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Dose Escalation with a Vessel Boost in Pancreatic Adenocarcinoma Treated with Neoadjuvant Chemoradiation

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Abstract

Purpose—Pancreatic adenocarcinoma (PAC) patients are often treated with neoadjuvant chemoradiation (NACRT) in hopes of downstaging their disease for potential surgical resection. We hypothesized that increasing the radiation dose to the area of the tumor abutting the vessel(s) of concern increases the rate of surgical resection in borderline resectable (BR) and locally advanced (LA) patients treated with NACRT.

Methods and Materials—We retrospectively reviewed consecutive cases of BR and LAPAC treated with NACRT from January 2006 to December 2013, with or without a vessel boost (VB), at a single institution. The primary endpoints were rate of R0/R1 potentially curative surgical resection and acute toxicity. Univariate analysis using Fisher's exact test was performed to evaluate effect of each variable. Multiple logistic regression was used to adjust for the following covariates: year of diagnosis, age, gender, CA19-9 at diagnosis, and BR or LA.

Results—Of the 104 patients identified, 22% (n=23) received a VB (median 54Gy, range 54–64Gy) and 78% (n=81) received no boost (median 50.4Gy, range 48.6–52.2Gy). More patients in the VB group were treated from 2010–2013 ($p<0.001$) and with IMRT ($p=0.002$). Other baseline characteristics were balanced. After adjusting for covariates, there was a statistical trend toward increased surgical resection in patients who received a VB (OR=2.77[0.89–8.57], $p=0.077$). Age (<70 , OR=0.42[0.16–1.05], $p=0.064$) and LAPAC (OR=0.32[0.09–1.09], $p=0.068$) also trended towards significance. CA19-9 >47.9 U/mL (OR=0.24[0.08–0.71], $p=0.010$) was significant on multivariate analysis. There was no significant difference in acute or late toxicity between groups.

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Conclusions—In our retrospective series, dose escalation was associated with an improved surgical resection rate in BR and LAPAC patients treated with NACRT, although this improvement was not statistically significant.

Introduction

Pancreatic adenocarcinoma (PAC) is a devastating disease with poor 5-year survival rates that have increased only slightly over the last 30 years.[1,2] While surgery offers the potential for cure[3,4], most patients with localized adenocarcinoma present with borderline resectable (BR) or locally advanced (LA) cancer[5] in which complete resection is unlikely. These patients are often treated with neoadjuvant therapy in hopes of downstaging their disease for potential surgical resection.

Neoadjuvant chemoradiation (NACRT) has many potential benefits compared with up-front surgery in patients with PAC. Receipt of neoadjuvant therapy has been associated with lower pathologic stage, high rates of negative margins, and lower rates of lymph node positivity at the time of resection compared with up-front surgery with no significant increase in postoperative morbidity or mortality. [6,7] Patients with evidence of disease progression during neoadjuvant treatment can then be spared the morbidity of surgery. In addition, a study comparing NACRT to up-front surgery found NACRT to be more cost-effective.[8]

Patients are deemed BR or LA due to tumor involvement of major vessels[9] and the margin at these vessels remains the area of greatest concern after a surgical resection.[10] Our practice has been to administer NACRT for patients who have BR or LAPAC. The rate of resection for patients with BRPAC after treatment with NACRT ranges from 24 to 62% in published series.[11–13] We hypothesized that increasing the radiation dose to the area of the tumor abutting the vessel(s) of concern increases the rate of surgical resection in BR and LA patients treated with NACRT.

Methods and Materials

From January 2006 to December 2013, we retrospectively reviewed consecutive cases of BR and LAPAC treated with NACRT, with or without a vessel boost (VB), at a single institution. Inclusion criteria for the study were PAC patients deemed BR or LA based on the current NCCN guidelines[9]. Acute toxicity was obtained prospectively from nursing assessments based on grading tools from CTCAEv2.0 between 2009 and 2013 for anorexia, nausea, and fatigue. Late toxicity was graded based on CTCAEv4.0. Patient-reported pain was reported on a 0–10 scale.

We excluded patients treated with palliative intent, those with metastatic disease at presentation, patients who were anatomically resectable but were given NACRT due to their borderline performance status and biliary or ampullary tumors. Patient demographics, relevant clinical history, tumor information, treatment, follow-up were abstracted from the relevant medical records in accordance with an Institutional Review Board approved protocol and the Health Insurance Portability and Accountability Act.

Chemoradiation

Radiation was delivered with linear accelerators using multiple-field techniques with a dose per fraction of 1.8Gy unless otherwise specified. Patients were immobilized in a cast. Daily cone beam computed tomography (CT) was utilized for all patients who received intensity modulate radiation therapy (IMRT). No planned breaks were given. A VB is defined as an increased radiation dose (54Gy) to the 5mm of tumor around the vessel(s) identified following multidisciplinary evaluation that render the tumor borderline resectable or locally advanced plus a 5mm expansion for setup error. (Figure 1) All other patients were categorized in the no boost (NB) group. All patients received concurrent chemotherapy. Patients were treated with 3-dimensional conformal radiation therapy (3DCRT) from June 2006 to April 2009. The pancreatic mass and regional lymph nodes were generally treated with a 4-field technique followed by a boost to the pancreatic mass plus a 2cm margin. The treatment dose was generally 45Gy plus 5.4Gy cone down.

All patients treated with IMRT underwent a 4DCT simulation for tumor motion analysis. Patients were treated with IMRT starting in 2007. The gross disease including the pancreatic mass and any grossly enlarged lymph nodes was combined with an internal target volume generated from the 4DCT. This volume was expanded by 5mm to form the clinical target volume. Another 5mm margin was added to create the planning target volume (PTV). The dose to the PTV was generally 50.4Gy. All patients who received a VB were treated with IMRT. The VB was generally performed with dose painting to 56Gy in 2Gy fractions.

Surgery

Patients were evaluated after the completion of their neoadjuvant therapy. Surgery was attempted in those who had preserved performance status in the absence of radiographic disease progression. Only patients who successfully underwent complete (R0) or microscopically positive (R1) resection were considered to have potentially curative surgery.

Statistical analysis

The primary endpoints are rate of R0 or R1 potentially curative surgery, and acute toxicity. Univariate analyses using Fisher's exact tests and Wilcoxon rank-sum tests were performed to evaluate effect of each variable. We then used multiple logistic regression models to determine the adjusted effect of VB and total dose on rate of surgical resection, accounting for the following covariates: year of diagnosis, age, gender, CA19-9 at diagnosis, and whether patients were BR or LA. Classification and regression trees were used to select the optimal cutpoint at which CA19-9 best predicts surgical resection, and we dichotomized patients based on this value in later analysis. Overall survival (OS) time was calculated from the completion of radiation to the date of death. Survival curves were calculated using Kaplan Meier methods, and significance was tested using the log-rank test. P-values of <0.05 were considered statistically significant.

Results

Of the 104 patients identified, 22% (n=23) received a VB and 78% (n=81) received NB. Median age was 69 years (range 38–90). Overall median follow-up was 11.4 months with

11.0 months (range 1.3–71.9) in the NB group and 11.4 months (1.7–46.4) in the VB group. Most patients were treated with concurrent gemcitabine (n=98, weekly 400–600mg/m²). Three patients received talabostat with gemcitabine on a Phase I protocol and three patients received 5-fluorouracil.

Median total radiation dose was 50.4Gy (range 46.0–52.2) in the NB group and 56Gy (range 54.0–64.0) in the VB group. More patients in the VB group were treated with IMRT (p=0.002) and from 2010–2013 (0<0.001) than in the NB group (Table 1). There was no association of BRPAC or LAPAC with dose level (p=0.580). Other patient and tumor characteristics were balanced in both groups. Of the patients who did not proceed to surgery, a higher percentage was due to local failure in the NB group, although this was not statistically significant (30% vs 8%). In the NB group, 31% underwent surgical resection (n=25, R0=76%) compared to 48% (n=11, R0=82%) in the VB group (p=0.144). Of the patients who underwent surgery, 61% received chemotherapy (typically gemcitabine) in addition to CRT but prior to their surgery, with no significant difference between the NB and VB groups (60% vs 64%).

Patients in the VB group had 17.6 months median OS vs 12.6 months in the NB group (p=0.100, Figure 2). OS was significantly higher in patients who underwent surgery (p<0.001, Figure 3) with median OS of 28.7 months vs 8.7 months. Patients who underwent surgery had lower CA19-9 (median 317U/mL vs 553U/mL, p=0.043) and were less likely to be locally advanced (11% vs 29%, p=0.049) compared with those not undergoing surgery. There was no association of BRPAC or LAPAC with dose level (p=0.580). There was also no increase in surgery resection rate based on radiation technique (3DCRT vs IMRT, p=0.503), year of treatment (2006–09 vs 2010–13, p=0.838), age (67 for NB vs 70 for VB, p=0.127), or gender (p=0.990). Those with lower presenting CA19-9 (<47.9U/mL, cutpoint based on CART analysis) were more likely to undergo surgery (55% vs 29%, p = 0.042).

After adjusting for covariates on multivariate analysis, there was a trend towards a statistically significant increase in surgical resection rate for patients who received a VB or not (OR=2.77[0.89–8.57], p=0.077, Table 2). Older age (> 70, OR=0.42[0.16–1.05], p=0.064) and LAPAC (OR=0.32[0.09–1.09], p=0.068) were also trending towards statistical significance for less likely to undergo surgery. Patients with CA19-9 > 47.9U/mL (OR=0.24[0.08–0.71], p=0.010) were less likely to receive surgery.

There was no significant difference in grade 2+ acute toxicity based on pain, fatigue, nausea, or anorexia at the start of treatment or maximum during treatment when comparing groups (Table 3). Patients had a mean 3.91lb weight loss over the course of the treatment with 3.79lb vs 4.00lb (p=0.78) weight loss for those with a VB vs NB respectively. There were 10 late toxicities in the NB group compared with 2 in the VB group (p=0.99). All but one late toxicity were upper gastrointestinal bleeds requiring transfusions and occurred in patients who did not undergo surgical resection. One patient in the VB group had a severe superior mesenteric vein stenosis 2 years after whipple resection without a known cause. Six of the 10 late toxicities in the NB group occurred in patients who underwent 3DCRT (19%) compared with 4 in the NB IMRT group (8%); both patients in the VB group who experienced a late toxicity underwent IMRT (9%, p=0.31). There was no statistically

significant difference in late toxicities in patients treated with 3DCRT vs IMRT (19% vs 8%, $p=0.18$).

Discussion

Surgical resection continues to offer the only potential for cure in patients with pancreatic adenocarcinoma and it has been associated with significantly increased survival both in our series and historically with an approximate doubling of median survival times.[14,15] Our study shows a statistical trend in increased rate of surgical resection and survival in patients who received a vessel boost. A VB was not associated with a significant increase in acute toxicity or any radiation associated late side effects and appears to be safe and well tolerated.

Radiation dose escalation has been shown in multiple cancer disease sites to be associated with an improvement in local control and/or survival[16,17] with recent population based study showing decreased survival in patients receiving $<40\text{Gy}$ compared with those receiving 55Gy in unresectable PAC.[18] The amount of dose escalation that can be achieved is largely limited by the normal tissue tolerance of nearby structures. This can be addressed in part by advanced techniques such as IMRT along with daily image guidance to conform radiation dose around dose-limiting normal structures with studies examining 3DCRT versus IMRT showing lower dose to normal critical structures utilizing IMRT.[19] In patients treated with our methodology, the volume of tumor and tissue receiving the boost radiation is small compared to the tumor volume. (Figure 1) This may account for the similar acute toxicity in the VB vs NB groups. Additionally, late toxicity was similar in the two radiation dose groups for patients who received IMRT (NB 8% vs VB 9%). We found a suggestion of decreased late toxicity with IMRT, although no differences approached statistical significance due to small number of observations.

Multiple single institutional series have examined the utilization of stereotactic body radiotherapy (SBRT) in the setting of BR and LA patients with promising pathologic response and survival rates.[20,21] Chuong et al demonstrated a 56% resectability rate in BRPAC patients after treatment with neoadjuvant chemotherapy followed by SBRT to the tumor with improved survival for patients undergoing surgery. Rajagopalan et al showed an 11% resection rate for LA patients treated with neoadjuvant chemotherapy and SBRT; patients undergoing resection had an impressive median survival of 47 months.[20] With the increase in tumor resectability and patient survival, concerns for late toxicity become more pronounced. In these SBRT series, the rate of late grade 3 toxicity ranged from 0 to 33% with perforations and bleeding being the most common late side effects.[20–22] We saw no increase in toxicity with increased radiation dose. These findings suggest that increasing radiation dose using standard fractionation may be a safer way to increase dose compared with a higher dose per fraction.

We also saw a significant increase in surgical resection rate in patients who had a lower presenting CA19-9. In our study, patients with a presenting CA19-9 below 47.9U/mL were more likely to undergo resection, which in turn significantly improved OS. This is in line with multiple studies that have shown the prognostic value of CA19-9 both in the

neoadjuvant and adjuvant setting.[23–25] CA19-9 remains an important prognostic factor in the management of patients with PAC.

Potential limitations of the study include its small retrospective, single institutional experience that is subject to selection bias with patients treated over a 7-year period. Due to the small sample of patients, it is possible that the absolute differences noted in rate of surgical resection and overall survival are purely due to chance and selection, especially given the borderline significant p-values. However, we have attempted to account for these differences in the regression model by including treatment time frame and percentage of BR and LA patients in each group. We acknowledge that despite our best efforts, all possible effects of selection bias cannot be eliminated. Additionally, patients received varying amounts of additional chemotherapy based on patient characteristics and at the discretion of the treating medical oncologist. Neoadjuvant chemotherapy has been shown to increase the rate of resectability compared with chemoradiation alone.[14] In our cohort, there was no significant difference in receipt of neoadjuvant chemotherapy in the VB vs NB groups.

In our retrospective series, dose escalation was associated with an improved surgical resection rate in BR and LAPAC patients treated with NACRT with no significant increases in toxicity, although this improvement was not statistically significant. Definitive confirmation of this finding would require prospective study.

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Figure 1.

CT scan of borderline resectable pancreatic adenocarcinoma. Superior CT image demonstrates abutment of the SMV and SMA. Inferior scan of the same patient and slice shows radiation target delineation with the purple showing gross tumor and orange showing the no boost PTV. Abbreviations: SMV, superior mesenteric vein; SMA, superior mesenteric artery; VB, vessel boost; PTV, planning target volume.

Figure 2.
Overall survival for patients who received a vessel boost vs no boost

Figure 3.
Overall survival for patients who underwent surgery vs no surgery

Table 1

Patient, Tumor, and Treatment Characteristics

	No boost(n=81)	Boost(n=23)	p-value
Dose (median [range])	50.4[48.6–52.2]	56 [54–64]	
Patient Age (median [range])	69[45–90]	69[38–81]	0.480
Patient Gender			0.990
Female	38(47%)	11(49%)	
Male	43(53%)	12(51%)	
Location			0.570
Head	65(80%)	17(74%)	
Tail/Body	16(20%)	6(26%)	
Borderline or Locally Advanced			0.570
Borderline	61(75%)	19(83%)	
Locally Advanced	20(25%)	4(17%)	
Technique			0.002
3D-Conformal	31(38%)	1(4%)	
IMRT (Intensity Modulated Radiation)	50(62%)	22(96%)	
Date of Treatment			<0.001
2006–2009	50(62%)	4(17%)	
2010–2013	31(38%)	19(83%)	
Primary Reason for no Surgery			
Distant Metastasis	31(55%)	9(75%)	0.230
Local Failure	17(30%)	1(8%)	
Poor Performance Status	4(7%)	2(17%)	
Patient Refusal/unknown	4(7%)	0	
Presenting CA 19-9			
Median (range)	322(0.1–38500)	488(2–11700)	0.450

Table 2

Multivariable Analysis for Predictors of Surgical Resection

	OR (95%CI)	p-value
No Boost vs Vessel Boost	2.77(0.89–8.57)	0.077
Year of Treatment (2006–09 vs 2010–13)	0.89(0.34–2.32)	0.816
Age <70 vs 70	0.42(0.16–1.05)	0.064
Borderline vs Locally Advanced	0.32(0.09–1.09)	0.068
Male vs Female	1.28(0.52–3.14)	0.589
CA19-9 <47.9u/mL vs 47.9U/mL	0.24(0.08–0.71)	0.010

Abbreviations: OR, odds ratio; CI, confidence interval

Table 3

CTCAE v2.0 Grade 2+ Acute Toxicity

	No Boost(n=32)	Vessel Boost(n=17)	p-value
Fatigue			
Start of treatment	9(28%)	4(24%)	0.53
Maximum during treatment	24(75%)	19(90%)	0.28
Nausea			
Start of treatment	0(0%)	0(0%)	0.99
Maximum during treatment	5(16%)	4(24%)	0.99
Anorexia			
Start of treatment	17(53%)	13(52%)	0.99
Maximum during treatment	25(78%)	17(81%)	0.99
Maximum Pain, mean(range)	3.6(0–10)	3.4(0–9)	0.59