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Neoadjuvant Chemoradiation with IMRT in Resectable and Borderline Resectable Pancreatic Cancer

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Abstract

Purpose—Neoadjuvant chemoradiation is an alternative to the surgery-first approach for resectable pancreatic cancer (PDA) and represents the standard of care for borderline resectable (BLR).

Materials and Methods—All patients with resectable and BLR PDA treated with neoadjuvant chemoradiation using IMRT between 1/2009–11/2011 were reviewed. Patients were treated to a customized CTV which included the primary mass and regional vessels.

Results—Neoadjuvant chemoradiation was completed in 69 patients (39 BLR and 30 resectable). Induction chemotherapy was used in 32 (82%) of the 39 patients with BLR disease prior to chemoXRT. All resectable patients were treated with chemoXRT alone. Following neoadjuvant treatment, 48(70%) of the 69 patients underwent successful pancreatic resection with 47 (98%) being margin negative (RO). In 30 of the BLR patients who had arterial abutment or SMV occlusion, 19 (63%) were surgically resected and all had RO resections. The cumulative incidence of local failure at 1 and 2 years was 2% (95% CI 0–6%) and 9% (95% CI 0.6–17%) respectively. The median overall survival for all patients, patients undergoing resection, and patients without resection were 20 months, 26 months, and 11 months respectively. Sixteen (23%) of the 69 patients are alive without disease with a median follow-up of 47 months (36–60).

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Conclusions—Neoadjuvant chemoXRT can facilitate a margin negative resection in patients with localized PCa.

Keywords

IMRT; Pancreatic cancer; Borderline resectable; Neoadjuvant chemoradiation

INTRODUCTION

Neoadjuvant treatment sequencing for PDA offers several potential advantages over adjuvant therapy including: (1) early initiation of systemic therapy in all patients in contrast to a surgery-first strategy in which up to 50% of patients fail to receive adjuvant therapy, (2) identification of patients with early disease progression at the time of post-treatment, preoperative restaging who therefore require systemic (not local) therapy, (3) downstaging of nodal metastases and increased rates of margin negative resection[1–3]. The application of intensity modulated radiation therapy (IMRT) is well suited for the treatment of PDA by allowing coverage of customized, high-risk volumes while minimizing normal tissue dose. The primary objective of this study was to evaluate the acute toxicity, clinical outcomes, and patterns of failure in resectable and BLR PDA patients treated with neoadjuvant chemoradiation utilizing an IMRT approach.

MATERIALS AND METHODS

We completed an IRB approved retrospective review of all patients with resectable and BLR PDA treated with neoadjuvant radiation therapy. Patients who started treatment between 1/1/2009–11/1/2011 were included. Staging consisted of CT of the abdomen and pelvis and monitoring of serum Ca19-9 levels at diagnosis and at each restaging. Diagnostic laparoscopy was performed at the time of pancreatotomy. Patients were reviewed in a multidisciplinary tumor board and were classified as resectable or BLR by institutional CT-criteria as summarized in table 1. Our institutional definitions of resectable and BLR PDA differ slightly from the National Comprehensive Cancer Network definitions in that resectable tumors may have less than 50% narrowing of the superior mesenteric vein or portal vein (SMV/PV) and BLR status also included patients with findings suspicious but not diagnostic for metastatic disease.

The treatment algorithms for patients with resectable and BLR disease were based on the previous publication of Evans, et al.[1] Resectable patients were treated with chemoradiation followed by restaging to include CT imaging prior to surgical resection. The majority of patients with BLR disease were treated with induction chemotherapy prior to chemoradiation. Induction chemotherapy consisted of four cycles of one of the following regimens: gemcitabine (1000 mg/m²), gemcitabine/cisplatin (gemcitabine 750 mg/m², cisplatin 30 mg/m²), gemcitabine/erlotinib (gemcitabine 1000 mg/m², erlotinib 100mg) or FOLFIRINOX (Bolus 5-FU 400 mg/m², leucovorin 400 mg/m², oxaliplatin 85 mg/m², irinotecan 180 mg/m²). In the absence of disease progression at the time of post-treatment, preoperative restaging, pancreatotomies were performed. Adjuvant chemotherapy following neoadjuvant treatment and surgery was considered based on the postoperative

performance status of the patient, the histologic evidence of response/lack of response based on the surgical pathology report, and the opinion of our multidisciplinary working group.

Radiation Treatment

Patients received concurrent gemcitabine- (400mg/m² weekly x6) or capecitabine- (825 mg/m² twice daily) based chemoradiation. The prescription dose was 50.4 Gy at 1.8 Gy per fraction using IMRT. For head and uncinate lesions, the CTV included the pancreatic head, SMA origin, SMA and SMV vessels adjacent to the pancreatic head, enlarged lymph nodes, +/- the celiac axis with a 1 cm expansion to PTV. For lesions in the tail, the CTV included the primary mass and celiac axis with an expansion. All patients were treated with daily image guidance (MV or KV CT) and respiratory gating was used if superior-inferior motion was > 1.0 cm. Patients were treated at the 40–60% respiratory phase. Using a 4D-CT, an Internal Target Volume of the primary mass was created if motion was < 1.0 cm using the 3D, 0, and 50% respiratory phases of respiration. Detailed target volumes for a representative case are displayed in figure 1 and the supplemental materials. IMRT constraints used in optimization are contained in the supplemental materials.

Pathologic Assessment of the Surgical Specimen

Standardized histologic evaluation of the specimen was performed as described by the American Joint Committee on Cancer. The SMA margin was defined as the margin along the proximal superior mesenteric artery. This area was identified and was considered positive if the tumor cells extended microscopically to the inked margin. Frozen sections are performed on the pancreatic and bile duct margins.

Follow-up and Statistical Analysis

Toxicities were graded according to the Common Terminology Criteria for Adverse Events (v4). Following completion of all treatment, patients were followed with cross-sectional imaging studies (CT or MRI) at 3–4 month intervals. Disease recurrence was based on review of the electronic medical record and was based on serial cross-sectional imaging studies. A new low density mass on CT or MRI consistent with recurrent local, regional, or metastatic disease was considered as such and tumor biopsy was rarely performed. Sites of first failure were classified as local (within the PTV) or distant. The local failure free interval was defined as the time from diagnosis to local failure or last documented normal cross-sectional imaging study of the abdomen (CT/MRI). Treatment plans were reviewed in patients with local-regional recurrence to analyze the PTV relationship to the site of failure. The cumulative incidence of local failure was assessed with the competing risk of death using a competing risk model. Overall survival was calculated from the date of histologic diagnosis to death. Disease-free survival was calculated from the date of diagnosis to date of first recurrence with sites of first recurrence defined as above. The Kaplan-Meier method was used to estimate overall survival for the population. Baseline demographic and clinical characteristics of the patients and the pathological factors were summarized using descriptive statistics and compared with the use of t-test or chi-square test, using STATA v11.

RESULTS

Treatment

The demographic and treatment characteristics of all 69 patients are outlined in table 2. We included only patients who received radiation therapy (neoadjuvant intent) at our institution. Of the 69 patients, 30 (43%) had resectable disease and 39 (57%) had BLR disease. The median baseline CA 19-9 was lower in resectable than borderline resectable patients (95 vs. 355, $p = 0.004$). Of the 39 patients with BLR disease, 30 (85%) had radiographic evidence of arterial abutment or SMV occlusion and fifteen (38%) had findings suspicious (but not diagnostic) for metastatic disease. The treatment sequencing by clinical stage is summarized in figure 2.

BLR patients

Prior to 2010 the common treatment algorithm for BLR PDA was chemoradiation alone and therefore, seven (18%) of the 39 patients received just chemoradiation prior to planned surgery. Of these seven patients, five (71%) developed metastatic disease progression at the time of restaging which precluded surgery. Of the two patients who underwent surgery, one had metastatic disease on laparoscopy and the other patient was successfully resected. After 2010, the treatment algorithm for BLR PDA evolved to include induction chemotherapy followed by chemoradiation. Prior to chemoradiation, 32 (82%) patients with BLR disease received induction chemotherapy; 27 (84%) patients received gemcitabine-based chemoradiation, and five (16%) patients received capecitabine-based chemoradiation. Following chemoradiation, three (9%) of the 32 patients were found to have metastatic disease at the time of restaging. Of the 29 patients who underwent surgery, seven (24%) were found to have metastatic disease and 22 (76%) underwent pancreatic resection.

Resectable patients

All patients with resectable disease received neoadjuvant gemcitabine-based chemoradiation ($n = 30$). Three patients were found to have disease progression at restaging prior to surgery. Of the 27 patients who underwent surgery, two (7%) patients were found to have metastatic disease and the remaining 25 (93%) patients were resected. Overall, 48 (70%) of the 69 patients completed all therapy to include successful resection of the pancreatic tumor (25 [83%] of 30 resectable and 23 [59%] of 39 BLR).

Toxicity

The median PTV volume for all patients was 296 cc (64–808 cc). The median PTV volumes for resectable and borderline resectable patients were 307 cc (153–808 cc) and 295 cc (64–516).

During chemoradiation, 13 (19%; 6 with resectable and 7 with BLR) of the 69 patients required hospital admission. Reasons for admission included nausea/dehydration ($n = 5$), cholangitis/cholecystitis ($n = 2$), lower gastrointestinal bleeding ($n = 1$), gastrointestinal bleeding secondary to tumor infiltration ($n = 1$), febrile neutropenia ($n = 2$), gemcitabine induced pneumonitis ($n = 1$), and subclavian thrombosis ($n = 1$). Grade II and III gastrointestinal toxicity occurred in 35% ($n = 24$) and 16% ($n = 11$) of patients respectively.

There were no Grade IV or V gastrointestinal toxicities. A treatment break was required in 10% of patients during chemoradiation, however, the prescribed radiation dose was delivered in 67 (97%) of the 69 patients. There were no deaths during neoadjuvant therapy.

Surgical outcomes and histopathology

Of the 69 patients, 58 (84%) underwent surgery. Ten (17%) of the 58 patients had metastatic disease at the time of diagnostic laparoscopy and were not resected. Curative intent surgery was performed in the remaining 48 (83%): 40 pancreaticoduodenectomy, 2 total pancreatectomy, and 6 distal pancreatectomy and splenectomy. Major complications occurred in 3 (6%) of 48 patients, including chylous ascites (n =1), delayed gastric emptying (n = 2) and one perioperative death due to a cardiac arrhythmia. There were no clinically significant pancreatic anastomotic leaks that required percutaneous drainage or reoperation.

PDA was confirmed in all 48 patients who underwent surgery. Surgical margins were grossly negative in all patients and a gross complete resection of the tumor was confirmed in all operative dictations. A microscopically positive margin was found in one (2%) of 48 patients who underwent successful pancreatectomy (25 resectable and 23 BLR). The distance from the tumor to the inked SMA margin was assessable in 43 (89%) of the 48 patients; the median distance to the SMA margin was 4 mm (range 1–14). The hepatic duct and pancreatic transection margins were negative for malignancy in all resected patients. Metastatic disease was found in regional lymph nodes in 14 (29%) of the 48 resected patients and the median number of lymph nodes removed was 22 (range 14–43). Of the 14 patients with positive nodes, the median number of positive nodes was 2.5 (mean, 5 nodes).

Survival

At last follow-up, 51 (74%) of the 69 patients have died, including 21 (100%) of the 21 patients who did not undergo resection and 30 (62%) of the 48 patients who underwent successful pancreatectomy. Of these later 48 patients, 18 (37%) are alive. This includes 16 (23%) of the 69 patients alive without disease with a median follow-up of 47 months (36–60). The median overall survival for the entire cohort was 20.4 months from the date of diagnosis. Comparison of the survival curves for patients who did and did not complete all therapy is shown in figure 3. The median overall survival for patients who did not undergo surgical resection was 11.2 months. In contrast, the median overall survival was 26.4 months patients that completed all therapy. The overall survival at one and two-year for those who completed all intended preoperative therapy to include pancreatic resection was 90% and 60%, respectively.

Thirty-two patients developed disease recurrence, at a median progression free survival of 11.5 months (14.2 months for patients with resectable disease and 9.9 months for patient with BLR disease). Secondary sites of disease progression (prior to death) were not available in all patients who recurred. Two patients who lived out of state were lost to follow-up after completion of therapy. Two patients died without disease: one due to a bowel obstruction and one from a perioperative cardiac arrest. The sites of first recurrence included: liver (n =10, 36%), lung (n=6, 21%), liver and peritoneal (n=1, 3%), liver and lung (n = 1, 3%), bone (n =4, 14%), peritoneal (n=2, 7%) local only (n=1, 3%), local and distant

site (n=4, 14%). Local recurrence was a component of first recurrence in five patients; one additional patient was found to have a local recurrence which occurred during on-going follow-up. In total, six patients developed radiographic evidence consistent with local recurrence at a median of 17 months (6–30 months) from the date of diagnosis and 13 months (3–25 months) following surgery. Local failures occurred in the resection bed in four patients, at the SMV/PV confluence in one patient, and at the SMA margin in one patient. Adjusting for the competing risk of death, the cumulative incidence of local failure at 1 and 2 years was 2% (95% CI 0–6%) and 9% (95% CI 0.6–17%). All local failures occurred within the PTV with no marginal recurrences.

DISCUSSION

Several phase II trials have evaluated neoadjuvant chemoradiation for resectable and BLR PDA. A summary of selected trials and retrospective series are outlined in table 3. The radiation dose, fractionation, and volume have varied in these trials. All treatment was delivered using 3D-conformal techniques. In two prospective trials for patients with resectable PDA, radiation treatment was delivered using 30 Gy (3 Gy/fx) with concurrent gemcitabine (400 mg/m²)[1,3]. Other protocols have used more protracted courses of radiation to 50.4 Gy (1.8 Gy/fx) or 36 Gy (2.4 Gy/fx)[4]. Radiation was delivered to the primary tumor and regional lymph nodes with a 2-cm block margin[1,3] or to the primary tumor plus a margin[4,5]. In our series, IMRT was used for all patients incorporating a customized high-risk target volume as an alternative to treating the gross tumor with a margin. For pancreatic head tumors, the clinical target volumes included the pancreatic head, any enlarged peripancreatic lymph nodes, the SMA origin, the SMA and SMV along the medial aspect of the pancreatic head and uncinate process, with or without the celiac axis.

IMRT may provide several advantages for treatment of PDA in the neoadjuvant setting. Several dosimetric studies have shown a reduction of dose to the kidneys, stomach, liver, and small bowel with use of IMRT compared to traditional 3D-conformal fields[6–9]. In the postoperative adjuvant setting, IMRT was associated with minimal treatment breaks and a reduction in the rate of grade 3–4 nausea and diarrhea compared to 3D-Conformal treatment[10]. In our series, neoadjuvant therapy was well tolerated with use of IMRT. The prescribed dose was completed in 97% of patients, with 19% requiring hospital admission. Importantly, a reduction in normal tissue dose and volume may increase the tolerance of concurrent chemoradiation and allow for more intensive regimens. IMRT may be even more advantageous for radiation dose escalation and dose painting techniques in patients with unresectable disease. The use of 4D-CT simulation was applied for all patients in the current series. Several studies have shown that pancreatic tumors are susceptible to respiratory motion[11–13]. Accounting for this motion may further improve treatment delivery.

An incidence of positive resection margins ranging from 15–35% has been reported in clinical trials where a surgery first approach was used in patients with resectable disease[14–16]. In two of the largest phase II trials that utilized neoadjuvant chemoradiation in patients with resectable disease, positive margins were observed in 4% and 6% of patients[1,3]. The current report also highlights the potential benefits of neoadjuvant chemoradiation on

margin status. In the 48 patients who underwent successful pancreatectomy, 47 achieved a margin negative resection.

A neoadjuvant approach is currently recommended for all patients with BLR disease[17]. One of the early reports from M. D. Anderson Cancer Center described 160 patients with BLR disease. Following neoadjuvant treatment, 66 (41%) of 160 patients underwent surgical resection and only 4 (6%) of the 66 resected patients had positive margins[2]. In the present series, 30 patients had evidence of arterial abutment and/or encasement of the superior mesenteric vein; 19 (63%) underwent surgery, and all had a margin negative resection. Neoadjuvant therapy using IMRT as delivered in this report was successful in sterilizing the periphery of the tumor to facilitate a complete microscopic resection of the primary tumor. To the extent that surgery is necessary for long-term survival in PDA, induction therapy as reported herein may increase the number of patients who receive a margin negative resection.

Local recurrence following resection for PDA is often reported as a component of the first site of failure. Because survival is often short after first recurrence, subsequent sites of disease are usually not reported. In the CONKO-001 trial, patients were randomized to receive adjuvant gemcitabine or observation without radiation therapy following surgical resection for resectable pancreatic adenocarcinoma. Local recurrence occurred as a component of first failure in 34% of patients treated with gemcitabine and in 41% of patients who did not receive adjuvant therapy[15]. In RTOG 9704, local recurrence was a component of first failure in 25–30% of patients[14]. In contrast, local failure rates in neoadjuvant series have ranged from 11–25%, understanding that this is usually a diagnosis made on serial cross-sectional imaging and the more rigorous the follow-up and more accurate the imaging, the more frequently one may diagnose local recurrence [1,3].

Further, as systemic therapies improve, local recurrence may carry even greater significance for the length and quality of patient survival. Local recurrence alone can also lead to disease-specific mortality as demonstrated in a rapid autopsy series of 76 patients in whom locally destructive disease was the cause of death in 30% of patients. At autopsy, 20 (91%) of 22 patients who initially presented with localized stage I/II disease had gross evidence of local recurrence[18]. In the current report, local failure was assessed in a cumulative incidence model with the competing risk of death. The cumulative incidence of local failure at 1 and 2 years was 2% and 9% respectively suggesting durable local control with this treatment approach. All local failures occurred within the initial PTV with no marginal recurrence suggesting that a conformal, IMRT technique maximizes local control relative to historically treated patients and is associated with reduced toxicity.

This study is subject to the inherent limitation in a retrospective review. Additionally, the cohort of patients with borderline resectable pancreatic cancer is limited to patients who received chemoradiation and does not include patients who were found to have metastatic disease after induction chemotherapy.

CONCLUSION

Neoadjuvant chemoradiation can facilitate a margin negative resection in patients with resectable and BLR PDA. IMRT allows for customized treatment of high-risk volumes to maximize local disease control and delivers a decreased dose to organs at risk. The importance of durable local control measures may increase as systemic therapy improves and prolongs survival in patients with localized PDA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Representative target volumes for preoperative treatment of resectable adenocarcinoma of the pancreatic head
(GTV-gross tumor volume, SMV-Superior Mesenteric Vein, SMA CTV- Superior mesenteric artery Clinical Target Volume, Celiac CTV- Celiac Artery Clinical Target Volume, PTV- Planning Target Volume)

Figure 2.
Treatment Received by Clinical Stage

Figure 3.
Kaplan Meier Survival Estimates by Resection Status

Table 1

Definition of Resectability Used by the Medical College of Wisconsin Multidisciplinary Pancreatic Cancer Working Group

Resectable	
Tumor-artery relationship:	No radiographic evidence of arterial abutment (celiac, SMA, or hepatic artery)
Tumor-vein relationship:	Tumor-induced narrowing < 50% of SMV, PV, or SMV-PV
BLR	
Artery:	Tumor abutment (< 180°) of SMA or celiac artery. Tumor abutment or short segment encasement (> 180°) of the hepatic artery
Vein:	Tumor induced narrowing of > 50% of SMV, PV, or SMV-PV confluence. Short segment occlusion of SMV, PV, SMV-PV with suitable PV (above) and SMV (below) to allow for safe vascular reconstruction.
Extrapancreatic disease:	CT scan findings suspicious, but not diagnostic of, metastatic disease (for example, small indeterminate liver lesions which are too small to characterize)
Marginal Performance status	
Locally Advanced	
Artery:	Tumor encasement (> 180°) of SMA or celiac artery
Vein:	Occlusion of SMV, PV, or SMV-PV without suitable vessels above and below the tumor to allow for reconstruction (no distal or proximal target for vascular reconstruction)
Extrapancreatic disease:	No evidence of peritoneal, hepatic, extra-abdominal metastases
Metastatic	
Evidence of peritoneal or distant metastases	

Table 2**Patient Demographics and Treatment**

	Resectable n = 30 (%)	BLR n = 39 (%)	p-value
Median Age (yr), (range)	68 (37–82)	64 (45–87)	0.40
Male gender	13 (43)	18 (46)	0.46
Site			
Head	28	34	
Body	2	2	
Tail	0	3	
Median Ca19-9 at dx* (mg/dL), (range)	95 (37–632)	356 (41–6242)	0.004
Type of BLR Disease			(%)
Arterial Abutment or SMV Occlusion	-	30 (87)	
Findings Susp for Metastatic Disease	-	15 (38)	
Marginal Performance Status Only	-	1 (3)	
Induction Chemotherapy	-	32 (82)	
Gemcitabine/Cisplatin	-	17 (44)	
FOLFIRINOX	-	11 (28)	
FOLFOX	-	1 (3)	
Gemcitabine/Capecitabine	-	1 (3)	
Gemcitabine/Erlotinib	-	1 (3)	
Gemcitabine	-	1 (3)	
Received Chemoradiation	30	39	
Median Dose (Gy), (range)	50.4 (45–50.4)		-

* Bilirubin normal at the time of measurement. Excludes Ca19-9 non-producers.

Outcomes for selected neoadjuvant trials of resectable and BLR pancreatic adenocarcinoma.

Table 3

Author	Phase	N	Induction Chemo	Concur Chemo	BLR (%)	Resected (% all patients)	Positive Margin	Median OS Resected Patients (mo)
Evans ¹	II	86	None	Gem	0	64 (74%)	6%	34
Varadhachary ³	II	90	Gem/Cis	Gem	0	52 (66%)	4%	31
Talamonti ⁴	II	20	Gem	Gem	30%	17 (87%)	6%	26
Landry ⁵	II	21	None vs Gem/Cis/5-Fu	Gem vs 5-Fu	100%	5 (24%)	40%	26.3
Katz ²	NA	160	Variable	Variable	100%	66 (41%)	6%	40
Current report	NA	69	FOLFIRNOX or Gem based	Gem or Cape	57%	48 (62%)	2%	26