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Patterns of Failure in Patients With Borderline Resectable/Locally Advanced Pancreatic Cancer After Preoperative Chemotherapy and Stereotactic Body Radiation Therapy

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Purpose: The role of preoperative stereotactic body radiation therapy (SBRT) in pancreatic cancer is controversial, and questions regarding the optimal dose and radiation treatment field remain. To better inform future investigations of SBRT dose and radiation fields, we evaluated the patterns of failure in patients with borderline resectable/locally advanced pancreatic cancer (BR/LAPC) after preoperative chemotherapy and SBRT in patients who underwent surgical resection.

Methods and Materials: We performed a single-institution retrospective review of consecutive patients treated from September 2017 to January 2022 with BR/LAPC. Patients who underwent preoperative chemotherapy and SBRT followed by surgical resection were reviewed. SBRT was delivered to a dose of 33 Gy in 5 fractions. Kaplan−Meier overall survival and progression-free survival estimates were calculated.

Results: In total, 18 patients (12 BRPC, 6 LAPC) were included. Median age was 69 years (range 41-84 years). Median follow-up was 30 months (range 13-59 months). Seventeen patients (94%) had a R0 resection and 13 (72%) underwent vascular reconstruction. Median overall survival and progression-free survival was 42 months (range 13-59 months) and 23 months (range 1-45 months), respectively. In total, 61% (11/18) patients experienced progression at any point during follow-up. Of the patients who experienced recurrence, 27% (3/11) experienced local progression as component of their first recurrence, whereas 100% (11/11) experienced distant progression as a component of their first recurrence. When examining all recurrences that occurred at any point in follow-up, 28% (5/18) of patients experienced local or locoregional recurrence and 61% (11/18) experienced distant progression.

Conclusions: Local control and margin negative resection rates were excellent with preoperative chemotherapy and nondose-escalated SBRT in surgically resected patients with BR/LAPC. Distant recurrence was the predominant site of failure with lower incidences of

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isolated locoregional recurrences. Additional research is needed to determine the ideal treatment volume and patients who may benefit from dose escalation.

Introduction

Pancreatic cancer is the fourth most common cause of cancer-related death in the United States in 2023, and its incidence is increasing.[1] Only 20% of patients present with upfront resectable disease, and most patients receive multimodal treatment, which can include chemotherapy and radiation therapy. Given the evolving and controversial role of preoperative radiation therapy, some institutions include preoperative radiation as a component of standard of care for patients with borderline resectable and locally advanced pancreatic cancer (BR/LAPC).[2-5]

In terms of the type of radiation used in the preoperative setting, stereotactic body radiation therapy (SBRT) has emerged as an alternative to conventionally fractionated radiation therapy.[6-13] It allows for improved convenience, minimizes prolonged breaks off systemic therapy, and has a favorable toxicity profile.[7,14,15] SBRT also allows for a greater, ablative biologically equivalent dose that may enhance tumor control.

However, the optimal SBRT preoperative dose and treatment field for BR/LAPC are not known, and multiple dose and fractionation schemes and treatment volumes are used.[6,14-16] The most commonly used doses range between 33 and 40 Gy delivered over 5 fractions. Although dose escalation with SBRT or hypofractionated stereotactic ablative RT are strategies being investigated for patients with unresectable pancreatic cancer, it is not clear whether these are needed in patients undergoing surgical resection. For example, some believe areas at greater risk of a positive margin should be dose escalated (ie, tumor vessel interface), whereas others do not,[17] and some include an elective nodal volume whereas others do not.[18] As SBRT continues to be integrated in the preoperative setting, it will be important to understand the ideal dose and treatment volume. In this study, we evaluated the patterns of failure for BR/LAPC following preoperative chemotherapy, 33 Gy delivered in 5 fraction SBRT, and definitive surgical resection.

Methods and Materials

Patient population

This was an institutional review board−approved retrospective study of 18 consecutive patients at our institution between September 2017 and January 2022 with biopsy-proven BR/LAPC according to National Comprehensive Cancer Network guidelines treated with preoperative chemotherapy and SBRT followed by definitive surgery. We excluded patients who received single-modality neoadjuvant treatment or patients who did not undergo definitive surgery.

Treatment

Patients underwent neoadjuvant/adjuvant chemotherapy with standard chemotherapeutic agents at the discretion of the treating medical oncologist but are standardly treated with 6 months of combined neoadjuvant/adjuvant chemotherapy. Patients without evidence of progression on restaging imaging subsequently underwent SBRT. At our institution, preoperative SBRT is routinely discussed and offered for patients with BR/LAPC. Gold fiducials were placed within or adjacent to the pancreatic tumor before radiation planning for all patients. Patients were simulated on a GE CT590 Discovery RT simulator (Boston, MA) using a slice thickness of 1.25 to 2.5 mm. All patients received intravenous and oral contrast. Abdominal compression or breath-hold techniques were used for motion management in all patients. Treatment plans were generated using Varian Eclipse (Palo Alto, CA). Gross tumor volume (GTV) was defined as gross disease evident radiographically using the computed tomography simulation scan, as well as any relevant additional diagnostic imaging. The clinical target volume (CTV) was equal to GTV. Planning target volume was a 3-mm expansion from the GTV without expansion into adjacent gastrointestinal mucosal structures. All patients were treated with 33 Gy in 5 fractions on nonconsecutive days. No patients received simultaneous integrated boost (SIB) to the tumor−vessel interface (TVI); however, 4 patients were treated with a simultaneous lower dose target volume 25 Gy in 5 fractions, which covered a variable amount of the celiac and/or superior mesenteric nodal regions. Dose constraints for organs at risk were followed from the published SBRT phase 2 trial from Herman et al.[6] After completion of SBRT, all patients underwent restaging and those who did not have evidence of progression or metastatic disease proceeded to definitive surgery.

Recurrences

Local recurrence was defined as radiographic evidence of recurrence at the primary site. These were classified as

in-field (≥95% of recurrent tumor volume was within the 95% isodose line) or out-of-field (if <95% of recurrent tumor volume was within 95% isodose line). Locoregional recurrence was defined as a nodal recurrence in the celiac, superior mesenteric, or portal region. Locoregional recurrences also were classified according to the proposed "triangle" space defined by the celiac artery, superior mesenteric artery, common hepatic artery, portal vein, and superior mesenteric vein.[19,20] Distant metastasis was defined as radiographic evidence of a recurrence in a distant site or other organ. Overall survival (OS) was defined from the date of diagnosis to death or last follow up. Local, locoregional, and distant progression were defined from the date of definitive surgery to time of radiographic progression.

Toxicities

Toxicities were graded using Common Terminology Criteria for Adverse Events, v5.0. Postoperative complications were graded using the Contracted Accordion System of Surgical Complications.[21]

Statistics

OS and progression-free survival estimates were derived using the Kaplan−Meier method.

Results

In total, 18 patients met inclusion criteria. Median follow-up was 30 months (range 13-59 months). Patient and tumor characteristics are shown in Table 1. Median age was 69 years (range 41-84 years). Sixteen patients (89%) had pancreatic head tumors. Median carbohydrate antigen 19-9 at diagnosis was 141 mg/dL (range 3-7669 mg/dL). A summary of treatment characteristics is described in Table 2. All patients received preoperative chemotherapy. Twelve patients (67%) received FOLFIRINOX, and 6 (33%) received gemcitabine/nab-paclitaxel. The median duration of preoperative chemotherapy was 4.25 months (interquartile range 2.5-6.0 months).

All patients completed 5 fractions of SBRT. The most common toxicities during treatment were grade 1 fatigue, which was reported by 5 (28%) patients, and grade 1 nausea, which was experienced by 3 (17%) patients. One patient (6%) required a treatment break during SBRT due to grade 2 diarrhea that resolved with medical management.

After SBRT, all patients underwent restaging imaging and did not have progression or development of distant metastases. Two patients underwent additional chemotherapy for 1.5 months after SBRT before surgical resection (one received FOLFIRINOX and the other received gemcitabine/Abraxane).

All 18 patients underwent definitive surgical resection. Fifteen patients (83%) underwent a pancreaticoduodenectomy, and 3 (17%) underwent a distal pancreatectomy. Vascular reconstruction was performed in 13 (72%) patients. The most common venous resection involved the superior mesenteric vein. One patient underwent a distal pancreatectomy with celiac axis resection (DP-CAR or Appleby procedure). Seventeen patients (94%) had a R0 resection. Final pathology was ypT1N0 (n = 5),

Table 1 Baseline characteristics of included patients with borderline resectable and locally advanced pancreatic cancer treated with neoadjuvant chemotherapy, non-dose-escalated SBRT, followed by surgical resection

Characteristic	N = 18
Median age (range), y	69 (41-84)
Sex	
Male	7 (39%)
Female	11 (61%)
Race	
White	8 (44%)
Black	0
Other	10 (56%)
Clinical T classification	
T1	2 (11%)
T2	13 (72%)
T3	2 (11%)
T4	1 (6%)
Clinical N classification	
N0	14 (78%)
N1	3 (17%)
N2	1 (6%)
ECOG	
0 or 1	17 (94%)
2+	1 (6%)
Median CA 19-9 at diagnosis (range)	141 (3 - 7669)
Resectability (according to NCCN)	
Borderline resectable	12 (67%)
Locally advanced	6 (33%)
Anatomic site	
Head	16 (89%)
Tail	2 (11%)

Abbreviations: CA = carbohydrate antigen; ECOG = Eastern Cooperative Oncology Group; NCCN = National Comprehensive Cancer Network; SBRT = stereotactic body radiation therapy.

Table 2 Treatment and pathologic characteristics

Characteristic	N = 18
Neoadjuvant chemotherapy	
Gemcitabine/Nab-Paclitaxel	6 (33%)
FOLFIRINOX	12 (67%)
Median duration of neoadjuvant chemotherapy (range), mo	4.25 (2.5-6)
Median CA 19-9 at time of SBRT (range), mg/dL	30 (0-189)
Radiation dose	
PTV33 Gy only	12 (75%)
Combined PTV33 Gy and PTV25 Gy	4 (25%)
Median volume of GTV33 Gy (interquartile range), cm^3	36.0 (19.9-50.0)
Surgery type	
Pancreaticoduodenectomy	15 (83%)
Distal pancreatectomy	3 (17%)
Margin	
R0	17 (94%)
R1	1 (6%)
ypT classification	
ypT0	0 (0%)
ypT1	8 (44%)
ypT2	8 (44%)
ypT3	2 (12%)
ypN classification	
ypN0	9 (50%)
ypN1	8 (44%)
ypN2	1 (6%)

Abbreviations: CA = carbohydrate antigen; GTV = gross tumor volume; PTV = planning target volume; SBRT = stereotactic body radiation therapy.

ypT1N1 (n = 4), ypT2N0 (n = 4), ypT2N1 (n = 3), ypT3N1 (n = 1), and ypT3N2 (n = 1).

Using the Contracted Accordion Grading System of Surgical Complications, 3 patients (17%) experienced a grade 3 or greater postsurgical complication. One patient developed biliary obstruction, the second developed cholangitis requiring hospitalization, and the third developed sepsis and bleeding. Of these patients, 2 patients had vessel reconstruction. There were no perioperative mortalities observed within 30 days of surgery.

Eight patients (44%) underwent adjuvant chemotherapy after definitive resection. Adjuvant chemotherapy most commonly consisted of FOLFIRINOX (n = 7, 88%) and gemcitabine/nab-paclitaxel (n = 1, 12%). The median total months of chemotherapy, including neoadjuvant and adjuvant, was 6 months (interquartile range 4-7 months).

Ten patients (55.6%) were alive at the time of last follow up. The median OS was 42 months (range 13-59 months) (Fig. 1). Median progression-free survival was 23 months (range 1 -45 months) (Fig. 2). Progression occurred in 61% (11/18) of patients at the time of analysis. All patients who experienced progression had distant recurrence as a component of their first site of recurrence. No patients experienced local only or locoregional only progression as their first site of recurrence. In patients with progression, 6 (33%) patients had distant, 2 (11%) patients had local and distant, 2 (11%) patients had locoregional and distant, and 1 (6%) patient had local, locoregional, and distant as a component of their first site of recurrence (Table 3). When examining sites of recurrence at any point during follow-up, 28% (5/18) patients experienced local or locoregional recurrence and 61% (11/18) experienced distant recurrence. All local recurrences (n = 3) were classified as in-field recurrences. Of the 5 patients who developed a local or locoregional recurrence, 80% (4/5) experienced recurrence overlapping with the "triangle space" (Fig. 3). Median time to local or locoregional recurrence was 7 months (range 3-9 months). Four patients received a simultaneous lower dose target volume of 25 Gy in 5 fractions to the nodal regions. Of these, 1 patient experienced locoregional and distant progression, whereas the other 3 patients experienced distant progression only at any point during follow-up.

Discussion

SBRT is an emerging strategy in the preoperative setting for the management of borderline resectable pancreatic cancer and for potentially converting locally advanced pancreatic cancer to resectable disease. However, the optimal radiation dose/fractionation and treatment volume have not been established. In this study, we found that patients with BR/LAPC who underwent preoperative multiagent chemotherapy and nondose-escalated SBRT before definitive surgical resection had a 94% R0 resection rate and high rates of local control. Most patients who developed disease progression had evidence of distant metastases as part of their first recurrence, with no patients developing isolated local or locoregional failure as the site of their first recurrence.

There is an interest in dose escalation of SBRT in the preoperative setting for pancreatic cancer with the goal of potentially maximizing tumor regression and promoting R0 resection. One area of particular interest is to dose escalate to the TVI, which is the region of vessel abutment or encasement with the tumor. A TVI SIB has the potential benefit of improving local control at sites of high risk of a close/positive margin. Multiple institutions have shown high rates of R0 resection (96%-97%) with this

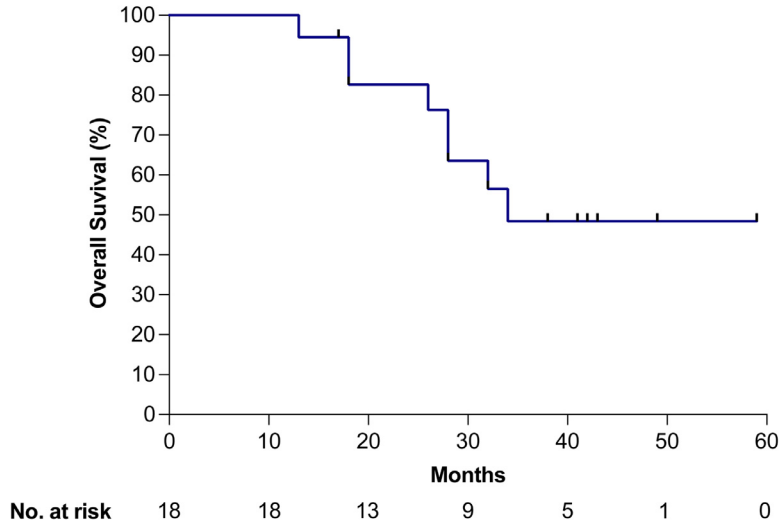

Figure 1 Overall survival.

approach.[14,15] The margin negative rate in our study of 94% is comparable, with no patients receiving a SIB to the TVI. Similar results were also reported by another study, with nondose-escalated SBRT of 33 Gy showing a similarly high R0 rate of 97%.[22] Direct comparison of R0 rates between studies is challenging, given the variations in preoperative treatments, different reasons patients are classified as borderline/locally advanced, differences in imaging, and rates of vessel reconstruction. These limitations speak to the heterogeneity in treatments that patients receive and the challenges this creates in comparing outcomes.

Another potential advantage of dose escalation with SBRT in the preoperative setting is to maximize locoregional control in patients undergoing surgical resection. Previous series have demonstrated local recurrence rates of ~30% to 40% following surgical resection.[23-25] These high rates of local failure have highlighted the need for continued improvement in the targeting and administration of radiation therapy. There have been several retrospective series demonstrating that dose-escalated ablative RT may result in improved locoregional control and OS in nonsurgical candidates.[26-28] However, there are limited series demonstrating the benefit for dose-escalated SBRT for patients who undergo surgery. Given that distant failures following surgery is noted to range between 60% and 90%, metastatic disease remains the primary culprit for poor survival in pancreatic cancer patients.[29-31] Thus, without improvement in systemic control, the role of dose escalation needs to be approached cautiously.

In addition, the role of preoperative SBRT has been further complicated by the recently reported Alliance A021501 trial in borderline resectable disease, which demonstrated worse OS (17.1 vs 29.8 months) for preoperative chemotherapy followed by SBRT compared with preoperative chemotherapy.[32] However, some controversial findings during the study included high rates of interval

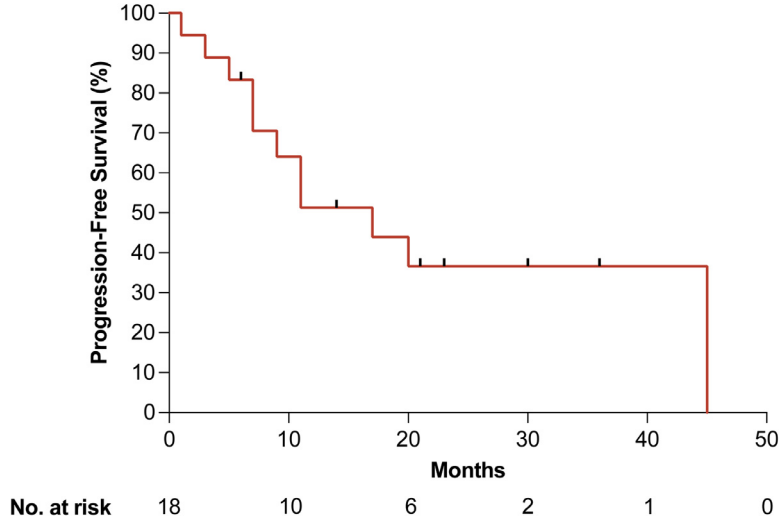

Figure 2 Progression-free survival.

Table 3 Patterns of failure: site of first recurrence and sites of all recurrence

Progression	N = 11
Site(s) of first recurrence	
Local only	0 (0%)
Locoregional only	0 (0%)
Distant only	6 (33%)
Local and distant	2 (11%)
Locoregional and distant	2 (11%)
Local, locoregional, and distant	1 (6%)
Site(s) of all recurrence	
Local only	0 (0%)
Locoregional only	0 (0%)
Distant only	6 (33%)
Local and distant	1 (6%)
Locoregional and distant	2 (11%)
Local, locoregional, and distant	2 (11%)

progression before SBRT and uncharacteristically low R0 resection (74%) rate in the SBRT arms. Of note, the Alliance trial allowed for a SIB up to 40 Gy in 5 fractions to the TVI and highlights the possibility that ultraconformal SBRT in a disease with a diffuse regional pattern of spread may influence outcomes.

Our analysis of patterns of failure allowed us to evaluate whether our target volume needs to be reconsidered. We found no patients with local or locoregional only recurrences as a first site of failure. This differs from a phase 2 trial of preoperative systemic therapy followed by SBRT with optional inclusion of an elective planning target volume, which showed that in the 12 patients who underwent surgery, 10 patients recurred, with the first site of failure being local only in 40%, distant in 40%, and both local and distant in 20%.[33] Our results are more similar to a retrospective study by Zakem et al[22] that included 103 patients with BR/LAPC treated with preoperative chemotherapy and SBRT. Of the 73 patients who underwent definitive resection, 30 experienced a recurrence with site of first recurrence local only in 3%, locoregional in 22%, distant in 44%, and both locoregional and distant in 22%.[22] Additionally, Hill et al[34] recently published a large retrospective series of 155 patients who underwent SBRT to a median dose of 33 Gy for borderline-resectable and locally advanced pancreatic cancer followed by surgical resection. Although the authors found locoregional failures in 33% of patients, local only failures were uncommon (14%) as the first site of progression.[34]

Recently there has been increased interest in a more extensive surgical dissection of the space between the peripancreatic vasculature called the "triangle operation" with the goal of improving locoregional failure rates.[19,20] When evaluating the locations of local and locoregional failures we found that 80% (4/5) of patients with locoregional failure recurred within the "triangle" space. This is consistent with recent data from Johns Hopkins, where they found 90% of their locoregional failures occurred in the "triangle."[35] This supports the idea that a larger area than just the gross disease perhaps needs to be routinely covered in our target volumes. Other studies also suggest larger treatment volumes than just the gross disease may be beneficial. Zhu et al[36] analyzed the patterns of

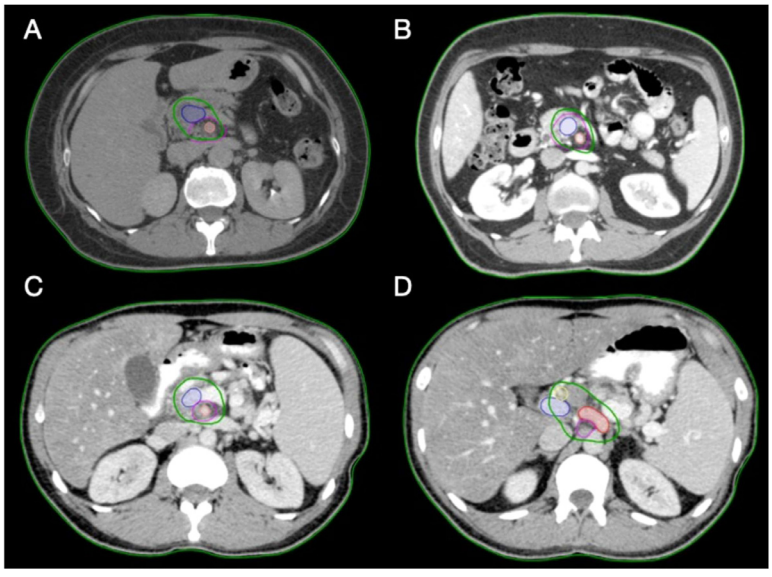

Figure 3 Axial-slice view of all 4 patients who developed locoregional recurrence overlapping the triangle volume. Recurrence (magenta); triangle volume (green); portal vein (dark blue); celiac artery (red); and superior mesenteric artery (pink). (A color version of this figure is available at 10.1016/j.adro.2024.101471.)

recurrence and found that the majority of local failures occurred near the celiac trunk or superior mesenteric artery after SBRT and chemotherapy. Nelson et al analyzed 47 patients with borderline resectable and resectable pancreatic cancer and found that the dose to the vascular CTV defined as a 5-mm margin around the superior mesenteric artery was associated with durability of local control after resection.[34] Patients who had a vascular CTV D95 ≥32.7 Gy EQD2 had significantly longer local failure-free survival at 12 months (91% vs 51%, respectively) and 24 months (86% vs 12%). These findings suggest that there may be a benefit to increasing the radiation treatment volume to encompass some elective nodal coverage and pancreatic vasculature. Whether there is also a place to be escalating the dose to these areas is an unanswered question.

There are several factors that may influence the low number of local recurrences in our population. The median duration of preoperative chemotherapy was 4.25 months, whereas chemotherapy duration is often 3 months.[22,33] Previous studies have demonstrated increased duration of preoperative multiagent chemotherapy of greater than 4 months is associated with improved OS[37] and allows for more time for patients to declare themselves as metastatic. Thus, the longer duration of chemotherapy before SBRT in our patient population may have contributed to our low local recurrence rates.

Another factor that may affect rates of local control is the high rate of vessel reconstruction, with 72% of patients undergoing vessel reconstruction in our population due to vessel involvement noted at the time of surgery. The rate of vessel reconstruction seems to vary across studies, noted to be 20% in a study by Zakem et al and 80% in the Alliance A021101 trial.[5,22] The clinical benefit of vessel reconstruction is not entirely clear, as previous studies have demonstrated that although resection of portovenous structures may result in greater rates of microscopically negative margins in patients with suspected involvement of adjacent vessels, this may come with increased risk of mortality and morbidity.[38,39]

Several limitations of our study should be considered. Given that this is a retrospective study, there can be selection bias. Our study population consists of a more favorable patient population, as we only included patients who underwent surgical resection after preoperative chemotherapy and SBRT. Although preoperative chemotherapy followed by SBRT is the standard of care at our institution for borderline resectable and locally advanced pancreatic cancer, not all patients are presented and referred for discussion of radiation and we are unable to determine the proportion of patients who eventually proceed to surgery. Although the goal is for patients to make it to definitive surgery after preoperative treatment, it may be difficult to determine whether a patient who is deemed borderline resectable or locally advanced upfront will have resectable disease after preoperative therapy. Given that this study only reports on results of resected patients and does not include an intention-to-treat population, cross-trial comparisons may be difficult due to high-risk of selection bias. Further research to evaluate preoperative predictors for resectability after preoperative treatment are warranted to help improve patient selection. In addition, new technologies such as stereotactic magnetic resonance-guided radiation therapy (SMART) may allow for dose-escalation to larger volumes of gross disease and elective volumes while limiting normal tissue toxicity.[27,40]

Conclusions

In patients with BR/LAPC treated with preoperative chemotherapy, SBRT, and surgery, distant recurrence was the predominant site of failure with lower incidences of isolated locoregional recurrences. All locoregional failures occurred within the "triangle." Further research is needed to determine whether expanding our clinical target to include the "triangle" would be beneficial as well as whether certain parts of the "triangle" should be dosed differently. Moving forward, it is important that standard target definitions be used in ongoing clinical trials evaluating the role of SBRT in pancreatic cancer.

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