Induction gemcitabine-based chemotherapy and neoadjuvant stereotactic body radiation therapy achieve high margin-negative resection rates for borderline resectable pancreatic cancer

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Abstract

Objectives Patients with borderline resectable pancreatic cancer (BRPC) have a higher probability of undergoing margin-negative resection after completing neoadjuvant therapy. Here, we describe a novel neoadjuvant approach using induction chemotherapy followed by stereotactic body radiation therapy (SBRT) for patients with BRPC.

Methods This analysis included patients with nonmetastatic BRPC treated with neoadjuvant gemcitabine-based chemotherapy and five-fraction SBRT. Chemotherapy consisted of 3 cycles of Gemzar, Taxotere, and Xeloda. Patients were restaged to determine resectability, and nonmetastatic resectable patients underwent surgical resection.

Results Thirty patients completed neoadjuvant treatment and were offered surgical exploration. Seventeen patients (56.7 %) reported no acute adverse effects during SBRT. No grade 3 or higher toxicity was observed from SBRT. Twenty-nine patients (96.7 %) underwent exploration. Twenty-one (95.6 %) of those who underwent pancreatic tumor resection achieved negative margins, with none requiring vessel resection. One (3.3 %) patient was resected

with microscopic positive margins. Median follow-up was 15.6 months (range, 6.3–26.1 months). Median and 1-year overall survival was 20 months and 91 %, respectively. Median and 1-year progression-free survival was 14.9 months and 61 %, respectively.

Conclusion SBRT-based neoadjuvant therapy for BRPC is well tolerated and can result in a high rate of margin-negative tumor resection.

Keywords Stereotactic body radiation therapy · Borderline resectable pancreatic cancer · GTX

Introduction

Pancreatic cancer is the fourth most common cause of cancer death in the USA [1]. While surgical resection remains the only chance for cure, the majority of patients are not surgical candidates at initial presentation due to either locally advanced or distant metastatic disease. Of the 20 % that are resectable, the 5-year estimated survival remains quite poor at approximately 20 % [2].

Approximately one third of patients presenting with locally advanced pancreatic cancer (LAPC) are classified as being borderline resectable. While variations on the definition of borderline resectable pancreatic cancer (BRPC) exist, these patients typically have abutment, but not complete encasement, of nearby vasculature [3, 4]. Such abutment significantly lowers the probability of achieving a margin-negative resection (R0), and consequently the likelihood of cure. Patients who undergo resection with positive surgical

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margins (R1 or R2) have outcomes similar to those who did not undergo resection [5–7]. Thus, the importance of achieving an R0 resection cannot be understated.

Neoadjuvant chemoradiation has been shown to have several theoretical and practical benefits for patients with BRPC. First, data from our institution as well as from others have shown that neoadjuvant chemoradiation for BRPC can significantly increase the likelihood of undergoing an R0 resection, which may improve overall survival [8–11]. Of note, these studies used radiotherapy techniques with standard fractionation over approximately 5 weeks. Second, exposure of the tumor to chemotherapeutic agents prior to resection allows for the sensitivity of the tumor to those agents to be assessed. If the tumor responds, then the same therapy may be employed if the patient has a recurrence. Third, intensive multiagent multimodality treatment programs may be better tolerated by patients preoperatively versus postoperatively. Patients who experience major complications after surgery may require very prolonged recovery times during which chemotherapy and radiation might not be given. Fourth, radiosensitizing oxygen and chemotherapy is more readily delivered within the tumor tissue prior to surgery, making radiation therapy more effective. Surgery may potentially disrupt blood flow to the operative bed and might limit the effectiveness of postoperative radiation. Finally, most successfully resected patients nevertheless recur, which is *de facto* evidence that micrometastasis is present at an early stage of the disease. Neoadjuvant therapy potentially allows for the early control of occult micrometastasis.

Just as the transition from 5-fluorouracil- to gemcitabine-based chemotherapy regimens has emerged, the evolution of radiation therapy (RT) techniques has also resulted in improvements in patient outcomes. When compared to 3D conformal RT (3D-CRT), intensity-modulated RT (IMRT) is able to produce more tightly conformal isodose distributions while better minimizing dose to nearby critical normal structures, decreasing acute and late complications [12–14]. A technique known as stereotactic body radiation therapy (SBRT) has been utilized in various extracranial sites, with the most experience being in early stage non-small cell lung cancer [15, 16].

SBRT allows very high ablative doses of radiation to be precisely given to small target volumes over several days compared to standard treatment that is commonly delivered over 5 weeks. While SBRT has been performed in the treatment of abdominal malignancies including in LAPC [17, 18], its use has not been reported in the treatment of BRPC. Previous SBRT studies in the setting of LAPC have demonstrated technical feasibility, high rates of local control, and minimal toxicity [19–24]. Based on these data, we developed a defined treatment pathway at our institution for the diagnosis, staging, and management of BRPC that involves the use of neoadjuvant chemotherapy followed by

SBRT. We now report on the outcomes of BRPC patients treated at our institution that completed treatment with induction gemcitabine-based chemotherapy and SBRT.

Methods

Patient details

After IRB approval, the medical records of non-metastatic BRPC patients who completed induction gemcitabine-based chemotherapy followed by SBRT at our institution were reviewed. Since a standard approach to treating BRPC does not exist, our institution developed a pathway for the management of BRPC that includes induction GTX (Gemzar, Taxotere, Xeloda) chemotherapy followed by SBRT and restaging. Published data have shown both GTX chemotherapy in combination with RT to be effective and well tolerated in locally advanced pancreatic cancer [8, 25]. All patients were treated with curative intent between December 2009 and July 2011. No patient had prior chemotherapy or abdominal radiation therapy.

Staging

The initial evaluation included a detailed history and physical examination and routine blood chemistries. We obtained a multi-detector thin-section pancreatic protocol computed tomography (CT) scan, endoscopic ultrasound (EUS), and positron emission tomography (PET) scan for each patient in accordance with our Multidisciplinary Pancreatic Cancer Clinic staging algorithm. Although PET scan is not considered to be standard for pancreatic cancer staging, our center is a participant in the National Oncologic PET Registry, which allows us to evaluate this imaging modality in pancreatic cancer. Our institutional data have shown that metabolic imaging can change management in 11 % of pancreatic cancer cases [26]. The diagnosis of BRPC was confirmed at our GI Multidisciplinary Tumor Board prior to each patient beginning treatment by a surgeon and radiologist who both specialized in GI malignancies.

Definition of borderline resectable pancreatic cancer

Borderline resectable pancreatic cancer was diagnosed based on EUS and CT findings. In the event of a discrepancy between imaging studies, the highest stage finding was used. The following criteria were used when defining borderline resectable disease: (1) $\leq 180^\circ$ circumferential tumor abutment with the superior mesenteric vein (SMV), portal vein (PV), or superior mesenteric artery (SMA); (2) short segment encasement (approximately 1.5 cm) of the PV/SMV amenable to partial vein resection and reconstruction;

or (3) gastroduodenal artery encasement up to the origin of the hepatic artery. Tumors of the head or body with involvement of both the PV/SMV and SMA that would require resection and reconstruction of both arterial and venous systems were classified as unresectable. Patients with encasement of the SMA, celiac artery, aorta, or inferior vena cava (IVC) were also classified as unresectable.

Chemotherapy

All patients received gemcitabine-based chemotherapy followed by SBRT. Each 21-day cycle of GTX was administered as follows: gemcitabine (Eli Lilly) 750 mg/m² on days 4 and 11, docetaxel (Sanofi Aventis) 30 mg/m² on days 4 and 11, and capecitabine (Roche) 750 mg/m² BID on days 1–14. Patients completed the prescribed 3 cycles with dose reductions as recommended by the treating medical oncologist (GS) for chemotherapy-related adverse effects.

Radiation treatment planning and delivery

Endoscopically placed Visicoil (Core Oncology, Santa Barbara, CA) fiducial markers were placed in the tumor prior to simulation to optimize target delineation, both during treatment planning as well as during daily setup verification after induction chemotherapy. One to three fiducial markers (0.35×1 cm) were implanted into the peritumoral tissue. Variability in the number of markers resulted from technical difficulties during placement. Prior to CT simulation, the extent of tumor motion from respiration was determined under fluoroscopy using the fiducial markers. Motion management strategies were personalized to each patient. Patients were assessed to determine whether respiratory-gated SBRT with delivery in maximum exhalation phase vs. abdominal compression vs. free breathing with larger margins and an internal target volume (ITV) approach would be utilized. The majority of patients in this series were treated with gated SBRT using 3D conformal techniques. Those patients who received IMRT all had verified motion with proper management strategies less than 1 cm.

CT simulation was performed with the patient supine and arms overhead in a BodyFIX (Elekta, Stockholm, Sweden) immobilization cradle. Oral gastrografin was administered 30 min prior to immobilization. A free breathing scan from the carina to iliac crest in 3-mm increments using IV and oral contrast was first done to set the isocenter. A 4D CT scan was then performed to quantify the degree of tumor movement with respiration.

To account for tumor motion during respiration, we used several techniques including abdominal compression. This minimized diaphragmatic excursion and, hence, primarily superior-to-inferior tumor motion. Respiratory gating has more recently become available at our institution, which allowed us to deliver dose to the target only during a particular

phase of the respiratory cycle, specifically during end expiration when tumor motion was typically the least variable. The respiratory cycle was recorded using an abdominal bellows strap placed at the inferior costal margin. The free breathing respiratory trace was divided into ten phases, of which the 50 % phase (usually maximum end expiration) was typically selected for treatment planning. The 50 % phase was fused to the 40 and 60 % phases, which defined the gating window during which the photon beam was turned on. Diaphragmatic excursion, and indirectly tumor position, was tracked during treatment using an infrared reflector placed along the right infracostal border.

After CT simulation, the images were transferred to a Pinnacle workstation where the target volumes were contoured by an attending radiation oncologist (SEH, RS). The intent was to use dose painting to selectively deliver a higher dose to the portion of the tumor abutting the vasculature. To achieve this, two planning target volumes (PTVs) were created, one to encompass the entire extent of radiographic disease and a second to encompass that portion of tumor adjacent to the vasculature resulting in the borderline designation. Elective nodes were not included to limit normal tissue toxicity. For the gating patients, tumor was contoured on the 40, 50, and 60 % phases to create an exhale ITV, accounting for motion in the gating window. For the abdominal compression patients, tumor was contoured on all phases to create an ITV. A 3–5-mm PTV expansion was intended to account for daily setup error.

SBRT began 1 week after completion of chemotherapy on a Varian Trilogy unit using 6–15-MeV photons. Eight patients (26.7 %) were treated using SmartArc (Philips, The Netherlands) with abdominal compression. Twenty-one patients (70 %) were gated. One (3.3 %) was treated in free breathing after not tolerating the weight belt, prior to the availability of respiratory gating at our center. Fiducial marker position was verified prior to treatment using cone beam CT and fluoroscopy.

Five-fraction SBRT was delivered with the intent to deliver up to 30–40 Gy to the tumor–vessel interface and up to 25–30 Gy to the remainder of the gross disease. Dosing was limited by the ability to meet normal tissue constraints, particularly with respect to the small bowel. Normal tissue constraints are as follows: kidney (mean<10 Gy), spinal cord (maximum 20 Gy), liver (mean<10 Gy), stomach, duodenum, and bowel (1 cc <35 Gy, 5 cc <30 Gy, mean <20 Gy).

Surgical resection

Restaging PET and pancreas protocol CT scans were obtained approximately 3–4 weeks after completion of SBRT and were reviewed at our GI Tumor Board for consideration of exploratory laparotomy and possible surgical resection. Those patients with tumors involving the pancreatic head underwent

pancreaticoduodenectomy, while those with tumors involving the body underwent distal pancreatectomy and splenectomy. The operating surgeon and pathologist determined whether an R0 or R1/2 resection was achieved. Vascular surgeons were available in the event that any patient required a vessel resection.

Follow-up

Adverse effects were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 [2]. Acute effects were considered to be those that occurred within 90 days of SBRT completion, and late effects were those that occurred more than 90 days after SBRT completion. Patients were seen in clinic every 3–6 months postoperatively or after SBRT completion if they remained unresectable.

Results

Thirty patients were identified who met inclusion criteria. Table 1 summarizes patient and tumor characteristics. The median age was 64 years (range, 44–77 years). Tumors were most commonly located in the head of the pancreas (90 %). One patient had biopsy-proven adenosquamous carcinoma, while all other tumors were adenocarcinoma. Blood vessels clinically involved by tumor based on staging workup most commonly involved the SMV alone (36.7 %), PV alone (26.7 %), or PV/SMV confluence (20 %). Multiple vessel involvement was diagnosed in eight patients (26.7 %). One patient (3.3 %) had clinical T4 disease, and 18 patients (60 %) had clinical node-positive disease by EUS staging. Twenty-seven of 30 (89 %) patients received GTX chemotherapy at our institution, and the rest received gemcitabine-based chemotherapy at our affiliated community practices. One patient had gemcitabine for 1 cycle followed by 2 cycles of GTX, one patient was treated with gemcitabine alone, and one patient received erlotinib with the GTX regimen. The median planning target volume encompassing the entire tumor versus the tumor–vessel interface alone was 116.5 cm³ (range, 72.0–255.4 cm³) and 17.5 cm³ (range, 6.9–75.1 cm³), respectively. The entire tumor volume received a median of 5 Gy per fraction (range, 5–6 Gy) for a total median dose of 25 Gy (range, 25–30 Gy). The tumor volume abutting vasculature received a total median dose of 32.8 Gy (range, 30–40 Gy) in 6–8 Gy fractions (median, 6.6 Gy). A typical BRPC case showing abutment of SMV, isodose distribution of dose-painted SBRT, and response to treatment is demonstrated in Fig. 1.

The median follow-up was 15.6 months (range, 6.3–26.1 months). Treatment was well tolerated. Seventeen patients (56.7 %) reported no acute adverse effects during

SBRT. There was no reported acute grade 3+ toxicity in any patient. Seven (23.3 %) reported grade 1 fatigue that self-resolved shortly after finishing treatment, two (6.6 %) had grade 2 diarrhea, four (13.3 %) had grade 2 abdominal pain, and one (3.3 %) had grade 2 nausea. The adverse events are summarized in Table 2. While long-term follow-up is limited, there were no reported late adverse effects.

Table 1 Patient and treatment characteristics

Characteristic	N (range)	%
Patients	30	
Median age (years)	64 (44–77)	
Clinical T stage		
T3	29	96.7
T4	1	3.3
Clinical N stage		
N0	12	40
N1	18	60
Tumor location		
Head	27	90
Body	3	10
Involved vessel(s)		
SMV alone	11	36.7
PV alone	8	26.7
SMV/PV	6	20
SMV/SMA	1	3.3
SMV/SV	1	3.3
SMA alone	1	3.3
SA	1	3.3
IVC	1	3.3
Chemotherapy		
GTX alone	27	27
Gemcitabine then GTX	1	3.3
Gemcitabine alone	1	3.3
Erlotinib then GTX	1	3.3
Median PTV (cm ³)		
Entire tumor	116.5 (72–255.4)	
Region of vessel abutment	17.5 (6.9–75.1)	
Median SBRT dose		
Entire tumor	25 Gy (25–30)	
Region of vessel abutment	32.8 Gy (30–40)	
SBRT technique		
3D-CRT	1	3.3
3D gating	21	70
IMRT	8	26.7

SMA superior mesenteric artery; *SMV* superior mesenteric vein; *PV* portal vein; *IVC* inferior vena cava; *SA* splenic artery; *GTX* Gemzar, Taxotere, Xeloda; *SBRT* stereotactic body radiation therapy; *3D-CRT* 3D conformal radiation therapy; *IMRT* intensity-modulated radiation therapy; *PTV* planning target volume

Fig. 1 **a** Pancreatic protocol CT of the abdomen (venous phase) illustrating abutment of pancreatic tumor to the SMV (*arrow*). **b** Isodose distribution of dose-painted SBRT treating the entire pancreatic tumor to 25 Gy and the area of vessel abutment (*thick arrow*) to 40 Gy in five fractions. **c** Radiographic response 4 weeks after SBRT showing a fat plane that developed between tumor and SMV (*arrow*) after neoadjuvant therapy

Table 3 describes the surgical outcomes. All 30 patients were considered to have had at least a partial radiographic

response to neoadjuvant therapy based on visualization of a potential plane for resection between the tumor and nearby vasculature. As a result, all patients were recommended to undergo at least surgical exploration and then ideally pancreatic resection based on the findings at the time of exploration. Twenty-nine patients (96.7 %) underwent surgical exploration. Nine patients (30 %) did not undergo surgical resection. One (3.3 %) developed cardiovascular instability after preoperative cardiac clearance, five (16.7 %) developed distant metastatic disease not detected during initial staging but detected intraoperatively, two (6.7 %) had unresectable disease, and one (3.3 %) declined surgery although was medically fit. Unresectable and metastatic patients were recommended to continue management with chemotherapy. Twenty-one patients (70 %) were deemed resectable and underwent either pancreaticoduodenectomy (60 %) or distal pancreatectomy (10 %). Segmental resection of the SMA, PV, or SMV/PV confluence was not required in any patient. Vessel repair was required in two patients. Twenty resected patients achieved negative margins (95.2 %). Two patients (6.7 %) achieved a pathologic complete response, and one patient (3.3 %) had a near complete response with <1 mm of residual disease. A pancreaticoduodenectomy was performed in one patient who was thought to have achieved negative margins intraoperatively, although ultimately was found to have a microscopically positive margin (4.8 %). Tumors were well differentiated (14.3 %), moderately differentiated (28.6 %), poorly differentiated (52.4 %), and undifferentiated (4.8 %). A median of 19 lymph nodes was resected (range, 1–46); 5 (23.8 %) resected patients were node-positive and 18 (76.2 %) were node-negative. The median length of hospitalization was 10 days (range, 7–14 days). Postoperative complications were minimal; three patients developed wound infection, three had a pancreatic leak, and one had an ileus.

Figure 2 illustrates survival outcomes of BRPC patients who completed neoadjuvant therapy. Median and 1-year overall survival (OS) was 20 months and 91 %, respectively. Median and 1-year progression-free survival (PFS) was 14.9 months and 61 %, respectively.

Table 2 Worst acute and late adverse effects after completing induction chemotherapy and SBRT

	Grade (%)			
	0	1	2	3+
Acute	17 (56.7)	7 (23.3)	7 (23.3)	0
Fatigue		6 (20)	0	0
Nausea		2 (6.7)	1 (3.3)	0
Diarrhea		0	2 (6.7)	0
Abdominal pain		0	4 (13.3)	0
Late	30 (100)	0	0	0

Table 3 Surgical characteristics after completing induction chemotherapy and SBRT

	<i>N</i> (range)	%
Surgical exploration	29	96.7
Tumor resection	21	70
Pancreaticoduodenectomy	18	60
Distal pancreatectomy	3	10
No tumor resection	9	30
Unresectable	2	6.7
Distant metastasis	5	16.7
Cardiac dysfunction	1	3.3
Patient declined	1	3.3
Surgical margin		
Negative (R0)	20	95.2
Microscopically positive (R1)	1	4.8
Grossly positive (R2)	0	0
Lymph nodes		
pN0 patients	16	76.2
pN1 patients	5	23.8
Median total nodes resected	19 (1–46)	
Median positive nodes resected	3 (1–5)	
Tumor grade		
Well differentiated	3	14.3
Moderately differentiated	6	28.6
Poorly differentiated	11	52.4
Undifferentiated	1	4.8

Discussion

The management of BRPC continues to evolve. The Gastrointestinal Tumor Study Group trials established chemotherapy and radiation therapy as being superior to either modality alone [27, 28]. This combined modality strategy has been adopted for the neoadjuvant treatment of borderline resectable pancreatic cancer, with the available data illustrating that it can markedly increase the likelihood of an R0 resection [8–10]. What is less certain is the optimal chemotherapy and radiation therapy regimen.

We previously published our initial results treating BRPC with induction GTX followed by radiation therapy [8]. The rationale behind using induction GTX was detailed in our initial study. It is important to note that our initial experience was performed using standard fractionation RT over several weeks. However, we have since transitioned to treating all BRPC patients with SBRT over 5 days based on the accruing SBRT data for LAPC. We now report the first series of BRPC treated with induction GTX followed by SBRT.

Our data show that SBRT is not only well tolerated, but also that dose painting the area of vessel abutment to a maximum of 8 Gy over five fractions effectively facilitated margin-negative pancreatic tumor resection without the

Fig. 2 Kaplan–Meier analysis of **a** overall survival (OS) and **b** progression-free survival (PFS) for patients with BRPC who completed neoadjuvant therapy

need for vessel resection. The importance of this cannot be understated since margin status is clearly associated with survival outcomes [5–7, 29, 30]. We also observed downstaging of lymph nodes despite them not being included within the RT target volumes. Of the 21 patients that were resected, 18 (60 %) were clinically node positive by EUS staging. Only five (23.8 %) patients were pathologically node positive after neoadjuvant therapy.

These data are similar to our previously published experience that included eight patients who achieved an R0 resection out of nine resected patients. Median OS and PFS were 15.6 and 10.5 months, respectively. The series has recently been updated and now includes 23 patients treated with neoadjuvant GTX-IMRT of which 14 were resected with 13 patients reported to be margin-negative and with 2 patients requiring vessel resection. Four (28.2 %) patients were pathologically node positive. In contrast, our published series of stage I and II resectable pancreatic cancer patients over a 20-year period revealed

that 65 (47 %) out of 137 patients were lymph node positive. This apparent ability of neoadjuvant regimens to downstage nodal involvement can be used as a rationale for giving neoadjuvant therapy to all resectable pancreatic cancer patients [31, 32].

The use of SBRT in pancreatic cancer was initially studied in LAPC. Koong et al. published single fraction phase I results demonstrating that up to 25 Gy was well tolerated with 100 % local control at a median follow-up of 4.5 months [20]. Furthermore, the maximum tolerated dose was not reached because the primary endpoint of local control was satisfied. The subsequent phase II study reported excellent local control in 15 of 16 patients incorporating SBRT as a boost [21]. Several other studies have since reported similar results with median survival ranging from 6 to 14.3 months, local control ranging from 45 to 100 %, with low rates of grade 3 toxicity [19, 23, 24, 33, 34]. The Danish experience, however, reported severe late mucositis, duodenal perforation, or ulceration in 42 % [33]. This toxicity was likely secondary to more generous PTV expansions (≤ 10 mm) than other similar trials (3–5 mm). For instance, although the Stanford experience included tumors of similar size, their median PTV volume was 46.6 cm³ (range, 21.5–84.2 cm³) compared to 136 cm³ (range, 38–376 cm³) [34]. Nevertheless, the early collective literature suggests that SBRT is a reasonable alternative to standard fractionation RT and merits further clinical evaluation.

The ultimate goal of neoadjuvant treatment is to create a plane of resection between the tumor and adjacent vasculature in BRPC, thus increasing the likelihood of an R0 resection. With respect to RT technique, there are several potential advantages for SBRT over standard fractionation techniques. First, delivering very high ablative doses to the area of vessel abutment likely results in higher rates of tumor response and R0 resection as a result of increased endothelial cell apoptosis [35]. Second, excellent local control has been demonstrated with SBRT in the locally advanced setting, which is particularly beneficial for patients who remain truly unresectable after chemotherapy and SBRT. The importance of local progression in unresectable patients should not be overlooked as it can markedly affect quality of life, resulting in pain, GI obstruction, and intestinal perforation. Third, treatment over several days is clearly more convenient for the patients, especially given their limited life expectancy. Fourth, expediting RT can minimize the time that systemic chemotherapy is not given for unresectable patients.

The primary concern when designing radiation treatment plans for pancreatic lesions is meeting normal tissue constraints, especially those of the duodenum and stomach. While rates of acute toxicity in the SBRT literature for locally advanced tumors are reasonable, the incidence of late complications, especially duodenal ulceration, should not be overlooked. We observed low rates of acute RT-

related complications with no grade 3 or higher adverse effects; more than 50 % of all patients in this analysis reported no acute effects. While our follow-up is limited, we have not reported late toxicity with the longest follow-up being over 26 months in one patient. We anticipate that the late toxicity in this series with continued long-term follow-up will be favorable as most underwent pancreatic resection, effectively removing most, if not all, tissue located within the PTV. However, we recognize the need for close follow-up in these patients and the potential for complications, particularly gastric or duodenal, as late as 1 year after treatment [34].

Finally, the high-dose PTV in this series, treated up to 40 Gy, was consistently at a sufficient distance from the duodenum and other mucosal structures. While the lower-dose PTV encompassed the entire pancreatic tumor volume, the prescribed dose (median, 25 Gy; range, 25–30 Gy) was within duodenal tolerance.

We recognize that a limitation of this review is its retrospective nature. We also recognize the small patient numbers. However, similar studies have not been previously published with large patient numbers [19, 20, 24]. In addition, an Eastern Cooperative Oncology Group prospective trial (E1200) evaluating neoadjuvant therapy for borderline resectable disease closed early due to poor accrual [36].

Conclusion

Neoadjuvant GTX and SBRT appear to be a well-tolerated and feasible local treatment modality for facilitating margin-negative resection in patients with BRPC. Longer follow-up is warranted to monitor potential outcomes including long-term adverse effects, but our experience to date is encouraging. Since we have found this treatment pathway to be promising, we hope to initiate a prospective trial to further evaluate this approach.

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