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Pathological and surgical outcomes of pancreatic adenocarcinoma (PA) after pre-operative ablative stereotactic magnetic resonance image-guided adaptive radiotherapy (A-SMART)

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Abstract

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

Methods and Materials: We describe our single-institution experience of high BED SMART prior to resection of localized PA. 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 (CAP-TRG).

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 (34 - 86). Most patients received chemotherapy (80.8%) prior to RT. All patients received A-SMART to a median dose of 50 (range 40 - 50) Gy in 5 fractions. Toxicity data was collected prospectively and there was no acute grade 2+ toxicities associated with RT. The median time to resection was 50 days (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 (TRG) ($p = 0.0003$). The median follow-up after RT was 16.5 months (3.9- 26.2). The derived median progression-free survival from RT was 13.2 months.

Conclusions: The initial surgical and pathological outcomes following A-SMART are encouraging. Preoperative A-SMART was associated with low toxicity rates and no surgical or radiotherapy-associated mortality. The surgical morbidity was comparable to historic rates after

upfront resection. These data also suggest that the time from SBRT 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 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 FOLFIRINOX is given to patients without evidence of progression after surgical resection due to 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 due to 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 40-80% positive margin rate without neoadjuvant therapy(9, 10). Approximately half of these patients will develop a local recurrence following a surgery-first approach(11, 12). While recent evidence utilizing 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 radiotherapy (SBRT) in the setting of BR disease remains controversial as a

recent phase II Alliance trial terminated the hypofractionated radiotherapy arm early due to 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 alpha/beta ratio of 10 (BED_{10}) offers improved local control (LC) that may in turn lead to an overall survival 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 radiotherapy (MRgRT)(22, 25, 26). Modern MRgRT is typically delivered with a system combining an 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 radiotherapy (SMART).

Pre-operative SBRT has been explored in unresectable PA and has been associated with high margin negative resection rates(29-32). However, pre-operative SBRT and dose escalation remains 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 A-SMART prior to potentially curative resection of localized PA.

Methods

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 to May 2021. Staging and assessment of tumor resectability were performed according to NCCN guidelines and all patients were discussed at multidisciplinary pancreatic tumor board prior to 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 MRI linac was incorporated in 2019.

Simulation was performed without fiducial marker placement due to the direct tumor visualization provided by the ViewRay MRIdian system, obviating the need for a surrogate marker. The patients laid supine with arms at side for patient comfort without immobilization. Simulation was performed with deep inspiration breath hold (DIBH) for 25-seconds to obtain a 3D MRI image and a representative sagittal slice where the primary tumor is identified. The Siemen MRI system within the MRIdian utilizes the balanced steady-state free precession sequence (TrueFISP). The patient is subsequently marked at the laser sites and taken to the CT simulator. The patient is then placed in an identical supine position and undergoes a DIBH with and without IV and oral contrast. Target and OAR contours were performed on the TrueFISP scan. The CT scan is deformably registered to TrueFISP scan for predictive dose calculation. The ViewRay MRIdian system utilizes a step-and-shoot IMRT treatment delivery technique. IMRT 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 is isotropically expanded by 3 mm to create the nominal planning target volume (PTV). The PTV is then isotropically expanded by 3 cm to create an OAR eval structure, within which OAR will be recontoured daily. OAR that require contours include 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, are combined into a single structure, and expanded by 5 mm to create planning organ at risk volumes (PRVs). This avoidance structure is then subtracted from the nominal PTV to generate a PTVopti structure that will be modified by the daily adaptation process. The densWater, densAir, and densOther structures must also be added prior to plan exportation to account for daily density changes. PTV prescriptions were 40 - 55 Gy, with lower doses utilized if considerable concern for toxicity was present during the treatment planning phase such as duodenal abutment or involvement. 40 Gy was also utilized 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.

Prior to treatment delivery, the base plan is 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 are then evaluated to determine if violations occur (**Table 1**). Online adaptation was triggered if there was insufficient PTV coverage or if critical OAR dose exceeded pre-determined allowed limits. Real-time tracking on a sagittal scan every 250 ms is performed with

automatic gating. Automatic gating parameters set to pause treatment if the target moves >5% outside of pre-specified region as determined prior to each treatment. DIBH is utilized during treatment to optimize duty cycle efficiency.

After completion of 5-fraction A-SMART, patients were re-staged in four weeks with PET/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 non-operable 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 six to eight 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 are assessed by an expert pancreatic pathologist. Tumor response was evaluated according to the College of American Pathologists tumor regression grading criteria (CAP-TRG): 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 (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 (CTCAE), version 5.0. Ordinal logistic regression model was used to assess the association between clinical factors and TRG (i.e., time interval from A-SMART to surgery, receipt of chemotherapy, and radiotherapy dose). Patient overall survival (OS) and progression free survival (PFS) was evaluated using Kaplan-Meier analysis from time of diagnosis to most recent in-person clinical follow up. Local control (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 re-imaging with contrast enhanced abdominal CT or MRI scans and CA19-9 at least every three 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 borderline resectable (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%) prior to 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%), or 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 pathological 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 = 0.0003). In an ordinal logistic regression modeling including the time interval from A-SMART until surgery (continuous variable), the receipt of neoadjuvant chemotherapy (categorical) and radiotherapy 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 = 0.007). The vast majority (96%) of patients had a R0 resection and the median post-operative 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 progression-free survival from diagnosis was 13.2 months (**Figure 1A**). Median overall survival 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 (FFLF) 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; **Figure 1B**). TRG score was significantly associated with PFS on KM analysis (p = 0.02; **Figure 2**). There were two patients who experienced grade 1 acute nausea and one patient who experienced grade 1 fatigue. There was no acute grade 2+ toxicities associated with RT in this cohort.

Between April 2019 to May 2021, our institution treated 128 PA patients with A-SMART and none of these patients were prevented from undergoing surgical resection due to RT related toxicities. Patients did not proceed to surgical resection either due to medically inoperability prior to A-SMART or due to their disease not meeting resectability criteria with restaging imaging. Two patients met NCCN resectability criteria and were recommended pre-operative A-SMART at multidisciplinary tumor board review due to high risk for positive margins. No post-

operative deaths occurred within 90 days. Post-operative 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 due to 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 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 due to 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 ICU 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 due to a non-ST-elevation myocardial infarction (NSTEMI). The patient had a 48-year smoking history with cessation in the week prior to their surgery in addition to poorly control type 2 diabetes mellitus. The last patient was hospitalized 9 days after their Whipple procedure due to 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 surviving 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 radiotherapy as well as favorable surgical and oncological results. The overall added 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 pathological response (TRG 0 - 2). This regimen afforded impressive local control, with only one local failure at 12 months (1-year FFLF 96%) in the patient who had an R1 resection. This robust local control 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 pre-operative 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). 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). Pre-operative SBRT helps to sterilize surgical margins to improve R0 resection rates(29-32) leading to improved local control 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 local control for these patients(33).

The R0 resection rate within this experience and other retrospective A-SMART cohorts(25, 34) are comparable to prior pre-operative SBRT for localized PA studies(29-32). Zakem et al. reported a negative margin rate of 97% for patients who underwent surgery after SBRT of 30-33 Gy(31). Bouchart et al. 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 when compared to CT-based ablative dose SBRT, as historical cohorts experience far higher grade 1 - 3 RT related acute toxicities, ranging from 50 – 100% (29, 32), compared to only 12% of patients within our cohort. While 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 due to the superior soft tissue visualization of MR and an ability to monitor inter- and intra-fraction OAR position and movement(34-36). Rudra et al. reported a series of 44 patients that 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 overall survival 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. 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 one surgery was aborted due to excessive fibrosis(34). Finally, Chuong et al. reported a series of 35 patients treated with 5-fraction A-SMART on a MR Linac 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(25). The 1-year local control and overall survival 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, one 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 radiotherapy dose. Within 90-days post-operatively, 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 post-operative 90-day mortality ranging from 2-3% and rehospitalization rates from 23-31%(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 post-surgical complication rates have been reported as high as 21% (32) compared to 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 pathological outcomes ($p = 0.0003$). To the best of our knowledge, this is the first reported analysis of time interval from RT to pathological outcome in PA. Increasing time interval between RT and improved pathological response has been reported for other gastrointestinal (GI) sites(39, 40). Data from rectal cancer in the TIMING 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 radiotherapy 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 impact of type or duration of chemotherapy, however time from radiotherapy was the only statistically significant predictor for improved pathological outcomes when compared to neoadjuvant chemotherapy and total radiotherapy dose. Our data confirms previously published reports demonstrating an association of PFS with TRG(43). As data mounts 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 and thus 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

pathological 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 consists of BR, LA, and resectable patients according to NCCN definitions contributing to overall patient heterogeneity. There is a relatively short follow up due to the recent implementation of this A-SMART regimen. There is 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 due to 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, overall survival, progression-free survival, 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 radiotherapy alone. We eagerly await these results in addition to their report on surgical outcomes for patients who undergo subsequent resections.

Conclusion

PA resection after A-SMART appears to be safe and well tolerated without pre-operative grade 2+ morbidity, post-operative grade 3-4 toxicity rates of 8%, and no 90-day post-surgical

mortality. No patients with localized PA and treated with A-SMART at our institution were prevented from undergoing surgical resection due to 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 finding suggesting that the time from SBRT to surgical resection is associated with pathologic response.

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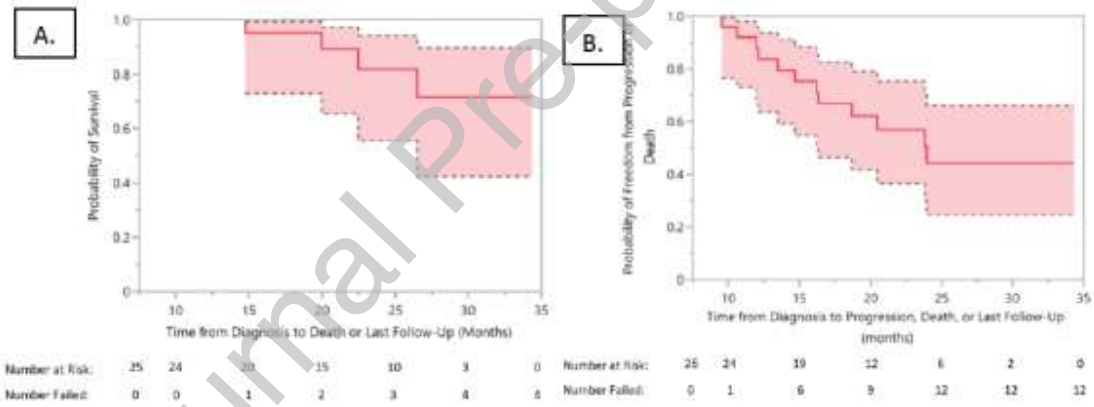
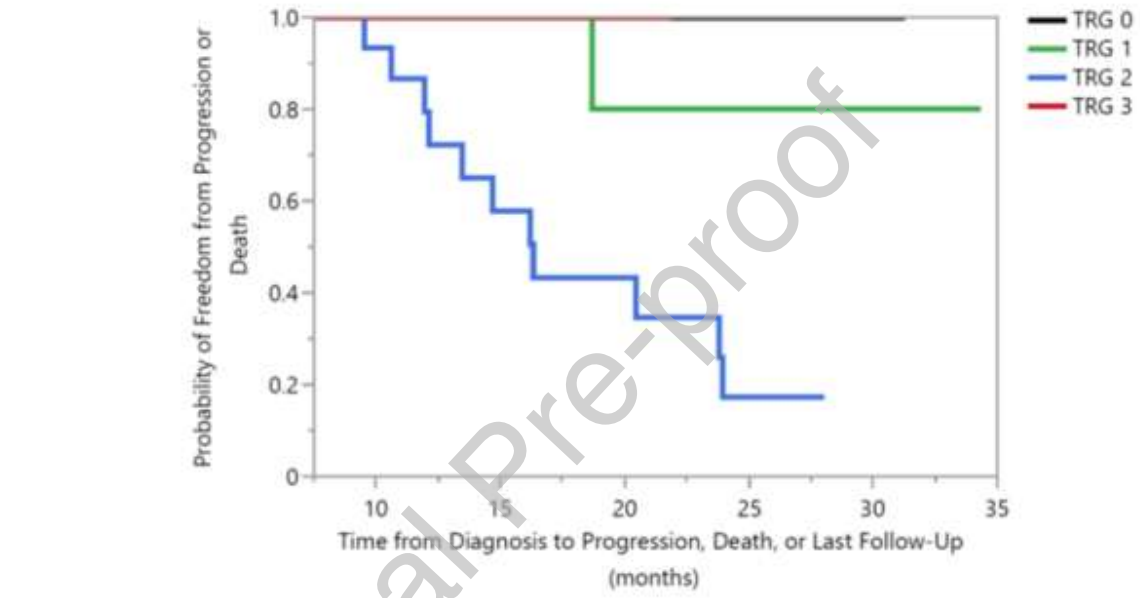


Figure 1. A) Kaplan-Meier plot of patient survival measured from time of diagnosis. Median OS was not reached (95% CI: 26.5 months – not reached). B) Kaplan-Meier plot of progression free survival measured from time of diagnosis. Median PFS was 24 months (95% CI: 16.2 months – not reached).



Number at Risk:	TRG 0	2	2	2	2	1	0
	TRG 1	6	6	6	4	3	1	1
	TRG 2	15	14	9	6	1	0	0
	TRG 3	3	2	2	1	0	0	0
Number Failed:	TRG 0	0	0	0	0	0	0	0
	TRG 1	0	0	0	1	1	1	1
	TRG 2	0	1	6	8	11	11	11
	TRG 3	0	0	0	0	0	0	0

Figure 2. Kaplan-Meier plot of time from diagnosis to clinically relevant outcomes stratified by TRG. Clinically relevant outcomes of death and disease progression are inversely correlated with

TRG (p = 0.02). Paradoxical improved clinical outcome of TRG 3 most likely due to limited number of patients with this pathological event (N=3).

Table 1. Dose constraints for five 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

*Hottest voxel is 10 Gy in 30% subvolume that receives the lowest overall dose

Table 2. Patient, tumor, and treatment characteristics

	N (range/%/hh:mm)
Age at diagnosis (year)	68 (34-86)
Gender	
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 α/β=10, median (Gy)	100.0 (72.0-115.5)
BED α/β=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, 2cc	25.46 (5.41-31.73)
Duodenum, max	35.70 (15.20-38.71)
Duodenum, 2cc	30.09 (5.41-31.73)
Stomach, max	34.56 (8.59-39.50)
Stomach, 2cc	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, days	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)

Table 3. RT toxicities, surgical outcomes, and pathological 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 days	0
Post-surgical complications, within 90 days	
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%)
Post-operative wound infection, grade 2	2 (8%)
Post-operative wound infection, grade 3	1 (4%)
Retroperitoneal abscess, grade 3	1 (4%)
Hemorrhage, grade 4	2 (8%)
Fistulae	0

Length of hospitalization, days	8 (4-13)
Re-hospitalization, within 90 days	4 (15%)
TRG- CAP	
0	2 (8%)
1	6 (23%)
2	15 (58%)
3	3 (12%)
Resection Status	
R0	25 (96%)
R1	1 (4%)
Post-surgical hospitalization length, median (d)	7 (4-13)
OS, median (months)	Not reached (95% CI: 26.5 months – infinity)
OS, 1-year	100%
OS, 2-year	82%
PFS, median (months)	24 (95% CI: 16.2 months – infinity)
FFLF, 1-year	96%