.96)	
Stomach V40 (cm^3)[b]				54.91 (77.405)	
Stomach V50 (cm^3)[b]				8.65 (40.62)	
Stomach V55 (cm^3)[b]				0.02 (0.5)	
Stomach V60 (cm^3)[b]				0 (0)	
Stomach Max Dose (Gy)[b]				56.70 (6.58)	
Stomach Mean Dose (Gy)[b]				25.51 (18.65)	
Jejunum V40 (cm^3)[b]				11.46 (21.40)	
Jejunum V50 (cm^3)[b]				0.74 (10.92)	
Jejunum V55 (cm^3)[b]				0 (4.12)	
Jejunum V60 (cm^3)[b]				0 (0)	
Jejunum Max Dose (Gy)[b]				54.77 (9.1)	
Small Bowel Max Dose (Gy)[b]				54.96 (12.30)	

5-FU, 5-fluorouracil; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; DKV, daily kV; EDR, escalated dose radiation; GI, gastrointestinal; IQR, interquartile range; SDR, standard dose radiation.

[a] Using 2 sample *t* test, χ^2 or Fisher's exact test as appropriate.

[b] Applies only to escalated dose patients.

[c] Bold font denotes $\alpha < .05$.

Treatment planning

The primary tumor was contoured on a simulation CT scan after fusion and registration with diagnostic imaging, most frequently pancreatic protocol CT scans. An internal gross target volume was contoured with information from all breath-hold scans and/or all phases of 4-dimensional CT scans to account for tumor motion. A 2 to 5 mm expansion from the gross tumor volume (GTV) was used for a simultaneous integrated boost (SIB) within the planning target volume. Volumes were contoured for any duodenum, jejunum, stomach, or small bowel near the high-dose area. Avoidance structures for these organs at risk (OARs) were delineated to avoid doses greater than 50, 55, or 60 Gy.

To design the simultaneous integrated protection (SIP),[8,16] an expansion (generally 0.5 mm) was added to create a planning risk volume, and GTV was subtracted to avoid OARs within the high-dose field. Patients were most often treated with daily CT on rails or cone beam CT aligned to soft tissue. Figure 1 demonstrates examples of patients treated with (a) standard IMRT technique up to 63 Gy in 28 fractions in accordance with the Radiation Therapy Oncology Group protocol 1201, (b) standard 4-field technique, and (c) up to 67.5 Gy in 15 fractions with an SIB/SIP technique. Figure 1d illustrates the contoured OARs (stomach and duodenum) with planning risk volume and GTV shaped to avoid these structures.

Statistical analysis

Descriptive statistics were generated for patient, tumor, and treatment characteristics and overall toxicity for both standard dose (n = 95) and EDR patients (n = 59). Differences between SDR and EDR patients were compared using 2 sample *t* tests for continuous covariates and χ^2 or Fisher's exact tests for categorical covariates. Toxicities in all patients who received EDR were compared with those who received SDR with a Pearson χ^2 or Fisher's exact test where appropriate. Univariate logistic regression was also used to analyze treatment type as a predictor of toxicity. Competing risk Kaplan-Meier curves were generated for late toxicity to categorize late toxicity or death as events versus death alone. A log-rank test was used to compare curves.

For EDR patients who received standard induction chemotherapy followed by standard chemoradiation (n = 59), a logistic regression analysis was performed for predictors of late toxicity, acute overall toxicity, and acute

Table 2 Univariate logistic regression for predictors of any CTCAE Version 4.0 acute toxicity in patients who received induction chemotherapy followed by escalated dose chemoradiation (n = 59)

	No Acute Toxicity (n = 22)	Acute Grade 1+ Toxicity (n = 36)	*P*-value[a,b]	Odds Ratio (95% CI)[b]
Radiation Dose (per Gy)			.21	1.08 (0.95-1.23)
Fractions (per Fraction)			**.03**	**0.89 (0.79-0.98)**
Year Treated (per Year)			**.007**	**0.74 (0.59-0.92)**
Surgery			.65	
No	19 (95%)	31 (89%)		0.36 (0.12-4.73)
Yes	1 (5%)	4 (11%)		–
T Stage			.26	
T4	17 (77.3%)	24 (66.7%)		0.99 (.00-)
T3	5 (22.7%)	8 (22.2%)		0.99 (.00-)
T2	0 (0%)	4 (11.1%)		–
Missing				
N Stage			.97	
N1	6 (27.3%)	10 (27.8%)		0.97 (0.31-3.34)
N0	16 (72.3%)	26 (72.2%)		–
Tumor Location			**.01**	
Head	2 (1%)	17 (4.7%)		**9.27 (1.73-49.66)**
Neck	7 (31.8%)	5 (13.9%)		0.78 (0.19-3.19)
Tail	1 (.05%)	4 (1.1%)		4.36 (0.42-45.26)
Body	12 (54.5%)	10 (27.8%)		–
Concurrent Chemotherapy			.18	
5-FU–based	19 (86.4%)	24 (66.7%)		0.42 (0.1-1.78)
Cetuximab-based	3 (1.4%)	9 (25%)		53849 (.000-)
Gemcitabine-based	0 (0%)	3 (1%)		–
Tumor Max Dimension (cm)			.68	0.92 (0.62-1.37)
Breath-Hold			**.02**	
No	9 (41%)	26 (72.2%)		**3.9 (1.3-12.4)**
Yes	13 (59%)	10 (27.8%)		–
CT on Rails			**.001**	
No	7 (31.8%)	27 (75%)		**6.67 (2.10-21.5)**
Yes	15 (68.2%)	9 (25%)		–
4-dimensional CT			**.003**	
No	17 (77.3%)	13 (36.1%)		**6.3 (1.9-20.9)**
Yes	23 (63.9%)	5 (22.7%)		–
Imaging During Treatment			**.03**	
CT on Rails	15 (68.2%)	9 (25%)		
DKV Only	1 (.05%)	2 (1%)		
Weekly cone beam CT (+DKV)	3 (1.4%)	14 (3.9%)		
Weekly kV Only	2 (1%)	5 (1.4%)		
Daily cone beam CT Only	1 (.05%)	6 (1.7%)		
Duodenal V40 (cm^3)			.94	
Duodenal V50 (cm^3)			.99	
Duodenal V55 (cm^3)			.56	
Duodenal V60 (cm^3)			.96	
Duodenal Max Dose (Gy)			.11	
Duodenal Mean Dose (Gy)			.45	
Stomach V40 (cm^3)			**.03**	
Stomach V50 (cm^3)			.14	
Stomach V55 (cm^3)			.99	
Stomach V60 (cm^3)			.99	
Stomach Max Dose (Gy)			.10	
Stomach Mean Dose (Gy)			.26	
Jejunum V40 (cm^3)			.50	
Jejunum V50 (cm^3)			.34	
Jejunum V55 (cm^3)			.33	
Jejunum V60 (cm^3)			.99	

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Table 2 (*continued*)

	No Acute Toxicity (n = 22)	Acute Grade 1+ Toxicity (n = 36)	*P*-value[a,b]	Odds Ratio (95% CI)[b]
Jejunum Max Dose (Gy)			.37	
Small Bowel Max Dose (Gy)			.94	

5-FU, 5-fluorouracil; CI, confidence interval; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; DKV, daily kV.

[a] *P*-values are based on univariate logistic regression with bootstrapping.

[b] Bold font denotes *P*-value with $\alpha < .05$.

gastrointestinal toxicity. Bootstrapping was performed, but multivariate logistic regression could not be performed because of the low event numbers and high collinearity of year treated, use of breath-hold, CT on rails, and 4-dimensional CT. These variables were instead analyzed using a recursive partition analysis with k-fold cross validation.

Results

Patient, tumor, and treatment characteristics

Patient, tumor, and treatment characteristics for both EDR and SDR patients are presented in Table 1. Fifty-nine of 154 patients (approximately 39%) received EDR with BED >70 Gy. The most frequent schedules were 63 Gy in 28 fractions (19 of 154 patients), 67.5 Gy in 15 fractions (10 of 154 patients), and 70 Gy in 28 fractions (15 of 154 patients).

Fifty-nine patients (35.7%) received induction chemotherapy followed by chemoradiation; because of the heterogeneity of the comparison groups, only these patients were included in the logistic regression analysis for predictors of toxicity. Toxicities of standard dose chemoradiation have been previously reported. Of these patients, 63% (43 of 59) received 5-fluorouracil–based concurrent chemotherapy, 20.3% (12 of 59) received gemcitabine-based concurrent chemotherapy, and 6.8% (4 of 59) received cetuximab-based concurrent chemotherapy. Thirty-nine percent of EDR patients (23 of 59) were treated between 2013 and 2016, 44.1% (26 of 59) between 2009 and 2012, and 17% (10 of 59) between 2005 and 2008. A total of 69.5% (41 of 59) of patients had T4 tumors and 27.1% (16 of 59) were radiographically N1. The median tumor dimension was 3.7 cm (interquartile range, 2.18). The breath-hold technique was used for 38.9% of patients (23 of 59), 4-dimensional CT for 49.2% (29 of 59), and CT on rails for daily image guidance for 40.1% (24 of 59). There was significant overlap between these 3 variables. The median total dose was 63.7 Gy (interquartile range, 7 Gy), and the median number of fractions 28 (interquartile range, 3).

Acute toxicity for patients receiving EDR

In the dose-escalated group, 57.6% (34 of 59 patients) had no acute gastrointestinal toxicity, 30.5% had maximal grade 1 acute gastrointestinal toxicity, and 11.7% had maximal grade 2 acute gastrointestinal toxicity. No overall acute toxicities were reported in 37.3% (22 of 59 patients); 44.1% experienced maximal grade 1 overall toxicity, and 15.3% experienced maximal grade 2 overall toxicity. Two patients (3.4%) experienced grade 3 toxicity. No grade 4 or grade 5 toxicities were reported. The grade 3 toxicities were both severe anorexia requiring feeding tube placement and hospitalization.

Factors predictive of any acute overall toxicity (Table 2; grade 1 or higher) included a smaller number of fractions (odds ratio [OR], 0.89; 95% confidence interval [CI], 0.79-0.98; $P = .03$), earlier year treated (OR per later year, 0.74; 95% CI, 0.59-0.92; $P = .007$), tumor location in pancreatic head (OR, 9.27; 95% CI, 1.73-49.67; $P = .01$), no utilization of breath-hold (OR, 3.9; 95% CI, 1.3-12.4; $P = .02$), no utilization of CT on rails (OR, 6.67; 95% CI, 2.10-21.5; $P = .001$), no utilization of 4-dimensional CT (OR, 6.3; 95% CI, 1.9-20.9; $P = .003$), and stomach V40 ($P = .03$). Acute gastrointestinal toxicity (Table 3; grade 1 or higher) was predicted by the following factors: earlier year treated (OR per later year, 0.75; 95% CI, 0.61-0.92; $P = 0.005$), tumor location in pancreatic head (OR, 4.10; 95% CI, 1.12-14.8; $P = .04$), no utilization of deep inspiration breath-hold (OR, 3.17; 95% CI, 1.02-9.88; $P = .007$), no utilization of CT on rails for daily imaging (OR, 5.07; 95% CI, 1.54-16.67; $P = .007$), and no utilization of 4-dimensional CT for simulation (OR, 5.40; 95% CI, 1.74-16.66; $P = .003$). Higher-grade gastrointestinal toxicity (grade 2+) was not associated with dose ($P = .4$), number of fractions ($P = .07$), year treated ($P = .4$), T stage ($P = .3$), N stage ($P = .9$), tumor location ($P = .8$), concurrent chemotherapy ($P = .7$), use of breath-hold ($P = .6$), CT on rails ($P = .5$), or 4-dimensional CT ($P = .7$). No factors were significantly associated with acute gastrointestinal toxicity grade >2 (Supplemental Table 1).

Multivariate logistic regression could not be performed due to the low event numbers and high

Table 3 Univariate logistic regression for predictors of any CTCAE Version 4.0 acute gastrointestinal toxicity in patients who received induction chemotherapy followed by escalated dose chemoradiation (n = 59)

	No Acute Toxicity (n = 33)	Acute Grade 1+ GI Toxicity (n = 25)	*P*-value[a,b,c]	Odds Ratio (95% CI)[b]
Radiation Dose			.10	0.90 (0.80-1.02)
Fractions			.12	1.1 (0.98-1.23)
Year Treated			**.005**	**0.75 (0.61-0.92)**
2005-2008	3 (8.8%)	4 (18.2%)		
2009-2012	12 (35.2%)	14 (63.7%)		
2013-2016	19 (55.6%)	4 (18.2%)		
Surgery			.66	
No	30 (91%)	20 (87%)		0.67 (0.05-9.50)
Yes	2 (6.1%)	3 (13%)		
T Stage			.90	
T4	23 (69.7%)	18 (72%)		0.78 (0.10-6.1)
T3	8 (24.2%)	5 (20%)		0.63 (0.07-5.97)
T2	2 (6%)	2 (8%)		–
N Stage			.95	
N1	9 (27.3%)	7 (28%)		1.04 (0.33-3.31)
N0	24 (72.7%)	18 (72%)		
Tumor Location			**.04**	
Head	6 (18.2%)	13 (52%)		**4.10 (1.12-14.8)**
Neck	9 (27.3%)	3 (12%)		0.63 (0.13-2.98)
Tail	4 (12.1%)	1 (.05%)		0.47 (0.05-4.93)
Body	14 (42.4%)	8 (32%)		–
Concurrent Chemotherapy			.70	
5-FU–based	25 (75.8%)	18 (72%)		1.1 (0.28-3.70)
Cetuximab-based	7 (21.2%)	5 (20%)		1.40 (0.15-13.57)
Gemcitabine-based	1 (.03%)	2 (1%)		–
Tumor Max Dimension (cm)				0.97 (0.66-1.43)
Breath-Hold			**.05**	
No	16 (48.9%)	19 (76%)		**3.17 (1.02-9.88)**
Yes	17 (51.5%)	6 (24%)		–
CT on Rails			**.007**	
No	14 (42.4%)	20 (80%)		**5.07 (1.54-16.67)**
Yes	19 (57.6%)	5 (20%)		–
4-dimensional CT			**.003**	
No	10 (30.3%)	18 (72%)		**5.40 (1.74-16.66)**
Yes	23 (69.7%)	7 (28%)		–
Imaging During Treatment			.05	
CT on Rails	19 (57.6%)	5 (20%)		
DKV Only	7 (21.2%)	10 (40%)		
Weekly cone beam CT (+DKV)	3 (10%)	4 (16%)		
Weekly kV Only	2 (6%)	5 (20%)		
Daily cone beam CT Only	2 (6%)	1 (4%)		
Duodenal V40 (cm^3)			.57	
Duodenal V50 (cm^3)			.52	
Duodenal V55 (cm^3)			.83	
Duodenal V60 (cm^3)			.63	
Duodenal Max Dose (Gy)			.08	
Duodenal Mean Dose (Gy)			.32	
Stomach V40 (cm^3)			.18	
Stomach V50 (cm^3)			.45	
Stomach V55 (cm^3)			.49	
Stomach V60 (cm^3)			.36	
Stomach Max Dose (Gy)			.07	
Stomach Mean Dose (Gy)			.14	
Jejunum V40 (cm^3)			.48	
Jejunum V50 (cm^3)			.77	

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Table 3 (*continued*)

	No Acute Toxicity (n = 33)	Acute Grade 1+ GI Toxicity (n = 25)	*P*-value[a,b,c]	Odds Ratio (95% CI)[b]
Jejunum V55 (cm^3)			.73	
Jejunum V60 (cm^3)			.99	
Jejunum Max Dose (Gy)			.30	
Small Bowel Max Dose (Gy)			.66	

5-FU, 5-fluorouracil; CI, confidence interval; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; DKV, daily kV; GI, gastrointestinal.

[a] *P*-values are based on univariate logistic regression with bootstrapping.

[b] Bold font denotes *P*-value with $\alpha < .05$.

[c] Year treated was analyzed as a continuous variable.

collinearity of year treated, use of breath-hold, CT on rails, and 4-dimensional CT; however, when all variables were analyzed with recursive partition analysis, the use of 4-dimensional CT appeared to be the most significant predictor of acute gastrointestinal toxicity (log worth, 2.64; k-fold cross validation area under the curve, 0.70), but daily use of CT on rails appeared to be the most significant predictor of acute overall toxicity (log worth, 3.07; k-fold cross validation area under the curve, 0.72).

Late toxicity of patients who received EDR

Of the 59 patients who were treated with EDR, 86% (51 of 59) did not experience any long-term toxicities (Table 4). Three patients developed gastrointestinal bleeding (ulcers, vascular ectasias, and gastritis) that did not require intervention. Two patients developed duodenal and esophageal strictures that required endoscopic intervention at 3 years postradiation with no evidence of tumor recurrence. Four patients developed gastrointestinal bleeding (ulcers and fistulas) that required endoscopic or interventional radiology (IR) intervention, including embolization, argon coagulation, and others. Two of these patients eventually underwent resection and developed complications postoperatively: one developed a splenic pseudoaneurysm 6 months after pancreaticoduodenectomy, requiring IR intervention, and the other developed an enterocutaneous fistula after pancreaticoduodenectomy. The third patient developed gastroduodenal artery bleeding due to stent erosion, requiring IR intervention. The final patient had a history of portal hypertension and developed severe gastrointestinal bleeding 3 months after radiation therapy (and prior to disease recurrence) that required 5 units of packed red blood cells and splenic vein embolization with no source identified on endoscopy. The bleeding did not recur after treatment.

Logistic regression analysis revealed no significant predictors of late toxicity (Table 4). Actuarial late toxicity-free survival was 16.7 months (95% CI, 6.5-26.8). The median time-to-event for late toxicity was 8.2 months (95% CI, 0.0001-18.3). The competing risks analysis (Supplemental Figure 1) showed no statistical difference between calculated late toxicity-free survival and overall survival ($P = .4$).

Comparison with SDR patients

Of 95 patients with LAPC treated during the same era, 88% (84/95) were treated with induction chemotherapy followed by standard dose chemoradiation with a 3-dimensional technique and were selected for comparison. Overall SDR patients (Table 1) were more likely to be treated with definitive surgery ($P < .001$), have a higher T stage ($P < .001$), and have a pancreatic head tumor ($P < .001$). There was no difference in median tumor size or type of concurrent chemotherapy administration. Some of these patients were selected from a previously reported cohort of patients and updated to include more patients who were treated in the most recent era.[11] Figure 2 demonstrates the rates of toxicity as compared between the 2 groups. The rates of acute grade 3 gastrointestinal toxicities (nausea, vomiting, and diarrhea) were significantly lower in patients who received EDR compared with SDR (1% vs 14%; $P < .001$). Similarly, the rates of acute grade 3 overall toxicities (dehydration, fatigue, and anorexia) were also lower for EDR compared with SDR (4% vs 16%; $P = .004$). The proportion of patients who experienced no acute toxicity with treatment was higher in the EDR group than in the SDR group (36% vs 15%; $P = .001$). The univariate logistic regression for all patients showed that SDR was associated with both acute grade 1 and gastrointestinal toxicity ($P < .001$) and acute grade 2 and gastrointestinal toxicity ($P = .02$).

Discussion

These data demonstrate that dose-escalated IMRT treatment using an SIB technique with image guidance and motion management for PDAC is safe and well tolerated in selected patients. The overall acute and late

Table 4 Univariate logistic regression for predictors of any late toxicity in all patients who received induction chemotherapy followed by escalated dose chemoradiation (n = 59)

	No Late Toxicity (n = 51)	Late Toxicity (n = 8)	*P*-value[a]
Radiation Dose			.27
Fractions			.11
Year Treated			.30
Surgery			.29
No	44 (93%)	6 (75%)	
Yes	3 (6%)	2 (2%)	
T Stage			.49
T4	34 (68%)	7 (8.8%)	
T3	12 (24%)	1 (1.3%)	
T2	4 (1%)	0 (0%)	
N Stage			.67
N1	13 (26%)	5 (6.3%)	
N0	37 (74%)	3 (3.8%)	
Tumor Location			.87
Body	20 (40%)	2 (25%)	
Head	16 (32%)	3 (37.5%)	
Neck	10 (20%)	2 (25%)	
Tail	4 (1%)	1 (12.5%)	
Concurrent Chemotherapy			.35
5-FU–based	38 (76%)	5 (62.5%)	
Gemcitabine-based	3 (1%)	0 (0%)	
Cetuximab-based	9 (2%)	3 (37.5%)	
Tumor Max Dimension (cm)			
Breath-Hold			.46
No	29 (58%)	6 (75%)	
Yes	21 (42%)	2 (25%)	
CT on Rails			.27
No	28 (56%)	6 (75%)	
Yes	22 (44%)	2 (25%)	
4-dimensional CT			.31
No	27 (54%)	3 (37.5%)	
Yes	23 (46%)	5 (62.5%)	
Imaging During Treatment			.06
CT on Rails	22 (43.14%)	2 (25.0%)	
DKV Only	15 (31.37%)	2 (25.0%)	
Weekly cone beam CT (+DKV)	7 (13.73%)	0 (0)	
Weekly kV Only	5 (9.80%)	2 (25.0%)	
Daily cone beam CT Only	1 (1.96%)	2 (25.0%)	
Duodenal V40 (cm^3)			.29
Duodenal V50 (cm^3)			.32
Duodenal V55 (cm^3)			.06
Duodenal V60 (cm^3)			.11
Duodenal Max Dose (Gy)			.86
Duodenal Mean Dose (Gy)			.61
Stomach V40 (cm^3)			.46
Stomach V50 (cm^3)			.99
Stomach V55 (cm^3)			.24
Stomach V60 (cm^3)			.33
Stomach Max Dose (Gy)			.25
Stomach Mean Dose (Gy)			.46
Jejeunum V40 (cm^3)			.99
Jejeunum V50 (cm^3)			.99
Jejeunum V55 (cm^3)			.99

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Table 4 (*continued*)

	No Late Toxicity (n = 51)	Late Toxicity (n = 8)	*P*-value[a]
Jejeunum V60 (cm^3)			.99
Jejeunum Max Dose (Gy)			.27
Small Bowel Max Dose (Gy)			.19

5-FU, 5-fluorouracil; CT, computed tomography; DKV, daily kV.
[a] *P*-values are based on univariate logistic regression with bootstrapping.

toxicity rates in this cohort were lower compared with those of a cohort of patients treated with standard 3-dimensional conformal radiation therapy, despite higher overall doses. The toxicity rates in our standard dose cohort were in line with previously reported outcomes for PDAC.

Several factors likely contribute to this finding. First, treatment with IMRT provides better dosimetric conformality of both high-dose and standard-dose regions, as demonstrated in Fig 1A versus Fig 1B. Rather than treating an entire 4-field box to 50.4 Gy, the dose can be shaped to minimize the dose to critical structures and

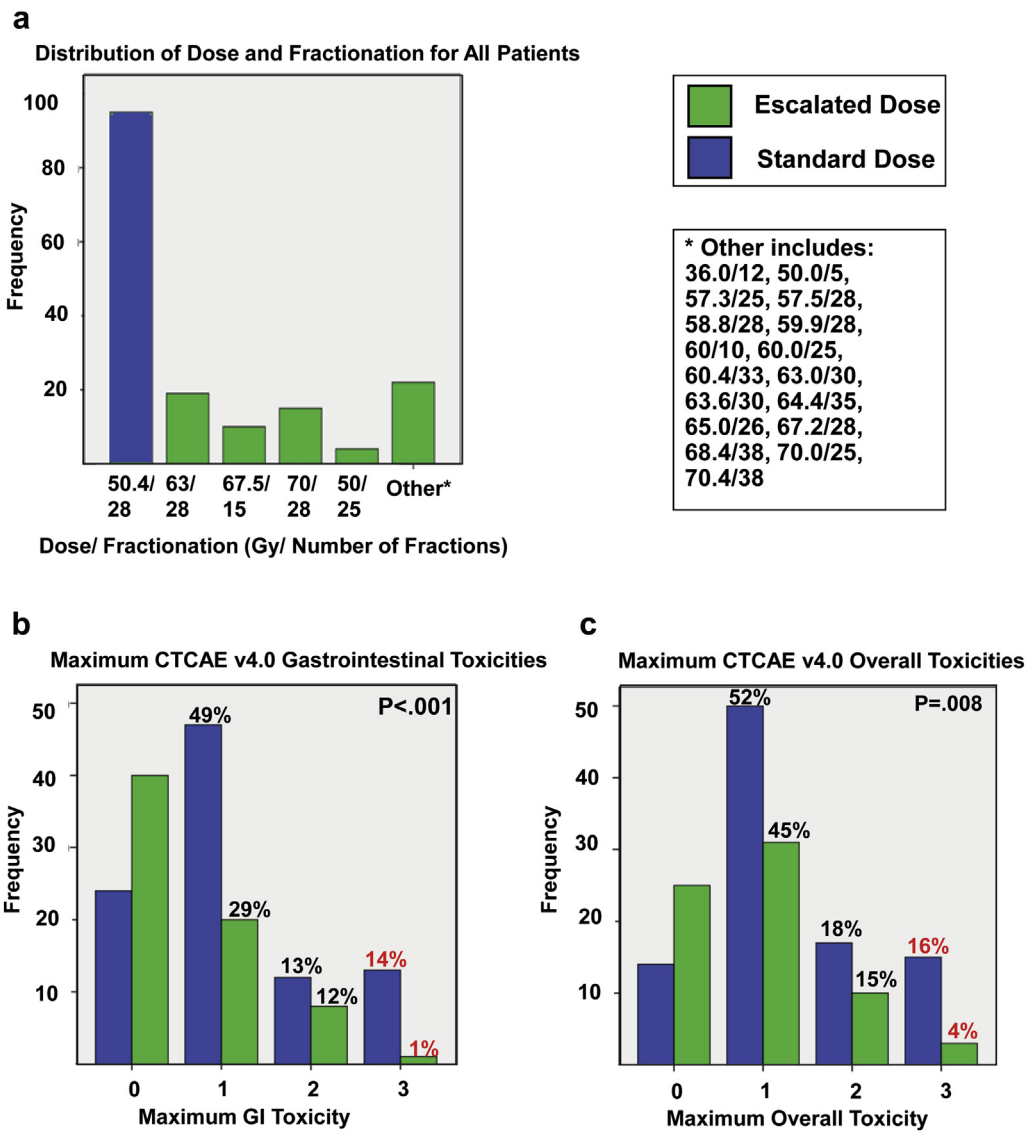

Figure 2 (a) Distribution of treatment fractionation schedules for all patients, (b) distribution of maximum Common Terminology Criteria for Adverse Events Version 4.0 toxicity grades for gastrointestinal toxicity, and (c) overall toxicity for all patients who received standard dose chemoradiation (n = 97) and escalated dose chemoradiation (n = 59).

provide adequate margins on these structures for both the high- and standard-dose regions. Thus, several groups have reported a lower toxicity with IMRT versus 3-dimensional conformal therapy.[12-15,17,18] Acceptable toxicities from dose-escalated IMRT have been reported previously in the treatment of liver tumors; the technique is similar to the technique in this study, but toxicities have not been reported for pancreatic radiation.[8,16]

Second, patients treated with escalated-dose IMRT were carefully selected.[11] Of note, the patients in this report had relatively stable local disease through induction chemotherapy, no development of metastatic disease, an anatomically favorable location in the pancreatic body, or tail tumors that were located >1 cm from the nearest gastrointestinal mucosa. This analysis provides no evidence for use of this technique in patients who do not meet these selection criteria. It is worth noting that all patients demonstrated stable disease through induction chemotherapy without developing metastatic disease before receiving radiation therapy, which indicates that they may also represent a subset of patients with biologically advantageous or locally predominant disease. Better selection for these patients with locally predominant disease, whether with radiomic biomarkers,[19,20] molecular biomarkers, or clinical decision making tools, may help elucidate those patients who may benefit.[3,4,21] The treatment algorithm of induction chemotherapy followed by concurrent chemoradiation for stable disease is well accepted for both locally advanced and borderline resectable pancreatic cancer[7,22,23] and may help in selecting patients that are candidates for more aggressive local management.

Third, the importance of accurate on-board imaging and motion management must be emphasized. Despite the differences between the patient groups, the use of both respiratory management and daily high-resolution CT imaging remained the most important factors in limiting both acute gastrointestinal and overall toxicity. Particularly when the ratio of potential therapeutic benefit to toxicity is low, further steps to minimize potential morbidity and toxicity are desirable. The use of IMRT, motion management, and on-board imaging even with SDR treatment would be expected to prevent patient toxicity and safely allow dose escalation to smaller volumes when possible. These factors are also critical to other treatment techniques, including SBRT, that may both shorten treatment time and prevent toxicity, improving the overall patient experience.

This study must be interpreted in light of the limitations that are inherent to a retrospective review, in addition to patient selection bias and provider recording bias of toxicities. These patient cohorts were carefully selected, as evidenced by the reported differences between the groups. Additionally, toxicities that are not recorded prospectively and inclusive of patient-reported outcomes are limited. For example, although our SDR cohort served as a clinically meaningful reference for toxicity rates, it lacked comparable dose-volume histogram data for the EDR group and thus should be interpreted with some caution.

In conclusion, this study elucidates 2 main points: dose escalation is safe and well tolerated with an IMRT-based technique, and both motion management and accurate on-board imaging should be considered strongly to decrease toxicity in the EDR technique to the pancreas. For those centers that are capable of delivering IMRT with advanced image guidance, clinicians should consider using this technology to deliver EDR while respecting the known constraints of nearby normal tissue. This is particularly important in the setting of locally advanced pancreatic cancer because this technique has shown the potential to improve recurrence-free and overall survival rates for these patients. These clinical and dosimetric principles should be applied to future studies examining the role of dose-escalated fractionated radiation and/or SBRT.

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Supplementary data

Supplementary material for this article (http://dx.doi.org/10.1016/j.adro.2017.02.004) can be found at www.advancesradonc.org.

References

1. American Cancer Society. *Cancer Facts & Figures 2015*. Atlanta: American Cancer Society; 2015.
2. Hattangadi JA, Hong TS, Yeap BY, Mamon HJ. Results and patterns of failure in patients treated with adjuvant combined chemoradiation therapy for resected pancreatic adenocarcinoma. *Cancer*. 2009;115:3640-3650.
3. Colbert LE, Fisher SB, Balci S, et al. High nuclear hypoxia-inducible factor 1 alpha expression is a predictor of distant recurrence in patients with resected pancreatic adenocarcinoma. *Int J Radiat Oncol Biol Phys*. 2015;91:631-639.
4. Iacobuzio-Donahue CA, Fu B, Yachida S, et al. DPC4 gene status of the primary carcinoma correlates with patterns of failure in patients with pancreatic cancer. *J Clin Oncol*. 2009;27:1806-1813.
5. Winter JM, Tang LH, Klimstra DS, et al. Failure patterns in resected pancreas adenocarcinoma: lack of predicted benefit to SMAD4 expression. *Ann Surg*. 2013;258:331-335.
6. Hammel P, Huguet F, van Laethem JL, et al. Effect of chemoradiotherapy vs chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: The LAP07 randomized clinical trial. *JAMA*. 2016;315:1844-1853.

7. Hammel P, Huguet F, Van Laethem JL, et al. Comparison of chemoradiotherapy (CRT) and chemotherapy (CT) in patients with a locally advanced pancreatic cancer (LAPC) controlled after 4 months of gemcitabine with or without erlotinib: Final results of the international phase III LAP 07 study. *J Clin Oncol*. 2013;31. abstract LBA4003.
8. Tao R, Krishnan S, Bhosale PR, et al. Ablative radiotherapy doses lead to a substantial prolongation of survival in patients with inoperable intrahepatic cholangiocarcinoma: A retrospective dose response analysis. *J Clin Oncol*. 2016;34:219-226.
9. Pollack A, Zagars GK, Starkschall G, et al. Prostate cancer radiation dose response: Results of the MD Anderson phase III randomized trial. *Int J Radiat Oncol Biol Phys*. 2002;53:1097-1105.
10. Bourhis J, Overgaard J, Audry H, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: A meta-analysis. *Lancet*. 2006;368:843-854.
11. Krishnan S, Chadha AS, Suh Y, et al. Focal radiation therapy dose escalation improves overall survival in locally advanced pancreatic cancer patients receiving induction chemotherapy and consolidative chemoradiation. *Int J Radiat Oncol Biol Phys*. 2016;94:755-765.
12. Prasad S, Cambridge L, Huguet F, et al. Intensity modulated radiation therapy reduces gastrointestinal toxicity in locally advanced pancreas cancer. *Pract Radiat Oncol*. 2016;6:78-85.
13. Yovino S, Poppe M, Jabbour S, et al. Intensity-modulated radiation therapy significantly improves acute gastrointestinal toxicity in pancreatic and ampullary cancers. *Int J Radiat Oncol Biol Phys*. 2011;79:158-162.
14. Abelson JA, Murphy JD, Minn AY, et al. Intensity-modulated radiotherapy for pancreatic adenocarcinoma. *Int J Radiat Oncol Biol Phys*. 2012;82:e595-e601.
15. Ben-Josef E, Schipper M, Francis IR, et al. A phase I/II trial of intensity modulated radiation (IMRT) dose escalation with concurrent fixed-dose rate gemcitabine (FDR-G) in patients with unresectable pancreatic cancer. *Int J Radiat Oncol Biol Phys*. 2012;84:1166-1171.
16. Crane CH, Koay EJ. Solutions that enable ablative radiotherapy for large liver tumors: Fractionated dose painting, simultaneous integrated protection, motion management, and computed tomography image guidance. *Cancer*. 2016;122:1974-1986.
17. Brown MW, Ning H, Arora B, et al. A dosimetric analysis of dose escalation using two intensity-modulated radiation therapy techniques in locally advanced pancreatic carcinoma. *Int J Radiat Oncol Biol Phys*. 2006;65:274-283.
18. Passoni P, Reni M, Cattaneo GM, et al. Hypofractionated image-guided IMRT in advanced pancreatic cancer with simultaneous integrated boost to infiltrated vessels concomitant with capecitabine: A phase I study. *Int J Radiat Oncol Biol Phys*. 2013;87:1000-1006.
19. Koay EJ, Amer AM, Baio FE, Ondari AO, Fleming JB. Toward stratification of patients with pancreatic cancer: Past lessons from traditional approaches and future applications with physical biomarkers. *Cancer Lett*. 2016;381:237-243.
20. Koay EJ, Truty MJ, Cristini V, et al. Transport properties of pancreatic cancer describe gemcitabine delivery and response. *J Clin Invest*. 2014;124:1525-1536.
21. Herman JM, Fan KY, Wild AT, et al. Correlation of Smad4 status with outcomes in patients receiving erlotinib combined with adjuvant chemoradiation and chemotherapy after resection for pancreatic adenocarcinoma. *Int J Radiat Oncol Biol Phys*. 2013;87:458-459.
22. Badiyan SN, Olsen JR, Lee AY, et al. Induction chemotherapy followed by concurrent full-dose gemcitabine and intensity-modulated radiation therapy for borderline resectable and locally advanced pancreatic adenocarcinoma. *Am J Clin Oncol*. 2016;39:1-7.
23. Katz MH, Shi Q, Ahmad SA, et al. Preoperative modified FOLFIRINOX treatment followed by capecitabine-based chemoradiation for borderline resectable pancreatic cancer: Alliance for clinical trials in oncology trial A021101. *JAMA Surg*. 2016;151:e161137.