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Postoperative complications after resection of borderline resectable and locally advanced pancreatic cancer: The impact of neoadjuvant chemotherapy with conventional radiation or stereotactic body radiation therapy☆,☆☆

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Abstract

Background: The impact of neoadjuvant stereotactic body radiation therapy on postoperative complications for patients with borderline resectable or locally advanced pancreatic ductal adenocarcinoma remains unclear. Limited studies have compared neoadjuvant stereotactic body radiation therapy versus conventional chemoradiation therapy. A retrospective study was performed to determine if perioperative complications were different among patients with borderline resectable or locally advanced pancreatic ductal adenocarcinoma receiving neoadjuvant stereotactic body radiation therapy or chemoradiation therapy.

Methods: Patients with borderline resectable or locally advanced pancreatic ductal adenocarcinoma who underwent neoadjuvant chemotherapy with stereotactic body radiation therapy or chemoradiation therapy followed by pancreatectomy at the Johns Hopkins Hospital between 2008 and 2015 were included Predictive factors for severe complications (Clavien grade ≥ III) were assessed by univariate and multivariate analyses.

Results: A total of 168 patients with borderline resectable or locally advanced pancreatic ductal adenocarcinoma underwent neoadjuvant chemotherapy and RT followed by pancreatectomy. Sixty-one (36%) patients underwent stereotactic body radiation therapy and 107 (64%) patients

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received chemoradiation therapy. Compared with the chemoradiation therapy cohort, the neoadjuvant stereotactic body radiation therapy cohort was more likely to have locally advanced pancreatic ductal adenocarcinoma (62% vs 43% $P = .017$) and a require vascular resection (54% vs 37%, $P = .027$). Multiagent chemotherapy was used more commonly in the stereotactic body radiation therapy cohort (97% vs 75%, $P < .001$). Postoperative complications (Clavien grade ≥ III 23% vs 28%, $P = .471$) were similar between stereotactic body radiation therapy and chemoradiation therapy cohort. No significant difference in postoperative bleeding or infection was noted in either group.

Conclusion: Compared with chemoradiation therapy, neoadjuvant stereotactic body radiation therapy appears to offer equivalent rates of perioperative complications in patients with borderline resectable or locally advanced pancreatic ductal adenocarcinoma despite a greater percentage of locally advanced disease and more complex operative treatment.

Introduction

Pancreatic cancer is an aggressive malignancy that remains a leading cause of cancer mortality. Approximately 53,670 new cases are anticipated in the United Stated in 2017 with an estimated 43,090 deaths. [1,2]Treatment has proven to be difficult and the prognosis remains dismal, with 5-year survival rates of only 8%. [1] A complete operative resection with negative margins (R0) is the best chance of cure and is associated with a 5-year survival rate of 20%. [3,4] Unfortunately, the majority of presenting patients are not amenable to resection. After neoadjuvant chemoradiation treatment, some patients with locally advanced (LAPC) or borderline resectable (BRPC) disease may achieve similar overall survival rates to those with resectable pancreatic cancer after a successful R0 resection. [5,6]

A combination of chemotherapy and radiation therapy has acceptable morbidity and is suggested to be associated with im- proved rates of R0 resection and overall survival compared with chemotherapy alone. [7,8] Stereotactic body radiation (SBRT) is a re- cent advancement that allows for the accurate delivery of high-dose radiation to a small targeted area in fewer fractions. SBRT has had encouraging results in pancreatic cancer because of advantages in quality of life with rates of toxicity and local control comparable to that of conventional chemoradiotherapy (CRT). [9–11] Because SBRT is delivered in only 5 days, as opposed to 5 to 6 weeks with CRT, the interval between neoadjuvant radiation therapy and operative exploration can be decreased by almost 5 weeks. This would allow less time off from systemic chemotherapy and likely decreases the potential of systemic progression while improving the quality of life. [12,13] These promising benefits have led to a recent increased use of SBRT in the neoadjuvant setting in combination with chemotherapy, resulting in a successful increase of resectability with minimal acute toxicities. [13–16] The impact of SBRT on postoperative complications compared with other neoadjuvant treatments for this advanced BRPC/LAPC cohort, however, remains poorly defined.

We performed this retrospective comparative study to deter- mine if the risk of perioperative complications was different among patients with BRPC/LAPC receiving neoadjuvant chemotherapy plus CRT versus SBRT.

Methods

Patient population

During the period of January 2008 to September 2015, all pa- tients with a BRPC/LAPC who received neoadjuvant treatment and underwent subsequent operative exploration at the Johns Hopkins Hospital were identified from a prospectively maintained pancrea- tectomy database.

Approval by our Institutional Review Board was obtained for creation and use of this deidentified database for research purposes with waiver of informed consent. All patients had a preoperative, multidetector, 3-dimensional, pancreatic-protocol com- puted tomography (CT) of the chest, abdomen, and pelvis. The diagnosis of BRPC/LAPC was determined in our Pancreas Multidisci- plinary Clinic or tumor board according to the published definitions for BRPC/LAPC. [17] Patients with metastatic disease identified radiographically before operative resection or during a diagnostic laparoscopy were excluded from the study.

Neoadjuvant therapy

All patients received neoadjuvant chemotherapy. The patients were then divided into 2 cohorts: (1) CRT and (2) SBRT. SBRT and operative resection for all patients were performed exclusively at our institution, however, chemotherapy and CRT were permitted at outside institutions. Chemotherapy regimens were deferred to the discretion of the medical oncologist and predominately included gemcitabine-based regimens such as gemcitabine and nab- paclitaxel, and 5-fluorouracil–based regimens such as FOLFIRINOX (5-fluorouracil, leucovorin, oxaliplatin, and irinotecan).

The SBRT treatment planning and delivery protocol has been described previously. [13] In brief, gold fiducials were implanted into the pancreatic tumor using endoscopic ultrasonographic guidance. The target volume received a total dose of 33 Gy in 5 fractions allowing up to 30% heterogeneity within the tumor, permitting more precise treatment planning to account for the tumor, vasculature, and the proximal structures—the duodenum, small bowel, and/or stomach. [18]

Because CRT was permitted at outside institutions, treatment planning and delivery were not standardized. A variety of CRT regimens were delivered, with most ranging from 45 to 54 Gy in 28 fractions. Patients underwent operative intervention typically within 6 to 8 weeks after completion of neoadjuvant therapy.

Operative resection

After completion of the neoadjuvant therapy, patients without evidence of distant metastasis or local disease progression on CT underwent operative exploration. Diagnostic laparoscopy was often performed first to rule out occult metastasis that may have been difficult to detect on CT. Pancreatoduodenectomy, distal pancreatectomy, or total pancreatectomy was subsequently performed as determined by the location and extent of tumor. To best obtain adequate oncologic tumor extirpation, vascular resections were performed if tumor

involvement of superior mesenteric vein, portal vein, celiac axis, or hepatic artery was appreciated.

Perioperative complications were scored by the grading system described by Clavien et al. [19] Both operative and nonoperative com- plications were assessed for 90 days from resection. Severe com- plications were defined as a Clavien grade III or more. In patients with more than 1 complication, the highest grade was identified. Pathologic data collected included tumor grade, tumor size, TNM classification, number of positive lymph nodes, resection margins, perineural invasion, and lymphovascular invasion.

Overall survival was calculated from the date of operation un- til the date of death or the last follow-up. Date of death was ob- tained from medical records, the Social Security Death Index, or local obituaries.

Statistical analysis

Statistical analysis was performed using the statistical software package, Stata/MP 12.1 (StataCorp, College Station, TX). Categorical variables were expressed as percentages and were compared using a χ^2 or a Fisher exact test. Continuous variables were presented as median and interquartile range (IQR) and were compared using a Wilcoxon-Mann-Whitney test or a Kruskal-Wallis test. Survival analysis was performed using Kaplan-Meier survival estimates and a log-rank test.

Results

Patients

A total of 168 patients with BRPC/LAPC completed neoadju- vant therapy and subsequent operative resection. Of these, 107 (64%) patients received neoadjuvant chemotherapy with CRT, and 61 (36%) underwent chemotherapy with SBRT. The median age of the entire cohort was 64 (IQR, 57–69), and 57% were male (Table 1). LAPC was represented in a larger proportion of the SBRT cohort than the CRT cohort (62.3% vs 43%, $P = .017$).

Neoadjuvant treatment and surgical resection

Multiagent chemotherapy was used more often in the SBRT co- hort (97% vs 75%, $P < .001$), with FOLFIRINOX being the most com- mon, multiagent chemotherapy regimen (72% in SBRT vs 25% in CRT, $P < .001$; Table 1). Median time from the initiation of neoadju- vant chemotherapy to resection was 6.7 months. This duration was greater in the SBRT versus CRT cohort (8.0 months vs 5.6 months, $P < .001$). Additionally, patients with locally advanced disease had a greater median time of neoadjuvant chemotherapy before resec- tion than patients with BRPC (7.3 months vs 5.2 months, $P < .001$).

Distribution of operation type was similar in SBRT and CRT cohorts, with pancreatoduodenectomy being the most common (72%), followed by distal (23%) and total (4.8%) pancreatectomy. Vascular resection was performed more often in the SBRT com- pared with the CRT cohort (54% vs 37%, $P = .027$; Table 2). Isolated venous resection was performed in 78% of cases, followed by arte- rial resection in 14% and both arterial and venous resection in 8%. Distribution and details of vascular reconstruction are displayed in

Table 3. The CRT cases occurred from the years 2008 to 2015, whereas the SBRT cases occurred from 2011 to 2015.

Pathologic features

The pathologic characteristics of the patients who received SBRT or CRT are summarized in Table 2. Median tumor size for the entire cohort was 2.4 cm (IQR, 1.2–3.4 cm) and was similar be- tween SBRT and CRT cohorts ($P = .169$). A greater median number of lymph nodes were harvested in the SBRT cohort than in the CRT cohort (19 vs 15, $P = .011$). Rates of lymph node metastases and perineural and vascular invasion were similar in both cohorts. An R0 resection was achieved similarly in the SBRT and CRT cohorts (84% vs 79%, $P = .423$). A pathologic complete response with no ob- servable cancer cells in the pancreas or lymph nodes was noted in 12% of the SBRT and 7% of the CRT patients ($P = .384$). Interestingly, despite the smaller radiation volumes with SBRT, the node-positive resection rates were similar between SBRT and CRT.

Postoperative complications

The median postoperative follow-up time was 17.3 months (IQR, 11.2–25.8) for all patients (16 months in SBRT vs 17.6 months in CRT). Any type of perioperative complication within 90 days of resection was appreciated in 74% of patients. Despite the greater prevalence of LAPC and significantly greater rate of vascular resection in patients who received SBRT, perioperative morbidity rates were similar in the SBRT and CRT cohorts (75% vs 72%, $P = .628$). Severe complications were reported in 23% and 28% of patients who received SBRT and CRT, respectively ($P = .471$) (Table 2). Four mortalities occurred within 90 days, 1 in the SBRT cohort and 3 in the CRT cohort (2% vs 2.8%, $P = .634$).

Table 4 describes the occurrence of clinically important, severe complications in the SBRT and CRT cohorts. The most common se- vere complication in the CRT cohort was reoperation in 8 patients (7.5%). Of these, 6 patients required operation as a result of dehiscence/evisceration secondary to infection. One patient underwent reoperation for small bowel ischemia secondary to volvulus and one was explored for bleeding from the falciform ligament. Three patients (5%) in the SBRT cohort underwent postoperative reopera- tion (5% vs 7.5%, $P = .519$). Two of these 3 patients returned to the operating room because of dehiscence/evisceration after infection and 1 was explored for presumed hemorrhagic shock.

The most common severe complication in the SBRT cohort was a postoperative bleeding event, which occurred in 4 patients (7%): 1 patient experienced bleeding from the gallbladder fossa requir- ing operative intervention, 2 had gastroduodenal artery pseudoaneursym requiring embolization, and 1 had an upper gastrointestinal bleed without pseudoaneurysm requiring transfusions and intensive care unit monitoring but no embolization. Four patients in the CRT cohort also had postoperative bleeding events (3.7%) with a similar distribution: 2 patients with gastroduodenal artery pseu- doaneursym requiring embolization, 1 intra-abdominal hematoma requiring operative evacuation, and 1 gastrointestinal bleed man- aged without embolization (6.6% vs 3.7%, $P = .409$; Table 4).

We performed univariate and multivariate analyses to evaluate possible factors associated with severe complications after pan- createctomy. By univariate analysis, vascular resection

($P = .012$) and large tumor size ($P = .024$) were associated with severe post- operative complications. Multivariate analysis revealed that only vascular resection (odds ratio [OR] = 2.09, 95% confidence interval [CI] = 1.02–4.28, $P = .043$) was an independent risk factor associ- ated with the development of severe complications (Table 5).

Discussion

Operative removal of pancreatic cancer remains the best option for patient survival, but only a small portion of patients present with low-stage disease amenable to immediate operative interven- tion, leading to an increasing use of neoadjuvant chemoradiation therapy either to downstage the disease or as initial therapy by some groups in an attempt to sterilize any distant metastases. Mul- tiple publications suggest that BRPC and LAPC can be resected af- ter neoadjuvant therapy. [5,7,9,13–15,20,21] Despite these encouraging re- sults, operative resection of advanced disease after neoadjuvant therapy is technically challenging with a subsequent greater risk of potential complications. Postoperative pancreatic fistula, wound in- fection, and delayed bleeding are common complications that can be clinically important and require further invasive intervention, such as reoperation or drain placement. [22–24] Furthermore, adjuvant therapy has been found to be beneficial and postoperative compli- cations can delay its delivery in up to 50% of patients. [8,25] There- fore, the impact of newer neoadjuvant modalities, like SBRT, on perioperative morbidity remains an important question.

A previously published study reported postoperative complica- tions in 7 of 9 patients with BRPC/LAPC treated with neoadjuvant chemotherapy with SBRT followed by resection. [26] A more recent, larger series of 61 patients with BRPC/LAPC treated with neoadju- vant and resected reported no significant difference in postopera- tive morbidity compared with those who underwent upfront resec- tion [27], however, a comparison of postoperative mortality between modalities of radiation in a large population has not been per- formed. Our study presented a cohort of patients with BRPC/LAPC treated with neoadjuvant combination therapy and subsequent re- section. The SBRT cohort had a greater proportion of LAPC patients who were more likely to require vascular resections. Despite hav- ing more advanced disease, there was no significant difference in clinically important postoperative complications in patients who received neoadjuvant SBRT compared with the CRT cohort.

Currently there is no standard neaoadjuvant approach for pa- tients with BRPC/LAPC. A combination of chemotherapy and radi- ation therapy has acceptable morbidity and is suggested to be as- sociated with improved rates of R0 resection and overall survival compared with chemotherapy alone. [7,8] Recently, Katz et al [21] re- ported favorable outcomes with FOLFIRINOX followed by chemora- diation in a single-arm, pilot study. The follow-up clinical trial to this study (Alliance A021501) will evaluate FOLFIRINOX versus FOLFIRINOX and SBRT followed by surgical evaluation in patients with BRPC (https://www.allianceforclinicaltrialsinoncology.org). We believe aggressive neoadjuvant chemotherapy with SBRT should continue to be pursued in selected patients with LAPC. Excellent surgical outcomes can be achieved for those patients who had suc- cessful resection with acceptable perioperative morbidity.

SBRT provides high-dose radiation to a small-targeted area in fewer fractions, allowing treatment to be completed over a shorter period with less time off from systemic chemotherapy. In our study, however, we noted a longer period from initiation of neoadjuvant chemotherapy to operative resection in the SBRT cohort compared with CRT. This paradox is most likely attributed to the selection bias for patients with more locally advanced disease in the SBRT cohort. SBRT has been found to have a comparable safety profile to CRT, with rates of early and late adverse events (grade ≥ 2) ranging from 2% to 3% and 5% to 11%, respectively. [12,13] A previous study from our institution reported a 22% conversion rate of BRPC/LAPC to resectability with neoadjuvant SBRT and chemotherapy. [13] This rate appears to have increased as our expe- rience with SBRT increases and as our patient selection process continues to improve, further mitigating late gastrointestinal tox- icities. Of the last 204 patients with LAPC who presented to the Johns Hopkins Hospital multidisciplinary clinic from 2013 to 2015, 117 (57.4%) received neoadjuvant chemoradiation therapy. Of these, 77 received SBRT and 40 CRT. Of those that received neoadjuvant SBRT, 25 (32.5%) proceeded to operative exploration without any neoadjuvant therapy. 7 (18%) patients who received CRT proceeded to operative exploration.

The R0 resection rate of 80% in our study is notable when com- pared with other reports, [9,14,15] considering that 50% of the patients presented with LAPC based on our multidisciplinary review. An R0 resection of BRPC and LAPC tumors is associated with improved overall survival when compared with unresectable patients who did not undergo a curative resection. [3,6,14,28] It should be noted, however, that exploration in this cohort with advanced disease has necessitated vascular resections to achieve complete resection in 44% of patients. Often the portal vein or superior mesenteric vein was amenable to primary repair; however, an end-to-end re- construction was used in 40% of our venous resections (Table 3). Rarely, arterial resection (22% of cases in this study) was neces- sary, but primarily with distal pancreatectomy and en bloc celiac axis resection (also known as the modified Apple by procedure) being the most frequent approach ($n = 10$, 63%). Our group has pre- viously published detail of our operative technique and postoper- ative management of these operative approaches. [29,30] Vascular re- sections with negative margins have been reported to be associ- ated with equivalent survival compared with standard pancreato- duodenectomy in patients with PDAC. [31,32] This finding underlines the importance of performing these complex operations at high- volume centers with surgeons and multidisciplinary teams experi- enced in managing advanced pancreatic disease.

In our total cohort, univariate (OR 2.45, $P = .012$) and multi- variate (OR 6.77, $P < .001$) analyses found that vascular resections were independently associated with severe postoperative compli- cations (Clavien grade ≥ III). The high rate of vascular resections in our population has thus lead to an anticipated sizeable number of severe postoperative complications; however, the overall rate in this study is similar to the 19% reported in a previous series of pancreatectomy with only a 6% vascular resection rate. [33] Of note, vascular resections were more common in patients who had re- ceived SBRT compared with CRT (54% vs 37%, $P = .027$). Despite the increased rate of vascular resections and the independent associa- tion of vascular resection with perioperative morbidity, the overall complication rate was similar between the SBRT and CRT cohorts and was unlikely to be attributed to radiation modality. We hy- pothesize that the fibrosis induced by the focused

SBRT makes the pancreatic anastomosis easier to perform when compared with a soft and friable pancreatic parenchyma. [34,35] Although not yet veri- fied by prospective data, this possibility conceivably mitigates risks of pancreatic fistula and associated complications. [24,36] Neverthe- less, with the increased inflammation and fibrosis comes increased difficulty with the actual pancreatic dissection. This observation further emphasizes the importance of experienced pancreatic sur- geons for these complex operative interventions.

Previous data have reported major hemorrhagic events (as high as 20%) after resection in patients treated with neoadju- vant SBRT. [15] We observed a much lesser incidence of postopera- tive bleeding complications across our total cohort at only 4.7%. Furthermore, no significant difference in postoperative bleeding events was noted between the SBRT and CRT cohorts (7% vs 3.7%, $P = .409$; Table 4).

Gillen et al [5] reported a meta-analysis of 57 studies including 4,394 patients with unresectable PDAC who were treated with neoadjuvant chemotherapy (mostly a gemcitabine-based regimen) and radiation therapy. After neoadjuvant therapy, those who underwent operative exploration had an R0 resection rate of 79% and similar median survival (20.5 months) to those patients who had resection of initially resectable disease and no neoadjuvant therapy (23.3 months). In contrast, those patients who did not have their tumors resected after neoadjuvant therapy had a median survival of only 10.2 months. [5] Our series suggests a similar survival bene- fit to patients with BRPC/LAPC who can undergo successful complete extirpation of tumor with a median survival of 29.7 months after neoadjuvant SBRT and 18.4 months in those treated with con- ventional CRT. Although the survival benefit in the SBRT cohort is encouraging, it cannot be attributed solely to the type of neoad- juvant radiotherapy. Conclusions concerning a comparison of sur- vivals should remain tempered, because there are considerable selection biases in our 2 cohorts. Although the SBRT cohort had a greater percentage of patients with LAPC, the SBRT cohort had a greater amount of newer and multiagent chemotherapies over a longer period before resection, possibly suggesting more effective chemotherapy. [20,37] Regardless of the inherent selection bias in this retrospective study, our data indicated that long-term survival was achievable in patients with advanced pancreatic cancer after neoadjuvant chemotherapy with SBRT and resection.

A pathologic complete response was noted in a small percent- age of patients in both the SBRT (12%) and CRT (7%) cohorts. Sim- ilar rates of 3% to 9% have been reported after combined neoadjuvant CRT. [6,14,21,38,39] The prognostic importance of a pathologic complete response in pancreatic cancer is unclear, because a complete response is not achieved very often, but has been suggested to be correlated with improved outcomes. [40] A retrospective study by Zhao et al [39] reported improved survival in pancreatic cancer patients who were found to have a pathologic complete response after neoadjuvant treatment and pancreatectomy. Further investigation on response rates and its potential survival benefits for pancreatic cancer is ongoing.

This retrospective study has several limitations. Only patients who were taken to the operating room after the neoadjuvant ther- apy were included. The time in which neoadjuvant therapy was delivered allowed selection for surgical patients with stable or

responding disease and excluded those whose disease was rapidly progressive or metastatic. This is additionally compounded in the SBRT cohort where time from neoadjuvant initiation to resection was significantly greater than the CRT cohort. Characterization and further detail of all patients who did not proceed to the operat- ing room is beyond the scope of this study of postoperative out- comes. Because of increasing interest in SBRT, patients who received newer regimens of chemotherapy such as FOLFIRINOX were more likely to get SBRT. In contrast, more patients in the CRT cohort received single-agent chemotherapy. Additionally, because the R0 resection rates remained high, our pancreatic surgery group have become more aggressive with resecting LAPC throughout this period, even if a vascular resection was required. This selection bias and change in practice patterns may explain the survival result of the SBRT cohort in our study. Furthermore, institutional bias may contribute to these outcomes, because the surgeons for this study practice at a tertiary, high-volume pancreatic center with an experienced multidisciplinary team. Finally, although median postoperative follow-up was similar in our 2 cohorts, a greater followup is needed for further analysis of long-term morbidity and over- all survival.

Conclusion

With careful patient selection by an experienced pancreatic multidisciplinary team, operative resection after neoadjuvant SBRT with concurrent chemotherapy appears to be well tolerated and feasible in patients with BRPC/LAPC when performed at high- volume pancreatic centers. Compared with patients who received neoadjuvant chemotherapy and CRT, SBRT was performed in a greater percentage of LAPC and required more complex operative resections with more vascular resections. Despite this, the rate of perioperative complications was similar. Neoadjuvant SBRT can be performed in an attempt to increase the resectability of BRPC/LAPC without increasing postoperative complications.

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Table 1

Demographics and treatment characteristics of study cohorts: Neoadjuvant chemotherapy with SBRT versus chemotherapy with CRT.

	Total ***N*** **= 168**	**SBRT** ***N*** **= 61**	**CRT** ***N*** **= 107**	***P***
Male, %	96 (57%)	35 (57%)	61 (57%)	.963
Age, median (IQR)	64 (57–69)	61 (57–67)	65 (57–69)	.103
Preoperative staging				
LAPC	84 (50%)	38 (62%)	46 (43%)	.017
BRPC	84 (50%)	23 (38%)	61 (57%)	
Chemotherapy regimen				
Capecitabine alone	18 (10.7%)	0	18 (16.8%)	< .001
5-fluorouracil alone	2	0	2	
Gemcitabine alone	9 (5.3%)	2	7 (6.5%)	
FOLFIRINOX *	70 (41.7%)	44 (72%)	26 (24.3%)	
Other multiagent	69 (41.1%)	15 (25%)	54 (50.5%)	
Total multiagent	139 (82.7%)	59 (97%)	80 (74.8%)	< .001

BRPC, borderline resectable pancreatic cancer; *LAPC,* locally advanced pancreatic cancer.

* FOLFIRINOX: 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan.

Table 2

Pathologic features and operative outcomes of study cohorts.

	Total ***N*** **= 168**	**SBRT** ***N*** **= 61**	**CRT** ***N*** **= 107**	***P***
R0 resection	135 (80.4%)	51 (84%)	84 (78.5%)	.423
Tumor size median (IQR), cm	2.4 (1.2–3.4)	1.9 (0.9–3.3)	2.5 (1.5–3.4)	.169
Complete response	14 (8.3%)	7 (12%)	7 (7%)	.384
T0: complete response	14 (8.3%)	7 (12%)	7 (6.6%)	.179
T1	46 (27.4%)	21 (34%)	25 (23.4%)	
T2	51 (30.4%)	19 (31%)	32 (29.9%)	
T3	48 (28.6%)	12 (20%)	36 (33.6%)	
T4	9 (5.4%)	2	7 (65%)	
Harvested lymph nodes, median (IQR)	16 (12–23)	19 (15–23)	15 (12–20)	.011
Lymph node positivity				
0 nodes	116 (69%)	43 (70%)	73 (68.2%)	.242
1–3 nodes	46 (27.4%)	14 (23%)	32 (29.9%)	
4 + nodes	6 (3.6%)	4 (7%)	2 (1.9%)	
Perineural invasion				
Yes	89 (53%)	31 (51%)	58 (54.2%)	.774
No	73 (43.5%)	27 (44%)	46 (43%)	
Indeterminate	6 (3.6%)	3 (5%)	3 (2.8%)	
Vascular invasion				
Yes	44 (26.2%)	15 (25%)	29 (27.1%)	.879
No	97 (57.7%)	37 (61%)	60 (56%)	
Indeterminate	26 (15.5%)	9 (15%)	17 (16.5%)	
Procedure type				
Pancreaticoduodenectomy	121 (72%)	41 (6%)	80 (74.8%)	.255
Distal pancreatectomy	39 (23%)	16 (26%)	23 (21.5%)	
Total pancreatectomy	8 (4.8%)	4 (7%)	4 (3.7%)	
Vascular resections	73 (43.5%)	33 (54%)	40 (36.7%)	.027
Complications	125 (74%)	46 (75%)	79 (72%)	.628
Clavien grade				

	Total $N = 168$	SBRT $N = 61$	CRT $N = 107$	P
< III	124 (74%)	47 (77%)	77 (72%)	.471
≥III	44 (26%)	14 (23%)	30 (28%)	
90-day mortality	4 (2.3%)	1 (2%)	3 (2.8%)	.634

Table 3

Operative detail and distribution of vascular resections in study cohorts.

Vascular resection type	Total *n* = 73	Neoadjuvant SBR1 *n* = 33 (54%)	r Neoadjuvant CRT H| *n* = 40 (37%)
Venous resection	57 (78%)	23 (70%)	34 (85%)
PV with primary repair	28	12	16
PV with end to end reconstruction	23	7	16
SMV with primary repair	4	3	1
SMV with saphenous bypass	1	1	0
SMV with PTFE typass	1	0	1
Anerial resection	10(14%)	6(18%)	4 (10%)
Celiac axis	7	4	3
SMA with primary repair	1	1	0
CHA with saphenous jump graft	2	1	1
Anerial and venous resection	6(8%)	4(12%)	2(5%)
Celiac axis + PV with primary repair	3	2	1
CHA + PV with primary repair	2	1	1
CHA + PV with end to end reconstruction	1	1	0

CHA, common hepatic artery; *PTFE,* polytetrafluoroethylene; *PV,* portal vein; *SMV,* superior mesenteric vein; *SMA,* superior mesenteric artery.

Table 4

Clinically Important severe complications greater than or equal to Clavien grade 3a in the neoadjuvant SBRT and neoadjuvant CRT groups.

Complication type	Neoadjuvant SBRT *n* = 14 (23.0% of the total of 61 patients)	Neoadjuvant CRT *n* = 30 (28.0% of the total of 107 patients)	*P*
Reoperation	3 (5%)	8 (8%)	.519
Postoperative pancreatic fistula requiring drain placement	3 (5%)	6 (6%)	.849
Clinically important bleeding event	4 (7%)	4 (4%)	.409
Sepsis with organ dysfunction requiring critical care	3 (5%)	8 (8%)	.519
Respiratory failure requiring intubation	2 (3%)	7 (7%)	.366
Other invasive procedure	3 (5 %)	4 (3.4%)	.713
Death	1 (2%)	3 (3%)	.634

Table 5

Univariate and multivariable analysis of factors contributing to severe complications (grade ≥3) after pancreatic resection in the total study population (*N* = 168) of resected pancreatic adenocarcinoma after neoadjuvant chemoradiation therapy.

		Univariate			Multivariate		
	Severe complication rate	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Age		1.01	0.98, 1.05	.494			
Sex				.761			
Female	25.0%	Ref.	0.55, 2.24				
Male	27.1%	1.11					
Therapy cohort				.468			
SBRT	23.0%	Ref.	0.63, 2.72				
CRT	28.0%	1.31					
Preoperative staging				.291			
LAPC	22.6%	Ref.	0.73, 2.90				
BRPC	29.8%	1.45					
Chemo agent				.235			
Capecitabine alone	44.4%	2.53	0.92, 6.90				
5FU alone	50.0%	2.86	0.17, 46.73				
Gemcitabine alone	10.0%	0.34	0.04, 2.77				
FOLFIRINOX	24.4%	1.08	0.54, 2.18				
Other multiagent	24.4%	0.67	0.33, 1.37				
Procedure type				.222			
Distal pancreatectomy	20.5%	0.67	0.28, 1.59				
Pancreatoduodenectomy	26.5%	1.05	0.49, 2.27				
Total pancreatectomy	50.0%	2.99	0.71, 12.55				
Vascular resections	36.1%	2.44	1.21, 4.94	.012	2.09	1.02–4.28	.043
Tumor size	—	1.32	1.04, 1.69	.024	1.24	0.96–1.57	.086
Tumor stage				.731			
T1–T2	27.0%	Ref.	0.42, 1.83				
T3–T4	25.6%	0.88					
Nodal status							

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		Univariate			Multivariate		
	Severe complication rate	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Positive	27.3%	1.21	0.58, 2.53	.602			
Negative	24.8%						
Duration of initial hospital stay	—	1.16	1.08, 1.24	<.001	1.21	1.12–1.33	<.001

5FU, 5-fluorouracil.