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Predictors of outcome in patients receiving stereotactic body radiation therapy for borderline resectable and locally advanced pancreatic cancers

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ABSTRACT

Aims: To evaluate the outcomes in borderline resectable (BRPC) and locally advanced pancreatic cancer (LAPC) receiving neoadjuvant chemotherapy (NACT) and stereotactic body radiotherapy (SBRT) followed by surgery when feasible.

Methods: Consecutive patients of BRPC and LAPC treated from May 2015 to December 2019 were included. All underwent NACT with FOLFIRINOX/Gem Nabpacli 4–6 cycles, followed by SBRT with differential planning target volume (PTV) dose of 36–46 Gy over 5–6 fractions. Local progression-free survival (LPFS), distant metastasis free survival (DMFS), overall survival (OS) were estimated.

Results: Eighty-nine (50 BRPC and 39 LAPC) patients with a median follow-up of 26.0 months were identified. Of the 33 (37%) patients surgically explored and 19 (47.5%) BRPC and 4 (10.2%) LAPC patients underwent surgery, 21 (91.6%) had R0 resection. The median OS and disease free survival (DFS) of patients who underwent surgery was 28.4 ± 3.4 and 23 ± 5 months, respectively. The patients who did not undergo surgery the median OS and LPFS were 19 ± 1.4 and 12 ± 1 months, respectively. Patients who underwent surgery in BRPC cohort had significantly better DFS (23 vs 12 months, p=0.001) and OS (28 vs 19 months, p=0.035). On multivariate analysis, Eastern Cooperative Oncology Group (ECOG) < 2 [hazard ratio (HR): 2.77 (1.2–6.2; 0.014)], head location [3.7 (1.44–9.6; 0.007)], and radiological response post-NACT-SBRT [4.38 (1.08–17.7; 0.039)] were significant predictors of outcome in both the cohorts. No grade ≥3 late radiotherapy (RT)-related toxicities were seen.

Conclusion: Stereotactic body radiotherapy is safe and effective for local control and aids in improving the outcomes in pancreatic cancers.

Keywords: Neoadjuvant chemoradiation, Pancreatic cancer, Stereotactic body radiotherapy

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INTRODUCTION

Pancreatic cancer is a highly lethal disease with a 5-year overall survival (OAS) of 6% approximately [1]. Even with the advancements in multimodality treatments, the incidence of pancreatic cancer still approximates its mortality rate [2]. Surgical resection is curative but unfortunately less than 20% are detected in the operable stage and of these, 30–50% are found to be unresectable intraoperatively. In resectable cases, 5-year OS rates only reach 25–30% at best, despite the advances in surgery [3]. Resection margin (RM) status is a key prognostic marker influencing outcome following a pancreatoduodenectomy (PD) resection [4]. Borderline resectable pancreatic cancers (BRPC) and locally advanced pancreatic cancers (LAPC) are given neoadjuvant chemotherapy with either FOLFIRINOX or Nab Pacli regimen followed by surgical assessment [5].

The role of radiotherapy (RT) is debatable in improving R0 resection rates and affecting survival. In the PREOPANC trial neoadjuvant RT resulted in improved R0 resection rates and DFS compared to upfront surgery [6].

Stereotactic body radiotherapy is high precision radiotherapy where radiobiologically very high and efficient doses (>6.6 Gy/fraction) can be delivered. Stereotactic body radiotherapy can be given over 5–10 days and the biologically equivalent dose appears to be higher than conventional fractionation schedules which are given over 5–6 weeks thereby leading to better integration of chemotherapy [7]. Though no studies have compared the conventionally fractionated and SBRT, a recent meta-analysis suggested that SBRT was associated with better 2-year OS with reduced acute and late toxicity. Currently, the role of SBRT is being tried mainly in locally advanced unresectable and borderline resectable pancreatic cancers.

MATERIALS AND METHODS

Initial staging and patients

After institutional review board approval, all consecutive patients diagnosed with pancreatic adenocarcinoma from May 2015 to December 2019 who received at least one dose of induction chemotherapy and SBRT were analyzed. Patients underwent physical examination, tumor markers including CA19-9, carcinoembryonic antigen (CEA), serum albumin, thin slice pancreatic protocol (triphasic) computed tomography (CT) scan, endoscopic ultrasound (EUS), pathology review, and were presented in the multidisciplinary gastrointestinal joint clinic.

Neoadjuvant chemotherapy

All patients received induction chemotherapy using four two weekly cycles of FOLFIRINOX as oxaliplatin 85 mg/m^2, folinic acid 400 mg/m^2, irinotecan 180 mg/m^2, fluorouracil 400 mg/m^2 intravenous (IV) bolus Day 1, and fluorouracil 1200 mg/m^2/day IV continuous 46-hour infusion on Days 1 and 2. Few patients also received Gemcitabine in three four-week cycles at 1000 mg/m^2 IV on Days 1, 8, and 15 with the addition of nab-paclitaxel 125 mg/m^2 IV.

Patients undergoing dose reductions and cycle interruption were considered as per protocol.

Radiation planning and treatment

Patients had undergone placement of three gold fiducial markers with the help of EUS guidance during neoadjuvant chemotherapy.

Patients were immobilized in supine position with the help of a body fix [8]. For few patients thermoplastic mold was also used. Oral contrast (diluted gastrografin) was given to them (20 mL) 15 minutes before taking the planning scan. Respiratory tumor motion management was done with Varian real-time positioning using breath-hold technique either inspiratory or expiratory whichever was considered anatomically feasible. Contrast-enhanced (CE) planning CT scan of the area interest was performed at 2.5 mm slice thickness.

Stereotactic body radiotherapy began at a median of two weeks after administration of the last chemotherapy. Five to six fractions were delivered at alternate days over 10–14 days with Varian Truebeam linear accelerator. Differential dose painting was done where the gross tumor received up to 36–40 Gy and there was an escalation of dose to about 46–50 Gy to the tumor vessel interface. The dose was limited for duodenum, small bowel, and stomach V33, V35, and V36 <1 cc, for combined kidneys V12<75% and for spinal cord max dose up to 20 Gy.

Patients were kept fasting for at least 4 hours and pre-medications (Antiemetics & Antacids) were given to the patient 45 minutes before the treatment. Treatment was done with daily image guidance using CBCT (Cone Beam Computed Tomography) before each treatment fraction. The daily CT image was fused with a planning CT scan to note the setup errors by which the treatment was delivered.

Post-SBRT patients continued to receive two to four cycles of chemotherapy and were reassessed for surgery with triphasic CECT in a multidisciplinary joint clinic. In the absence of radiological progression patients were referred for surgery.

Surgery and pathology

Surgery was usually performed at a median of six weeks post-SBRT. Patients with pancreatic head tumors underwent pancreaticoduodenectomy (Whipple procedure) and with pancreatic body or tail tumors were removed by distal pancreatectomy and splenectomy (Appleby procedure). Whenever required necessary repair or resection of the superior mesenteric vein (SMV),

portal vein (PV), superior mesenteric artery (SMA), or coeliac trunk was done along with anastomosis.

College of American Pathology protocols was used which included tumor response grade. Margin negative was defined as no tumor cells at the inked margin of the specimen. The margins that were evaluated were the proximal cut, distal cut, common bile duct, pancreatic neck cut, anterior and posterior pancreatic surface, medial/SMV surface, and retroperitoneal SMA surface. The nodal evaluation was also done with anterior and posterior pancreaticoduodenal nodes, superior, and inferior pancreatic nodes, nodes along with the lesser and the greater curvature, common hepatic and periportal nodes.

Follow-up and analysis

Patients were evaluated every three months for the first two years followed by six months till five years. They were evaluated for radiation-related acute and late toxicity. Acute side effects were defined as those occurring within 90 days of radiation treatment which were graded as per the Radiation Therapy Oncology Group (RTOG) criteria. Late side effects were graded according to version 5.0 of the Common Terminology Criteria for Adverse Events.

Statistical analysis was performed with SPSS version 23 software (SPSS Inc. Chicago, IL). Demographic, clinical, and disease-related variable was presented as frequency (percentage), and mean (SD), median appropriate. The overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan–Meier method and comparison was done using the log-rank test. Overall survival and PFS were estimated from the date of diagnosis to date of death from any cause and development of progression (local, regional, distant, or death) whichever occurred earlier respectively. The quantitative variables were compared between BRPC and LAPC using the student *t*-test or Mann–Whitney *U* test depending on the normality. The quantitative variables were compared pre- and post-treatment using paired *t*-test or Wilcoxon signed-rank test depending on the normality. A p-value of < 0.05 was considered statistically significant.

RESULTS

A total of 89 consecutive patients were identified of which 50 were BRPC and 39 LAPC. All patients received NACT followed by SBRT. The demographic and neoadjuvant treatment details are shown in Table 1.

Of the 89 patients, 33 (37%) patients were explored and 19 (47.5%) BRPC and 4 (10.2%) LAPC patients underwent surgery (Whipples: 21, Appleby Procedure: 2)

Table 1: Patient characteristics and neoadjuvant treatment

	Overall (n=89)	Borderline resectable (n=50)	Locally advanced (n=39)
Median age (range)	58 years (38–77)	58.5 years (38–77)	54 years (40–74)
Male:Female	1.8:1	1.8:1	1.8:1
Comorbidities			
None	38 (42.6%)	18 (36%)	20 (51%)
Diabetes and/or hypertension	51 (57.4%)	32 (64%)	19 (49%)
Presenting complaints			
Jaundice	38 (42.7%)	28 (31.5%)	10 (11.2%)
Pain	62 (69.6%)	33 (37%)	29 (32.6%)
Weight loss	43 (48.3%)	29 (32.5%)	14 (15.7%)
Tumor location			
Head	63 (70.7%)	41 (82%)	22 (56%)
Body/tail	26 (29.2%)	9 (18%)	17 (44%)
Local nodes radiologically at diagnosis	48 (54%)	25 (50%)	23 (59%)
SEMS placement needed	38 (42.7%)	26 (52%)	12 (31%)
Duodenum infiltration			
Yes	12 (13.5%)	6 (12%)	6 (15%)
NACT regimen			
FOLFIRINOX	53 (59.5%)	30 (60%)	23 (59%)
Gem NAB	36 (40.5%)	20 (40%)	16 (41%)
Median dose			
GTV	36/6	36/6	36/6
TVI	42/6	42/6	42/6

GTV: Gross tumor volume
TVI: Tumor vessel interface

of which 21 (91.6%) achieved R0 (negative margin) and 2 patients had R1 (microscopic margin positive) resection. Three patients (3.3%) refused surgery and seven patients (7.8%) were deemed medically unfit although the tumor showed radiological regression. The median OS and DFS of patients who underwent surgery was 28.4 ± 3.4 and 23 ± 5 months, respectively, and none of the patients had locoregional recurrence. The patients who did not undergo surgery the median OS and median LPFS was 19 ± 1.4 and 12 ± 1 months, respectively, as depicted in Figure 1A.

Patients who underwent surgery in BRPC cohort had significantly better DFS (23 months vs 12 months p=0.001) and OS (28 months vs 19 months p=0.035) as depicted in Figure 1B.

On univariate analysis location of tumor in BRPC patients in head of pancreas as compared to tail had better local control (LC) and survival outcomes [2.75 (1.24–6.1; 0.013)] and underwent surgery more often (21 vs 2). Among LAPC post-SBRT patients having more than 180 encasement of common hepatic artery (CHA) had higher rates of local progression [0.083 (0.008–0.849; 0.036)], distant metastasis [0.13 (0.033–0.55; 0.005)] and poor survival outcomes [0.35 (0.12–0.99; 0.04)] as compared to patients where CHA was free and SMA was having more than 180° encasement.

Patients having radiological response post-NACT and further post-SBRT as depicted in Figure 1C and D had higher resection rates, better LPFS [13.87 (1.59–120.5; 0.017)], fewer distant metastasis [9 (1.18–68.38; 0.034)] and better OS [8.14 (1.06–62.4; 0.04)]. Good performance status influenced better LPFS [4.2 (1.69–10.6; 0.002)], DMFS [5.35 (2.19–13.06; 0.0001)], and OS [3.19 (1.11–9.17; 0.03)] in both BRPC and LAPC cohorts.

Radiological tumor size and lymph nodes, presence of duodenum infiltration, venous involvement, regimen of chemotherapy used and radiotherapy dose had no correlation with the survival outcomes in both the cohorts.

On multivariate analysis, ECOG < 2 [HR: 2.77 (1.2–6.2;0.014)], head location [3.7(1.44–9.6; 0.007)] and radiological response post-NACT-SBRT [4.38 (1.08–17.7; 0.039)] were significant as shown in Table 2.

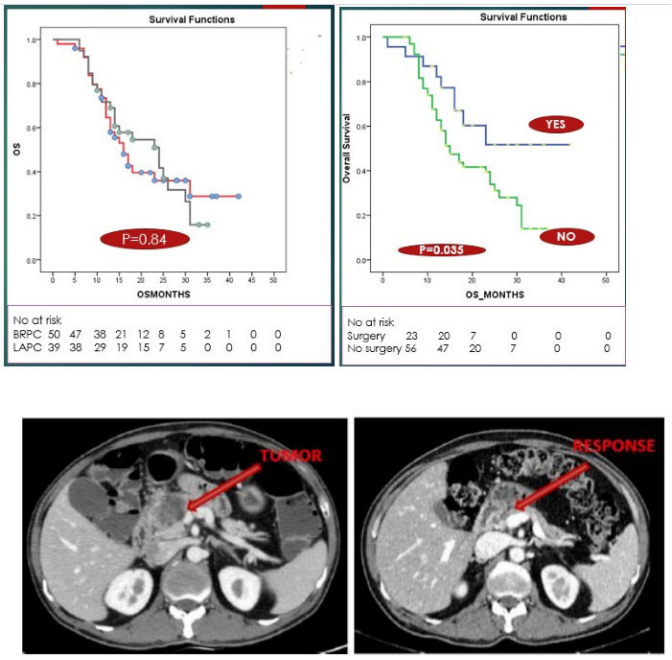

Figure 1: (A) Kaplan–Meier estimated OS for BRPC and LAPC, (B) estimated OS for patients who underwent surgery and who did not undergo surgery. (C) and (D) CECT showing radiological response post-NACT and SBRT, with involution of the hypodense and heterogeneous mass in the head of the pancreas (arrow).

Radiation toxicity

With SBRT, minimal toxicity was noted. 19 (21%) patients experienced grade 1 and 5 (5.6%) developed grade 2 skin toxicity (RTOG), 34(38.2%) reported grade 1 anorexia and fatigue. Other events of notice include one patient developing deep vein thrombosis with pulmonary thromboembolism a week post-SBRT, later developing septic shock and death. One patient on follow-up developed gastrointestinal bleeding likely related to local disease progression. Apart from this, two patients developed a second malignancy of carcinoma esophagus (middle one-third) at 24 and 29 months post-SBRT.

Surgical details and morbidity

Superior mesenteric vein and PV resection was done for 9 (39%) patients. Intraoperatively there was no adhesions or fibrosis seen at the primary tumor site. Three patients (13%) developed grade 3 CTCAE v5.0 postoperative complications (gastroparesis, blood antidiuretic hormone abnormality, and postoperative hemorrhage) while two patients (8.6%) developed grade 5 toxicity (ascites, intra-abdominal hemorrhage, and sepsis).

DISCUSSION

In literature the surgical resection rate for BRPC ranges from 25% to 60% [9]. In our study, the resection rate was 37% which is at par with published studies despite 20% of patients refusing exploration. In patients who underwent surgery, 91.3% achieved R0 resection which was similar to the published literature. There was no fibrosis or RT-related changes observed at the tumor site which could impede the surgical resection. There was an edematous plane observed between the tumor and the vessels leading to better resectability. In most published series using NACT 5–10% of patients require arterial resections, and more patients can avoid vascular resection due to downstaging with SBRT [10]. In our series, none of the patients required SMA resection despite four patients in whom SMA > 180. This indicates that SBRT-induced downstaging played a role in mitigating the requirement of vascular resection which is surgically challenging and is associated with higher surgical morbidity.

Table 2: Univariate and multivariate analysis for various factor in entire cohort

Variables	N	Univariate analysis Hazard ratio [95% Confidence Interval; p value]		Multivariate analysis Hazard ratio [95% Confidence Interval; p value]	
ECOG(0+1	93		p value		p value
v/s 2)	3				
Local progression free survival		4.2 [1.69–10.6]	0.002	2.77 [1.2–6.2]	0.014
Distant metastasis free survival		5.35 [2.19–13.06]	0.0001	3.8 [0.23–61.5]	0.34
Overall survival		3.19 [1.11–9.17]	0.03	4.9 [0.17–137.48]	0.34
Radiological tumor size	41				
(<3 vs >3)	48	1.07 [0.75–1.5]			
Local progression free survival			0.7		
Distant metastasis free survival		0.91 [0.56–1.48]	0.72		
Overall survival		1.11 [0.54–2.3]	1.11		
Location (head/body vs tail)	67				
Local progression free survival	22	2.07 [1.2–3.6]	0.01	3.7 [1.44–9.6]	0.007
Distant metastasis free survival		2.8 [0.96–8.6]	0.7	2.5 [0.27–22.7]	0.41
Overall survival		1.42 [0.28–7.1]	0.67	0.005 [0–1.39]	0.06
Locoregional lymph nodes (yes vs no)	26 63				
Local progression free survival		1.1 [0.83–1.5]	0.407		
Distant metastasis free survival		0.94 [0.59–1.5]	0.81		
Overall survival		3.22 [1.4–7.3]	0.5		
Common hepatic artery involvement (<180+free vs >180)	49 30				
Local progression free survival		0.083 [0.008–0.849]	0.036		
Distant metastasis free survival		0.13 [0.033–0.5]	0.005		
Overall survival		0.35 [0.12–0.99]	0.04		
Coeliac artery involvement (free vs encased)	49 30				
Local progression free survival		0.62 [0.106–3.65]	0.59		
Distant metastasis free survival		2.23 [0.734–6.8]	0.15		
Overall survival		1.008 [0.4–2.53]	0.98		
Superior mesenteric artery involvement (<180+absent vs >180)	36 53				
Local progression free survival		2.85 [0.96–8.5]	0.06		
Distant metastasis free survival		1.3 [0.63–2.7]	0.46		
Overall survival		2.76 [0.53–14.2]	0.22		
NACT (FOLFIRNOX vs Gem Nabpacli)	51 38				
Local progression free survival		0.67 [0.34–1.3]	0.26		
Distant metastasis free survival		0.44 [0.16–1.2]	0.11		
Overall survival		2.19 [0.82–5.8]	0.116		
Dose (42/6 vs 36/6)	64 25				
Local progression free survival		1 [0.64–1.5]	0.9		
Distant metastasis free survival		0.78 [0.43–1.42]	0.42		
Overall survival		1.2 [0.67–2.08]	0.54		
Radiological response post SBRT (PR and SD vs LP)	38 51				
Local progression free survival		13.87 [1.59–120.5]	0.017	4.38 [1.08–17.7]	0.039
Distant metastasis free survival		9 [1.18–68.38]	0.034	2.48 [0.59–10.3]	0.21
Overall survival		8.14 [1.06–62.4]	0.04	12.05 [0.89–161.9]	0.06

Previous systematic reviews have reported a surgical mortality rate of <5% with surgery alone and 0–4% with either NACT or NACT along with SBRT. In the present study 2 patients expired (8%) which is similar to the world surgical mortality rate. Hence, neoadjuvant chemotherapy/SBRT is safe from a perspective of postoperative complication, without significant increases in complication rates compared with surgery alone. Two LAPC patients who underwent resection attained pCR (50%) whereas 5 BRPC patients attained pCR (25.6%). Previous reports of complete pCR in LAPC patients post-SBRT have not been documented although there has been documentation of near pCR for a patient treated at Stanford [11].

Post-SBRT local recurrences have been reported in the range of 0–50% [12, 13]. In our study, none of the patients post-R0 resection had local recurrence at a median follow-up of 26 months. This could be since we included the prophylactic nodal regions in the lower dose volumes of 25 Gy.

For LAPC patients who were unresectable the LC was 53.6% at one year. Every patient was able to complete NACT and SBRT with minor toxicities. No grade 3 toxicity was potentially attributable to radiation therapy. Only one patient had presented with melena and was found to have duodenal invasion after SBRT; it is unclear whether bleeding was caused by tumor progression or treatment.

We have used differential PTV dosage to deliver a higher dose to the region of tumor-vessel abutment/encasement to maximize tumor regression. Mahadevan et al. at Harvard reported a similar approach which was termed “adaptive tolerance-based SBRT,” by which the fraction size (8, 10, or 12 Gy) was determined by the distance between the tumor and bowel [14].

The data presented here compare similarly in some respects with other retrospective series of induction chemotherapy and SBRT.

This study is comparable to the 2008 report of BRPC by Katz et al. [15] which included 125 patients who completed neoadjuvant conventional chemoradiotherapy for BRPC. In their study, 66 (53%) patients underwent surgery, with 94% R0 resection rate and 6% pathologic complete response (pCR). The median OS was 40 months for resected patients,13 months for unresected patients, and 18 months for all patients. In our study the median OS was 28.4 months for resected patients and 19.3 months for unresected patients, and 17 months for all patients.

As compared to the recent meta-analysis by Jannsen et al. which analyzed the survival and resection outcomes of BRPC and LAPC patients post-FOLFIRINOX regimen, the overall patient-level median OS was 22.2 months for BRPC patients (95% CI = 18.8–25.6 months) and 24.2 months for LAPC (95% CI = 21.7–26.8 months) which was similar to our study of 22.1 and 20.9 months [12]. The median PFS for unoperated patients was 18.0 months for BRPC patients (95% CI = 14.5–21.5 months) at a median follow-up of 22.7 months whereas in our study the median PFS was 16 months for the BRPC patients at a median follow-up of 27 months. The pooled resection rate was 67.8% (95% CI = 60.1–74.6%) and the pooled R0 resection rate was 83.9% (95% CI = 76.8–89.1%) for BRPC and 27% for LAPC patients. The resection rate in our study for BRPC patients was 47% and the R0 resection rate was 89.4%, for LAPC the resection rate was 20.5% in our study. For LAPC, post-neoadjuvant therapy the resection rate ranges from 15% to 30%. In this series, 4 patients (10%) underwent curative resection.

In literature, it has been seen that tumors of the tail perform poorly as they lie in the close proximity of the peritoneum leading to higher rates of metastasis [16]. In our study the head of pancreas had much better LC and survival outcomes as compared to tail of pancreas.

Arterial compared to venous encasement is known to have poor outcomes. In literature there is not much clarity on arterial encasement of SMA versus coeliac versus hepatic artery. We observed that CHA encasement of more than 180° was unlikely to proceed with surgery and had higher rates of tumor progression.

In many studies radiological response post-neoadjuvant treatment may or may not necessarily impact outcomes [12]. Therefore all patients in absence of progression of disease must be explored. In this study the patients who had a radiological response or post-NACT continued to have further response with SBRT and proceed toward surgery. These factors depict that patient selection is important for SBRT. Selected group of patients who have CHA encasement with no response or progression post-NACT are the least to benefit post-SBRT.

Stereotactic body radiotherapy may be at least as effective as conventionally fractionated treatment regimens with shorter duration and minimal toxicity. Our SBRT patients had similar rates of conversion to resectability (41% vs 30%) and R0 resection (94% vs 92%) when compared to 160 BRPC patients treated with conventional fractionation [5, 12, 17–20].

The limitation of this study is being a retrospective analysis with 20% of patients not undergoing surgery in spite of being deemed resectable which led to a decline in the resection rate. The strength of this study is that we could identify the cohort of patients where SBRT does or does not improve outcomes. This observation needs further validation [16, 21, 22].

CONCLUSION

Stereotactic body radiotherapy appears to be a promising tool in improving outcomes of pancreatic cancer patients undergoing neoadjuvant therapy. It is feasible because of its short duration, efficacy, and favorable toxicity profile. It plays an important role, minimizing the need for vascular resection as well as improving the R0 resection rate. Its role in neoadjuvant therapy needs a detailed evaluation for future studies.

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