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Scientific Article

Surgical and Pathologic Outcomes of Pancreatic Adenocarcinoma (PA) After Preoperative Ablative Stereotactic Magnetic Resonance Image Guided Adaptive Radiation Therapy (A-SMART)

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Abstract

Purpose: Preoperative radiation therapy (RT) for pancreatic adenocarcinoma reduces positive surgical margin rates, and when delivered to an ablative dose range it may improve local control and overall survival for patients with unresectable disease. Use of stereotactic body RT to achieve a higher biologically effective dose has been limited by toxicity to adjacent radiosensitive structures, but this can be mitigated by stereotactic magnetic resonance image guided adaptive radiation therapy (SMART).

Methods and Materials: We describe our single-institution experience of high biologically effective dose SMART before resection of localized pancreatic adenocarcinoma. Toxicity was evaluated according to Common Terminology Criteria for Adverse Events (V 5.0). Tumor response was evaluated according to the College of American Pathologists tumor regression grading criteria.

Results: We analyzed 26 patients with borderline resectable (80.8%), locally advanced (11.5%), and resectable (7.7%) tumors who received ablative dose SMART (A-SMART) followed by surgical resection. Median age at diagnosis was 68 years (range, 34-86). Most patients received chemotherapy (80.8%) before RT. All patients received A-SMART to a median dose of 50 (range, 40-50) Gy in 5 fractions. Toxicity data were collected prospectively and there were no acute grade 2+ toxicities associated with RT. The median time to resection was 50 days (range, 37-115), and the procedure types included Whipple (69%), distal (23%), or total pancreatectomy (8%). The R0 resection rate was 96% and no perioperative deaths occurred within 90 days. Pathologic response was observed in 88% of cases. The time from RT to surgery was associated with tumor regression grade (P = .0003). The median follow-up after RT was 16.5 months (range, 3.9-26.2). The derived median progression-free survival from RT was 13.2 months.

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Conclusions: The initial surgical and pathologic outcomes after A-SMART are encouraging. Preoperative A-SMART was associated with low toxicity rates and no surgical or RT-associated mortality. The surgical morbidity was comparable to historic rates after upfront resection. These data also suggest that the time from stereotactic body RT to surgical resection is associated with pathologic response.

Introduction

Pancreatic adenocarcinoma (PA) is one of the most common and deadliest cancers worldwide, with an estimated 10-year overall survival (OS) of 10%.[1] PA is the third leading cause of cancer-related death in the United States[2] and fourth leading cause of cancer-related death in Europe.[3] Historically, prolonged survival has only been achievable with surgical resection.[4]

Standard of care for resectable PA is surgical resection followed by adjuvant chemotherapy.[5,6] Adjuvant chemotherapy regimen of Leucovorin Calcium (Folinic Acid), Fluorouracil, Irinotecan Hydrochloride, and Oxaliplatin (FOLFIRINOX) is given to patients without evidence of progression after surgical resection because of improvements in survival.[7] For borderline resectable (BR) cancer, the National Comprehensive Cancer Network (NCCN) guidelines recommend neoadjuvant therapy as part of a study or at high volume centers because of paucity of evidence.[5] However, only 15% of patients with BR PA are able to undergo surgery.[8] These patients are at risk of a 40% to 80% positive margin rate without neoadjuvant therapy.[9,10] Approximately half of these patients will develop a local recurrence after a surgery-first approach.[11,12] Although recent evidence using neoadjuvant chemoradiation demonstrates reduced positive surgical margin rates,[13-15] increased pathologic tumor response,[16] and improved survival,[17,18] the role of stereotactic body radiation therapy (SBRT) in the setting of BR disease remains controversial, as a recent phase II Alliance trial terminated the hypofractionated RT arm early because of failure of meeting the prespecified endpoint of margin negative resection.[19]

Evidence from inoperable patients suggests that escalation of the biologically effective dose calculated with an α/β ratio of 10 (BED_{10}) offers improved local control (LC) that may in turn lead to an OS benefit.[20-24] The use of SBRT to achieve a higher BED_{10} (>70 Gy[22]) has historically been limited by toxicity to adjacent radiosensitive structures. However, these toxicities can be mitigated by the employment of magnetic resonance-guided RT (MRgRT).[22,25,26] Modern MRgRT is typically delivered with a system combining a magnetic resonance imaging (MRI) device with a traditional linear accelerator (MRL). This combination allows for improved soft-tissue visualization, real-time tracking of tumor and organs at risk (OAR) during treatment, beam gating based upon tumor position, and daily on-table adaptive replanning.[27,28] These advantages increase the therapeutic window and allow for stereotactic MR-guided adaptive RT (SMART).

Preoperative SBRT has been explored in unresectable PA and has been associated with high margin negative resection rates.[29-32] However, preoperative SBRT and dose escalation remain contentious due to concerns of greater surgical complication rates secondary to increased tissue density and fibrosis. To the best of our knowledge, we describe the first clinical experience of ablative dose SMART (A-SMART) before potentially curative resection of localized PA.

Methods and Materials

We performed a single-institution retrospective analysis with institutional review board approval of all patients with localized PA who received A-SMART, defined as $BED_{10} \geq 70$ Gy, on the ViewRay MRIdian system (Oakwood Village, OH), followed by surgical resection with curative intent between April 2019 and May 2021. Staging and assessment of tumor resectability were performed according to NCCN guidelines, and all patients were discussed at multidisciplinary pancreatic tumor board before therapy. Patients treated with or without neoadjuvant chemotherapy were included for analysis. Gross tumor volume (GTV) was defined as primary tumor as well as any regional lymph nodes involved. SBRT has been integrated into our consensus treatment pathway at our institution for the last 15 years. We adopted higher BED_{10} dosing for PA when the MRL was incorporated in 2019.

Simulation was performed without fiducial marker placement because of the direct tumor visualization provided by the ViewRay MRIdian system, which obviated the need for a surrogate marker. The patients laid supine with arms at the side for patient comfort without immobilization. Simulation was performed with deep inspiration breath hold (DIBH) for 25 seconds to obtain a 3-dimensional MRI and a representative sagittal slice where the primary tumor was identified. The Siemen MRI system within the MRIdian uses the balanced steady-state free precession sequence (TrueFISP). The patient is subsequently marked at the laser sites and taken to the computed tomography (CT) simulator. The patient is then placed in an identical supine position and undergoes a DIBH CT scan with and without intravenous and oral

contrast. Target and OAR contours were performed on the TrueFISP scan. The CT scan was deformably registered to TrueFISP scan for predictive dose calculation. The ViewRay MRIdian system uses a step-and-shoot intensity modulated RT treatment delivery technique. Intensity modulated RT plans were generated with Monte Carlo dose calculation and magnetic field corrections.

GTV and tumor vessel interface were defined as gross tumor within pancreas as seen on diagnostic imaging and simulation CT or MR scans. This volume was isotropically expanded by 3 mm to create the nominal planning target volume (PTV). The PTV was then isotropically expanded by 3 cm to create an OAR eval structure, within which OAR were recontoured daily. OAR that required contours included the stomach, duodenum, small bowel, large bowel, kidneys, liver, and spinal cord, as they are in conventional pancreatic SBRT plans (full constraints summarized in Table 1). OAR that may trigger adaptation, including the duodenum, stomach, and bowel, were combined into a single structure and expanded by 5 mm to create planning OAR volumes. This avoidance structure was then subtracted from the nominal PTV to generate a PTV_{opti} structure that was modified during the daily adaptation process. The $dens_{Water}$, $dens_{Air}$, and $dens_{Other}$ structures were also added before plan exportation to account for daily density changes. PTV prescriptions were 40 to 55 Gy, with lower doses used if considerable concern for toxicity was present during the treatment planning phase, such as duodenal abutment or involvement. Forty Gy was also used for the initial patients treated with our MRL when our system came online in March 2019. Daily adaptation was added to our workflow for PA in July 2019.

Before treatment delivery, the base plan was used to determine the predicted dose distribution on the anatomy of the day. The new target and OAR metrics achieved by the base plan upon the daily anatomy were then evaluated to determine whether violations occured (Table 1). Online adaptation was triggered if there was insufficient PTV coverage or if critical OAR dose exceeded predetermined allowed limits. Real-time tracking on a sagittal scan every 250 ms was performed with automatic gating. Automatic gating parameters were set to pause treatment if the target moved >5% outside of the prespecified region as determined before each treatment. DIBH was used during treatment to optimize duty cycle efficiency.

After completion of 5-fraction A-SMART, patients were restaged in 4 weeks with positron emission tomography/CT scans, as well as CT scans of the chest, pelvis, and the pancreas with a specific protocol scan. Patients without evidence of disease progression continued the operable management track if that aligned with the pancreas tumor board recommendation. In rare cases, initially nonoperable localized PA converted to an operable type, and they were then transitioned to an operable management workflow track within our institution. Surgical resection was typically performed between 6 to 8 weeks after RT. After appropriate surgical screening, the patients underwent surgical exploration and resection via total pancreatectomy, pancreaticoduodenectomy (aka Whipple procedure), or distal pancreatectomy based upon tumor anatomic position and geometry. Only those patients who underwent definitive surgery with curative intent were included in this study.

The resected tumor specimens were examined at the time of grossing to confirm anatomic tumor site. If there was no residual grossly visible tumor, then the residual area with fibrosis was submitted for further evaluation. All the sections derived from the tumor bed were assessed by an expert pancreatic pathologist. Tumor response was evaluated according to the College of American Pathologists tumor regression grading (CAP-TRG) criteria, ranging from CAP grade 0, indicating pathologic complete response (pCR); CAP grade 1, indicating marked response (minimal residual cancer with single cells or small groups of cancer cells); CAP grade 2, indicating moderate response

Table 1 Dose constraints for 5 fraction A-SMART

OAR	Objective*
Bowel	39.5 Gy max dose, <25 Gy mean
Stomach and duodenum	38 Gy max dose, <38 Gy mean
Stomach, duodenum, and bowel	V32 Gy cc ≤ 2 cc
Stomach, duodenum, and bowel	V35 Gy cc ≤ 0.5 cc
Kidneys (right and left)	Mean < 10 Gy
Spinal cord	20 Gy max dose
Critical constraints triggering online adaptation	
Stomach, duodenum, and bowel	Point dose max ≥ 39.5 Gy
Stomach, duodenum, and bowel	Max 0.5 cc ≥ 35 Gy

Abbreviations: A-SMART = ablative dose stereotactic magnetic resonance-guided adaptive radiation therapy; OAR = organs at risk.
*Hottest voxel is 10 Gy in 30% subvolume that receives the lowest overall dose.

(residual cancer outgrown by fibrosis); or CAP grade 3, indicating no response (extensive residual cancer).

Toxicity was prospectively evaluated and recorded at time of patient follow-up and according to Common Terminology Criteria for Adverse Events, version 5.0. Ordinal logistic regression model was used to assess the association between clinical factors and TRG (ie, time interval from A-SMART to surgery, receipt of chemotherapy, and RT dose). Patient OS and progression free survival (PFS) were evaluated using Kaplan-Meier analysis from time of diagnosis to most recent in-person clinical follow-up. LC was defined as absence of radiographic or clinical disease progression or recurrence within the treatment field. PFS was defined as the interval between the time of biopsy with tissue diagnosis to failure or death. Statistical analyses were performed using JMP version 16 Pro (SAS Institute Inc, Cary, NC). Follow-up included reimaging with contrast-enhanced abdominal CT or MRI scans and carbohydrate antigen 19-9 at least every 3 months.

Results

We retrospectively identified 26 patients with localized PA tumors who received A-SMART followed by surgical resection with curative intent. Patient, tumor, and treatment characteristics are summarized in Table 2. Median age at diagnosis was 68 (range, 34-86) years. Localized PA types consisted of BR (80.8%), locally advanced (LA) (11.5%), and resectable (7.7%). Most tumors were located at the head/neck of the pancreas (69%). Four patients had clinically node positive disease (16%) at time of diagnosis. Most patients received neoadjuvant chemotherapy (84.6%) before RT, with 81.8% receiving FOLFINIRNOX and 18.2% receiving gemcitabine/nab-paclitaxel. Median total cycle count was 6.5 (range, 3-12) for FOLFINIRNOX and 5 (range, 4-10) for gemcitabine/nab-paclitaxel. All patients received MR-guided ablative dose SBRT to a median dose of 50 (range, 40-50) Gy in 5 fractions. Median GTV of delivered plans, which is defined as the mean of appropriately weighted delivered base plan and adaptive plans, was 84.6 (range, 18.9-100) cm^3. Median delivered max dose to the bowel, duodenum, and stomach of delivered plans were 34.64 (range, 16.93-39.25) Gy, 35.70 (range, 15.20-38.71) Gy, and 34.56 (range, 8.59-39.50) Gy, respectively. On-table adaptive replanning was performed in 88% of patients, with 74% having all 5 fractions adapted. The median time to resection was 50 (range, 37-115) days, and the procedure types included Whipple (69%), distal (23%), and total pancreatectomy (8%). Median intraoperative time was 7 hours and 10 minutes (range, 3:57-12:12). Most patients received adjuvant chemotherapy (61.5%), with the majority receiving FOLFIRINOX (56.3%) and the rest receiving gemcitabine/nab-paclitaxel (43.7%). The median chemotherapy cycle count was 3 (range, 1-12). Total therapy duration, including both neoadjuvant and adjuvant, was 119 (range, 14-273) days.

Clinical and pathologic outcomes and toxicities are summarized in Table 3. The majority (88.5%) of patients demonstrated moderate-to-significant treatment response (TRG grade 0-2), with 2 patients (8%) achieving pCR. Increasing time from RT was associated with lower TRG (R^2 = 0.22, P = .0003). In an ordinal logistic regression modeling including the time interval from A-SMART until surgery (continuous variable), the receipt of neoadjuvant chemotherapy (categorical), and RT dose (continuous), interval time from A-SMART was the only variable significantly associated with TRG, where increased time interval was associated with decreased TRG (P = .007). The vast majority (96%) of patients had an R0 resection and the median postoperative hospital stay was 7 days (4-13). All treated lymph nodes were negative at time of resection.

The median follow-up after RT was 16.5 (range, 3.9-26.2) months, during which 9 patients recurred, and 3 patients died of disease. There were no deaths associated with toxicities related to A-SMART or surgical resection. The derived median PFS from diagnosis was 13.2 months (Fig. 1A). Median OS was not reached (95% confidence interval [CI], 26.5 months − not reached). The 1- and 2-year OS rates were 100% (95% CI, 0.87-1.00) and 82% (95% CI, 0.61-0.93), respectively. The 1-year freedom from local failure rate was 96%, with the only local recurrence occurring in the patient with a R1 resection. The median PFS from diagnosis was 24 months (95% CI, 16.2 months − not reached; Fig. 1B). TRG score was significantly associated with PFS on Kaplan-Meier analysis (P = .02; Fig. 2). There were 2 patients who experienced grade 1 acute nausea and 1 patient who experienced grade 1 fatigue. There were no acute grade 2+ toxicities associated with RT in this cohort.

Between April 2019 and May 2021, our institution treated 128 patients with PA with A-SMART, and none of these patients were prevented from undergoing surgical resection because of RT-related toxicities. Patients did not proceed to surgical resection either because of medical inoperability before A-SMART or their disease not meeting resectability criteria with restaging imaging. Two patients met NCCN resectability criteria and were recommended preoperative A-SMART at multidisciplinary tumor board review because of their high risk for positive margins. No postoperative deaths occurred within 90 days. Postoperative complication rates were low, with infection/abscess formation being the most common (19%) and chyle leak (15%) being the second-most common. Hemorrhages were rare (2/26; 8%) but both were grade 4. One patient had a hematoma formation because of hemorrhage from their celiac stump that required urgent stenting 17 days after their total pancreatectomy, splenectomy, and cholecystectomy with celiac axis resection. The other patient who experienced a grade 4

Table 2 Patient, tumor, and treatment characteristics

	n (range/%/hh:mm)
Age at diagnosis (y)	68 (34-86)
Sex	
Female	16 (62%)
Male	10 (38%)
Histology	
Adenocarcinoma	26 (100%)
Tumor location (on pancreas)	
Head/neck	18 (69%)
Body/tail	8 (31%)
Tumor cT stage	
1	5 (19%)
2	13 (50%)
3	4 (15%)
4	4 (15%)
Tumor cN stage	
0	22 (85%)
1	3 (12%)
2	1 (4%)
Resectability	
Resectable	2 (8%)
Borderline	21 (80%)
Locally advanced	3 (12%)
Neoadjuvant chemotherapy	
None	4 (15%)
FOLFIRINOX	18 (69%)
Gemcitabine/abraxane	4 (15%)
Cycle count, median	6 (3-12)
Time from last cycle to RT start (day)	20 (5-88)
RT dose and fractionation	
Total dose, median (Gy)	50 (40-55)
Number of fractions, median	5 (5-5)
BED $\alpha/\beta = 10$, median (Gy)	100.0 (72.0-115.5)
BED $\alpha/\beta = 3$, median (Gy)	216.7 (146.7-256.7)
$EQD2_{10}$ (Gy)	83.3 (60.0-96.2)
$EQD2_3$ (Gy)	130.0 (88.0-154.0)
Median delivered plan RT target volumes and dose	
GTV, prescription (cm^3)	84.6 (18.9-100)
GTV D95 (cGy)	4248.8 (3052.2-5379)
GTV V55 (%)	40.3 (0-83)
GTV V50 (%)	75.7 (0-100)
GTV V45 (%)	90.4 (0.4-100)
GTV V40 (%)	94.6 (45.8-100)
Median delivered plan RT organs at risk dose (Gy)	
Bowel, max	34.64 (16.93-39.25)
Bowel, 2 cc	25.46 (5.41-31.73)
Duodenum, max	35.70 (15.20-38.71)
Duodenum, 2 cc	30.09 (5.41-31.73)
Stomach, max	34.56 (8.59-39.50)
Stomach, 2 cc	26.06 (5.12-31.32)
Post-RT surgery	
Whipple	18 (69%)
Total pancreatectomy	2 (8%)
Distal pancreatectomy	6 (23%)
Time from RT to surgery, d	50 (37-115)
Intraoperative time	7:10 (03:57-12:12)
Intraoperative time, Whipple	7:41 (05:51-12:12)
Intraoperative time, distal panc.	4:26 (03:57-06:01)
Intraoperative time, total panc.	10:17
Adjuvant chemotherapy	
None	10 (38%)
FOLFIRINOX	9 (35%)
Gemcitabine/abraxane	7 (27%)
Cycle count, median	3 (1-12)
Cycle count, total (neo + adjuvant)	8.5 (1-18)

(*continued on next page*)

Table 2 (*Continued*)

Abbreviations: BED = biologically effective dose; cN = clinical nodal stage; cT = clinical tumor stage; EQD2 = equivalent dose in 2 Gy per fraction; FOLFRINOX = Leucovorin Calcium (Folinic Acid), Fluorouracil, Irinotecan Hydrochloride, and Oxaliplatin; GTV = gross tumor volume; panc =; RT = radiation therapy.

hemorrhage presented to an outside hospital 18 days after their Whipple procedure with a minor hemorrhage from gastrostomy-jejunostomy tube. This was presumed to be a rectus sheath hematoma. They were subsequently started on enoxaparin as an inpatient because of their history of pulmonary embolism and cardiac thrombi formation. Their hemorrhage rapidly progressed to a grade 4 that required emergent coil embolization of left superior epigastric artery, 5 units of packed red blood cells, and an intensive care unit stay of approximately 3 days before transfer to our institution where the rest of their course was noncomplicated. One patient was hospitalized 15 days after their distal pancreatectomy because of a non-ST-elevation myocardial infarction. The patient had a 48-year smoking history with cessation in the week before their surgery in addition to poorly controlled type

Table 3 RT toxicities, surgical outcomes, and pathologic outcomes

	n (range/%)
RT toxicity	
Acute, grade 1	3 (12%; 2 nausea, 1 fatigue)
Acute, grade 2+	0
Late, grade 1+	0
Surgical mortality, within 90 d	0
Postsurgical complications, within 90 d	
Pancreatic anastomosis leak, grade 1	2 (8%)
Chyle leak, grade 1	2 (8%)
Chyle leak, grade 2	2 (8%)
Delayed gastric emptying, grade 2	1 (4%)
Postoperative wound infection, grade 2	2 (8%)
Postoperative wound infection, grade 3	1 (4%)
Retroperitoneal abscess, grade 3	1 (4%)
Hemorrhage, grade 4	2 (8%)
Fistulae	0
Length of hospitalization, d	8 (4-13)
Rehospitalization, within 90 d	4 (15%)
CAP-TRG	
0	2 (8%)
1	6 (23%)
2	15 (58%)
3	3 (12%)
Resection status	
R0	25 (96%)
R1	1 (4%)
Postsurgical hospitalization length, median (d)	7 (4-13)
OS, median (mo)	Not reached (95% CI, 26.5 months − infinity)
OS, 1 y	100%
OS, 2 y	82%
PFS, median (months)	24 (95% CI, 16.2 months − infinity)
FFLF, 1 y	96%

Abbreviations: CAP-TRG = College of American Pathologists tumor regression grading;
CI = confidence interval; FFLF = freedom from local failure; OS = overall survival; PFS = progression free survival; RT = radiation therapy.

2 diabetes mellitus. The last patient was hospitalized 9 days after their Whipple procedure because of a grade 2 chyle leak that resolved with diet modification. They stayed overnight for observation and were discharged in the morning. There were no fistulae formation toxicities observed. In total, 4 patients were hospitalized within 90 days and all patients survived to discharge. An additional 4 other patients were hospitalized through the entire follow-up time, but none of these hospitalizations were related to surgical or RT toxicity. There are no known deaths related to either A-SMART or surgical resection within the entire follow-up time.

Discussion

In this study, we explored the feasibility and safety of A-SMART followed by surgical resection of PA and demonstrated low rates of toxicity from RT as well as favorable surgical and oncological results. The overall added

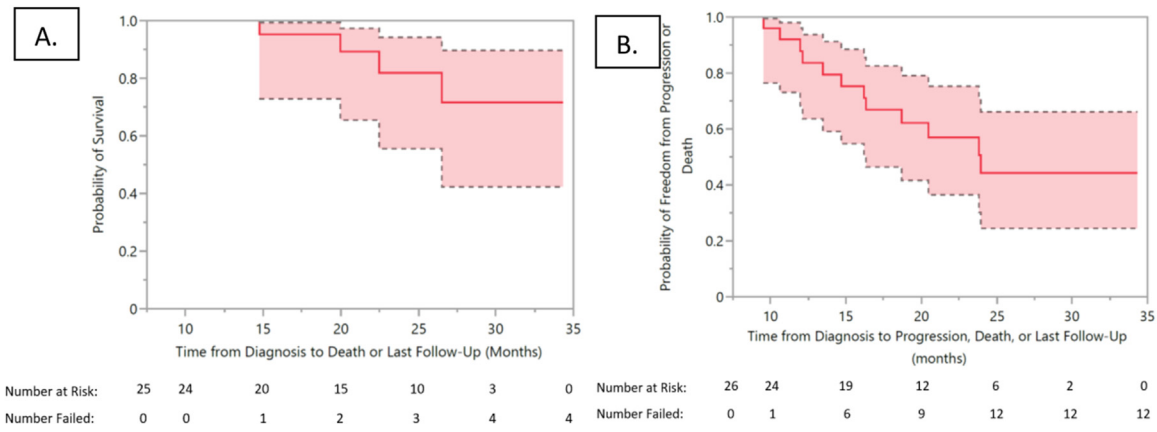

Figure 1 (A) Kaplan-Meier plot of patient survival measured from time of diagnosis. Median overall survival (OS) was not reached (95% confidence interval [CI], 26.5 months – not reached). (B) Kaplan-Meier plot of progression free survival (PFS) measured from time of diagnosis. Median PFS was 24 months (95% CI, 16.2 months – not reached).

surgical complexity was low, evidenced by low rates of surgical complications and high rates of margin negative resection (96%) despite a high proportion of initially BR and LA patients (92%). Eighty-eight percent of patients demonstrated a pathologic response (TRG 0-2). This regimen afforded impressive LC, with only 1 local failure at 12 months (1-year freedom from local failure 96%) in the patient who had an R1 resection. This robust LC facilitated long-term disease control with an excellent 1-year OS of 100% and PFS of 24 months (95% CI, 16.2 months – not reached). Importantly, toxicity related to A-SMART has not prevented any patients treated at our institution from proceeding to surgical resection. These results may offer an opportunity for further investigation into ablative preoperative treatment for localized PA.

R0 resection remains the best path to potential cure for localized PA. However, with a surgery-first approach, up to 50% of patients will develop a local recurrence.[11,12]

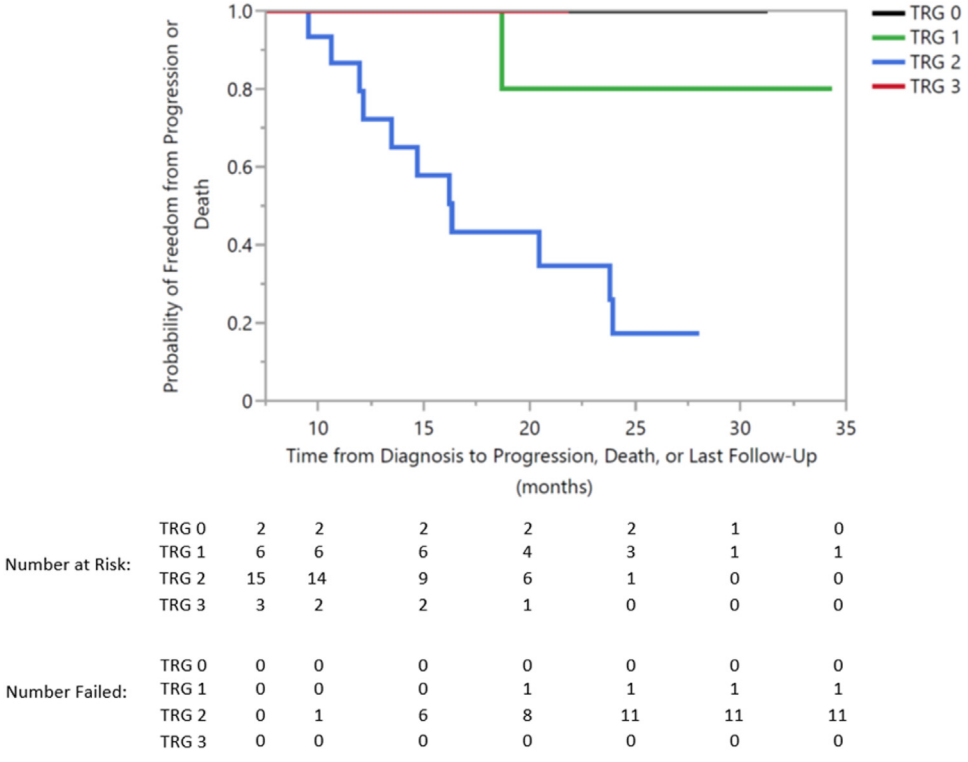

Figure 2 Kaplan-Meier plot of time from diagnosis to clinically relevant outcomes stratified by tumor regression grading (TRG). Clinically relevant outcomes of death and disease progression are inversely correlated with TRG (P = .02). Paradoxical improved clinical outcome of TRG 3 most likely due to limited number of patients with this pathologic event (n = 3).

In approximately 25% of these patients, local disease recurrence is the sole site of disease progression.[9] Preoperative therapy allows for biological selection of patients for curative resection, and despite the oncological benefits of preoperative therapy for localized PA,[17] only 50% of BR[19] and 10% of LA patients undergo successful resection after undergoing neoadjuvant chemotherapy.[8] Preoperative SBRT helps to sterilize surgical margins to improve R0 resection rates,[29-32] leading to improved LC for resected patients. However, a significant portion of patients with BR or LA disease will never make it to resection, and an ablative dose may improve LC for these patients.[33]

The R0 resection rates within this experience and other retrospective A-SMART cohorts[25,34] are comparable to prior preoperative SBRT for localized PA studies.[29-32] Zakem et al[31] reported a negative margin rate of 97% for patients who underwent surgery after SBRT of 30 to 33 Gy. Bouchart et al[32] reported on 19 patients treated with CT-based ablative dose SBRT that resulted in R0 rates congruent with lower dose SBRT historical cohorts and 18-month OS rate of 87%.[32] Almost all patients within this cohort experienced grade 1 to 2 acute toxicities, and the acute grade 3 toxicity rate approached 10%.[32] A-SMART appears to be better tolerated compared with CT-based ablative dose SBRT, as historical cohorts experienced far higher grade 1 to 3 RT- related acute toxicities, ranging from 50% to 100%,[29,32] compared with only 12% of patients within our cohort. Although these acute toxicities did not appear to have prevented surgical resection,[29,32] decreased patient morbidity appears to be facilitated by adaptive treatment.

Isotoxic dose-escalation may be best facilitated through MRgRT, offering a unique advantage over previous pancreatic SBRT techniques because of the superior soft tissue visualization of MR and an ability to monitor inter- and intrafraction OAR position and movement.[34-36] Rudra et al[22] reported a series of 44 patients who were treated with MRgRT by conventionally fractionated, hypofractionated, or SBRT approaches for their localized PA. Upon stratified analysis of standard ($BED_{10} \leq 70$ Gy) versus ablative ($BED_{10} > 70$ Gy) dose, significant improvements of clinical outcomes, including higher OS and lower grade 3+ gastrointestinal toxicity, were associated with ablative dose MRgRT.[22] Previously, there have been limited descriptions of patients undergoing successful tumor resection after A-SMART in other retrospective experiences. Hassanzadeh et al[34] reported on a series of 44 patients treated with A-SMART, and reported on 4 patients able to proceed to surgery, with 3 patients undergoing tumor resection with 1 patient with a positive margin; however, 1 surgery was aborted because of excessive fibrosis. Finally, Chuong et al[25] reported a series of 35 patients treated with 5-fraction A-SMART on an MR linear accelerator with localized and unresectable PA and demonstrated a very favorable toxicity profile with no acute or late grade 4 or 5 toxicities and less than 3% acute and late grade 3 toxicities. The 1-year LC and OS rates were 87.8% and 58.9%, respectively. In this experience, 5 patients (60% BR) underwent a Whipple procedure performed at a median of 2 (range, 1-9) months after completion of A-SMART to median radiation dose of 50 Gy. All resected patients received induction FOLFIRINOX (n = 4) or gemcitabine/nab-paclitaxel (n = 1). Four patients were successfully resected with negative margins, 1 patient experienced a complete response (TRG 0), and 2 patients had a near complete pathologic response (TRG 1). None of the resected patients had evidence of tumor recurrence after median 10.8 months follow-up.[25]

Despite these results, there is hesitation with preoperative ablative dose SBRT due to concerns of increased surgical morbidity and mortality secondary to increased degree of local fibrosis associated with higher RT dose. Within 90-days postoperatively, in our experience there was no mortality, and only 4 patients (15%) were readmitted. These outcomes compare favorably with historical open and robot-assisted Whipple surgery rates, with postoperative 90-day mortality ranging from 2% to 3% and rehospitalization rates from 23% to 31%.[37] Furthermore, the median hospitalization of 8 days (range, 4-13) within our cohort is comparable to post-Whipple hospitalization stays that can range from 4 days to as high as 5 months.[17,37,38] In comparison to conventional SBRT experiences, grade 4 postsurgical complication rates have been reported as high as 21%[32] compared with 8% within our A-SMART cohort.

Lastly, a notable finding in this study is the positive correlation between time interval between RT and improvement in pathologic outcomes ($P = .0003$). To the best of our knowledge, this is the first reported analysis of time interval from RT to pathologic outcome in PA. Increasing time interval between RT and improved pathologic response has been reported for other gastrointestinal sites.[39,40] Data from rectal cancer in the Timing of Rectal Cancer Response to Chemoradiotherapy Trial demonstrated that longer neoadjuvant chemotherapy durations after chemoradiation were associated with improved pCR rates of up to 38%.[41] The mechanism for this continuing effect of RT after SBRT may be secondary to fibrosis of local vasculature that reduces nutrient supply to the tumor and an in vivo immunization to the localized tumor antigens produced with ablative doses.[42] Our study was not powered to assess the effect of type or duration of chemotherapy; however, time from RT was the only statistically significant predictor for improved pathologic outcomes compared with neoadjuvant chemotherapy and total radiation therapy dose. Our data confirm previously published reports demonstrating an association of PFS with TRG.[43] As data mount in support of neoadjuvant therapy for PA, we await

prospective validation of TRG as a surrogate endpoint of clinical significance.

Limitations of our study include its retrospective design, making it subject to underreporting of toxicities, although these were prospectively recorded at time of follow-up. We have multiple pancreatic cancer pathologists at our institution and thus could not control for interpersonal pathologic evaluation bias. There is a significant variance of neoadjuvant and adjuvant chemotherapy in both regimen type and total cycles, and thus the effect of chemotherapy on clinical outcomes in this cohort was unable to be assessed. The cohort consisted of BR, LA, and resectable patients, according to NCCN definitions, contributing to overall patient heterogeneity. There was a relatively short follow-up because of the recent implementation of this A-SMART regimen. There was no comparator arm of patients treated with standard-dose CT-based SBRT. Lastly, it should be noted that there may be limited generalizability of these results because of the nature of our experience as a high-volume institution.

Looking forward, we await the results of the Stereotactic MRI-Guided On-Table Adaptive Radiation Therapy (SMART) for Locally Advanced Pancreatic Cancer trial (NCT03621644), which is the first prospective trial to evaluate A-SMART in BR and LA PA. In this trial, they are delivering 50 Gy in 5 fractions to these lesions to determine toxicities, OS, PFS, and quality of life metrics. Additionally, other novel strategies to mitigate the potential OAR toxicities from high BED SBRT include the integration of radioprotectors.[44,45] Despite these considerable advancements, PA is still considered an incurable cancer with RT alone. We eagerly await these results in addition to their report on surgical outcomes for patients who undergo subsequent resections.

Conclusions

PA resection after A-SMART appears to be safe and well tolerated without preoperative grade 2+ morbidity, postoperative grade 3 to 4 toxicity rates of 8%, and no 90-day postsurgical mortality. No patients with localized PA and treated with A-SMART at our institution were prevented from undergoing surgical resection because of A-SMART–associated toxicity. Results from prospective studies using A-SMART in combined modality therapy against PA are eagerly awaited and may potentially validate our novel findings, suggesting that the time from SBRT to surgical resection is associated with pathologic response.

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