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CLINICAL INVESTIGATION

A Multi-Institutional Phase 2 Trial of Ablative 5-Fraction Stereotactic Magnetic Resonance-Guided On-Table Adaptive Radiation Therapy for Borderline Resectable and Locally Advanced Pancreatic Cancer

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Purpose: Magnetic resonance (MR) image guidance may facilitate safe ultrahypofractionated radiation dose escalation for inoperable pancreatic ductal adenocarcinoma. We conducted a prospective study evaluating the safety of 5-fraction Stereotactic MR-guided on-table Adaptive Radiation Therapy (SMART) for locally advanced (LAPC) and borderline resectable pancreatic cancer (BRPC).

Methods and Materials: Patients with LAPC or BRPC were eligible for this multi-institutional, single-arm, phase 2 trial after ≥3 months of systemic therapy without evidence of distant progression. Fifty gray in 5 fractions was prescribed on a 0.35T MR-guided radiation delivery system. The primary endpoint was acute grade ≥3 gastrointestinal (GI) toxicity definitely attributed to SMART.

Results: One hundred thirty-six patients (LAPC 56.6%, BRPC 43.4%) were enrolled between January 2019 and January 2022. Mean age was 65.7 (36-85) years. Head of pancreas lesions were most common (66.9%). Induction chemotherapy mostly consisted of (modified)FOLFIRINOX (65.4%) or gemcitabine/nab-paclitaxel (16.9%). Mean CA19-9 after induction chemotherapy and before SMART was 71.7 U/mL (0-468). On-table adaptive replanning was performed for 93.1% of all delivered fractions. Median follow-up from diagnosis and SMART was 16.4 and 8.8 months, respectively. The incidence of acute grade ≥3 GI toxicity possibly or probably attributed to SMART was 8.8%, including 2 postoperative deaths that were possibly related to SMART in patients who had surgery. There was no acute grade ≥3 GI toxicity definitely related to SMART. One-year overall survival from SMART was 65.0%.

Conclusions: The primary endpoint of this study was met with no acute grade ≥3 GI toxicity definitely attributed to ablative 5-fraction SMART. Although it is unclear whether SMART contributed to postoperative toxicity, we recommend caution when pursuing surgery, especially with vascular resection after SMART. Additional follow-up is ongoing to evaluate late toxicity, quality of life, and long-term efficacy.

Introduction

The use of radiation therapy (RT) for pancreatic ductal adenocarcinoma (PDAC) remains controversial. Contemporary studies have shown no apparent effect on overall survival (OS).[1-3] Large retrospective studies that employ modern chemotherapy regimens such as (modified)FOLFIRINOX also do not clearly demonstrate that adding RT to chemotherapy improves OS for inoperable PDAC.[4]

Prior prospective studies of 5-fraction RT for PDAC have used nonablative radiation dose because of the proximity of nearby gastrointestinal luminal organs at risk (GI-OARs) and concerns about causing severe toxicity. Emerging data suggest that increasing the prescribed radiation dose to an ablative range improves local control (LC) and potentially OS.[5,6]

Stereotactic Magnetic resonance-guided Adaptive Radiation Therapy (SMART) is a novel approach that uses magnetic resonance imaging (MRI) scans acquired both before and continuously during treatment delivery. SMART facilitates on-table RT treatment plan modification to account for daily anatomic changes while delivering ablative radiation to the target with respiratory motion management using real-time cine images. Retrospective outcomes of 5-fraction SMART for inoperable PDAC have been favorable with respect to treatment efficacy and safety.[7-10] However, 5-fraction SMART has not previously been studied in a prospective manner.

We conducted the first multi-institutional prospective phase 2 trial of ablative 5-fraction SMART for locally advanced pancreatic cancer (LAPC) and borderline resectable pancreatic cancer (BRPC) (NCT03621644) and herein present the initial study outcomes.

Methods and Materials

Study design and eligibility criteria

This multi-institutional, single-arm, phase 2 trial enrolled 136 patients across 13 sites in 3 countries (United States [n = 11], Italy [n = 1], Israel [n = 1]). All enrolled patients had pathologically confirmed LAPC or BPRC based on

institutional resectability criteria. Study participants were required to receive at least 3 months of any systemic chemotherapy without evidence of distant progression before study enrollment. Study eligibility also included that participants have Eastern Cooperative Oncology Group performance status ≤1 and CA19-9 ≤ 500 U/mL after induction chemotherapy.

Participating institutions were in compliance with the protocol approved by study sites' respective institutional review boards/ethics committees and in accordance with the ethical and regulatory guidelines for their country.

Study data were reviewed by an independent Data Safety Monitoring Board (DSMB) and a separate independent Clinical Events Committee (CEC), both comprised of clinicians with expertise in PDAC management. Both committees were independent of the primary investigators of the study, as recommended in Food and Drug Administration guidance material (https://www.fda.gov/media/75398/download). Further, the DSMB and CEC were not composed of the same individuals. The DSMB reviewed the study for safety at least on an annual basis. The CEC adjudicated all grade ≥3 GI toxicity events.

SMART

SMART was delivered using an integrated 0.35T MR-cobalt (n = 2, 1.5%) or MR linear accelerator (LINAC) system (n = 134, 98.5%) (MRIdian; ViewRay, Inc, Denver, CO). Details regarding the MR-cobalt and MR-LINAC technologies and associated workflow have previously been reported.[11,12] Integral to the workflow is the prediction of the radiation dose that would be delivered to the target volume and OARs, assuming the original plan was used, based on anatomic changes visualized on volumetric pretreatment MRI scans acquired each treatment day on the Magnetic Resonance-guided Radiation Therapy (MRgRT) system. When OAR constraints were violated because of anatomic changes, the study required that on-table adaptive replanning be performed to primarily ensure that OAR constraints were met; optimizing target volume coverage was a secondary objective. The original plan was not delivered if on-table adaptive replanning was required. On-table plan adaptation, plan evaluation, and adaptive quality assurance occurred while the patient remained in the treatment position. During treatment delivery, sagittal planar MR images were continuously acquired during treatment delivery at either 4 or 8 frames per second, and the radiation beam was automatically paused when the tracked pancreatic tumor moved out of a defined gating boundary, which typically was due to respiratory motion.

SMART was delivered with a prescribed dose of 50 Gy in 5 fractions (biologically effective dose $[BED]_{10}$ = 100 Gy) with at least 2 fractions delivered per week and a minimum interval of 18 hours between fractions. Focal hotspots were permitted if they were located within the gross tumor volume (GTV), with no specified maximum dose limit. GI-OAR dose constraints are listed in Table 1. The GTV included radiographically visible tumor in the pancreas and involved locoregional lymph nodes. The study protocol allowed for the optional use of a clinical target volume (CTV) to cover potential microscopic disease. The extent of the CTV was not defined in the study protocol and was at the discretion of the treating physician; this could have included an isotropic expansion of the GTV alone or inclusion of specific anatomic regions and structures (eg, local vascular structures) considered to be at high risk of harboring micrometastatic disease. A "comprehensive" nodal volume was never included. The planning target volume (PTV) was developed as a 3-mm uniform expansion from the GTV, or otherwise the CTV if one was used. For dose planning, OAR dose limits superseded dose coverage to the PTV.

Table 1 Gastrointestinal organ-at-risk constraints

Structure	Goal
Liver	Mean dose < 20 Gy
	Keep 700 cm^3 under 15 Gy
Duodenum maximum dose	V33 ≤ 0.5 cm^3
Stomach maximum dose	V33 ≤ 0.5 cm^3
Small bowel maximum dose	V33 ≤ 0.5 cm^3
Large bowel maximum dose	V33 ≤ 0.5 cm^3
Spinal canal	V25 < 0.5 cm^3
Kidney (each)	Mean < 12 Gy
	Two-thirds of each kidney < 14 Gy

Post-SMART therapy

Additional PDAC therapy after completion of SMART, including chemotherapy and/or surgery, was permitted at the discretion of the treating physician.

Patient assessments

Routine follow-up was scheduled at 90 days, 6 months, 12 months, and every 6 months through 5 years after initiation of study treatment. Physical examination, assessment of performance status, and cross-sectional imaging were performed at each visit. Adverse events were graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Patient-reported quality of life (QoL) was measured using the Functional Assessment of Cancer Therapy Hepatobiliary Cancer Symptom Index (FACT FHSI-18) survey instrument at baseline and 3 and 12 months after SMART.

Each RT plan delivered in the study was sent to a central DICOM (Digital Imaging and Communications in Medicine) storage section for central review at the end of the study (ProKnow DS, version 1.32.0). Post hoc central review

of contours and plans was performed after all patients had been treated. Dosimetric outcomes including OAR violations within the current analysis were reported by each institution and had not undergone central review at the time of this analysis. Metrics regarding target coverage were collected on a per-fraction basis.

Statistical evaluation

The primary endpoint was to determine Common Terminology Criteria for Adverse Events grade 3 or greater definitely related GI toxicity up to 90 days after initiation of SMART. Secondary endpoints were (1) OS at 2 years defined from the time from tissue diagnosis of PDAC, (2) distant progression-free survival (DPFS) at 6 months from the end of SMART, and (3) patient-reported QoL measured using the Functional Assessment of Cancer Therapy Hepatobiliary Cancer Symptom Index (FACT FHSI-18) survey instrument.[13]

The sample size for this trial was determined using PASS 14 (NCSS, Kaysville, UT). Data from a minimum of 113 participants provided 80% power to detect a statistically significant ($P \leq .05$) and clinically important reduction from a historic comparison of 15.8% to 8% in grade 3 toxicity rates at 90 days.[14] To account for attrition, predicted at 15%, we planned to enroll a minimum of 133 patients. A statistically significant P value of <.05 and an observed value of the 1-sided upper 95% confidence bound were used. Statistical analyses were conducted using SAS (version 9.4; SAS Institute, Cary, NC). Follow-up time was calculated from the first day of SMART until the last study contact date, which is the latest date of all follow-up visits, assessments, adverse event onset or resolution, and study exit, including date of death. OS, LC, and DPFS were obtained from Kaplan-Meier analyses. Descriptive statistics of target coverage for each RT plan were analyzed with Excel.

An exploratory analysis was done for patients who had surgery versus no surgery after SMART and, unlike the primary endpoint evaluation, was not limited to 90 days after SMART. Each treating institution was asked to submit details for resected patients, including type of surgery, time interval from SMART to surgery, and margin status. Surgery was not required to be done at the institution where SMART was delivered. The primary investigators categorized each toxicity using the Clavien-Dindo classification.

Results

From January 2019 to January 2022, 136 participants completed 5-fraction SMART and were included in the primary endpoint evaluation. Of these 136 patients, all had at least 90 days of follow-up, except for 6 patients who died within 90 days of SMART.

The mean age of the study participants at enrollment was 65.7 years (range, 36-85 years). Most received induction (m)

Table 2 Baseline tumor characteristics

Characteristic	N = 136
Histology	
Adenocarcinoma	99.3% (135/136)
Other histology: carcinoma with squamous differentiation	0.7% (1/136)
Location of lesion	
Pancreatic head	66.9% (91/136)
Body	18.4% (25/136)
Overlapping body/tail	7.4% (10/136)
Pancreatic neck	3.7% (5/136)
Overlapping head/body	2.9% (4/136)
Tail	0.7% (1/136)
Size of primary lesion (cm)	
No.	134
Mean ± SD	3.1 ± 1.20
Min, max	0.6, 6.6
Stage T	
T1	3.7% (5/135)
T2	24.4% (33/135)
T3	12.6% (17/135)
T4	59.3% (80/135)
Stage N	
N0	68.9% (93/135)
N1	24.4% (33/135)
NX	6.7% (9/135)
Stage M	
M0	100.0% (135/135)
Stage TNM category	
I	16.3% (22/135)
II	23.7% (32/135)
III	60.0% (81/135)
Tumor marker CA19-9 at diagnosis (U/mL)	
No.	134
Mean ± SD	537.5 ± 1254.01
Min, max	1.0, 9600.0
Tumor classification	
Borderline resectable pancreatic cancer	43.4% (59/136)
Locally advanced pancreatic cancer, unresectable	56.6% (77/136)

Values are percentages (counts/sample size) unless otherwise stated. Table contains site-reported data.

Abbreviations: max = maximum; min = minimum; SD = standard deviation; TNM = tumor, node, metastases; CA19-9 = carbohydrate antigen 19-9.

Table 3 Adaptive radiation therapy characteristics

Characteristic	Fraction 1	Fraction 2	Fraction 3	Fraction 4	Fraction 5	Average across fractions
Fraction adapted	94.9% (129/136)	91.9% (125/136)	91.9% (125/136)	94.1% (128/136)	92.6% (126/136)	-‡
GI-OAR constraints violated*	95.3% (123/129)	93.6% (117/125)	95.2% (119/125)	96.9% (124/128)	96.8% (122/126)	-‡
Other reason for adaptation†	9.3% (12/129)	12% (15/125)	7.2% (9/125)	5.5% (7/128)	8.7% (11/126)	-‡
Dose covering 95% of GTV (Gy)						
No.	131	127	125	128	128	134
Mean ± SD	42.6 ± 7.2	43.0 ± 7.4	42.1 ± 8.3	42.5 ± 8.0	41.9 ± 8.0	42.4 ± 7.8
(Min, max)	(24.5, 56.6)	(23.7, 57.3)	(9.2, 59.3)	(22.5, 55.9)	(21.3, 57.4)	(9.2, 59.3)
GTV (cm^3)						
No.	131	126	125	128	128	134
Mean ± SD	90.3 ± 47.4	91.5 ± 47.6	91.9 ± 47.3	93.1 ± 47.3	90.7 ± 48.9	91.5 ± 47.6
(Min, max)	(17.5, 282.9)	(19.3, 285.3)	(21.2, 284.6)	(20.8, 274.8)	(18.1, 274.8)	(17.5, 285.3)
GTV V50Gy (%)						
No.	127	124	122	126	122	127
Mean	84.9	86.1	85.4	85.8	85.4	85.5
(Min, max)	(30.0, 99.5)	(45.8, 100.0)	(36.2, 99.8)	(48.7, 100.0)	(50.4, 99.9)	(30.0, 100.0)

Values are percentages (counts/sample size) unless otherwise stated. Table contains site-reported data.
Abbreviations: GI-OAR = gastrointestinal organ at risk; GTV = gross tumor volume; max = maximum; min = minimum; SD = standard deviation.
* GI-OARs included the duodenum and stomach, as well as the large and small bowel.
† Other reasons for adaptation included liver, spine, kidney, and tumor coverage.
‡ No averages were recorded for these characteristics.

FOLFIRINOX (n = 89; 65.4%) or gemcitabine/nab-paclitaxel (n = 23; 16.9%), and 22 patients had multiple sequential chemotherapy regimens (16.2%) before study enrollment; the mean induction chemotherapy duration was 5.1 ± 2.0 months. The mean time from completion of chemotherapy until the start of SMART was 1.3 ± 0.8 months.

Of the participants, 43.4% (n = 59) had BRPC and 56.6% (n = 77) had LAPC. The mean primary tumor size was 3.1 ± 1.2 cm (range, 0.6-6.6 cm), with most located in the pancreatic head (69.9%; n = 91). The mean CA19-9 at diagnosis was 537.5 ± 1254.01 U/mL (n = 134), which decreased to 71.7 ± 106.05 U/mL after chemotherapy and before study enrollment. Table 2 describes baseline tumor characteristics; all data were not available for 2 patients.

The mean GTV and PTV were 91.5 ± 47.6 cm^3 (range, 17.5-285.3) and 133.4 ± 67.15 cm^3 (range, 32.8-444.2), respectively. The average D95 of the GTV was 42.4 Gy (range, 9.21-59.3). A CTV was used for 54.4% of patients; 93.1% (633/680) of the total delivered fractions were adapted, most commonly because of predicted GI-OAR constraint violations (96% of adapted fractions). Violations of the duodenum, stomach, small bowel, and large bowel constraints occurred in 79%, 65%, 47%, and 26% of fractions, respectively. Each fraction delivered met all GI-OAR constraints after plan adaptation. Table 3 describes additional adaptive MRgRT characteristics.

Additional treatment after SMART included chemotherapy (n = 27; 19.9%) and surgery (n = 44; 32.4%). Most resected patients had BPRC (n = 33; 75%), whereas the minority had LAPC (n = 11; 25%). Surgery was performed after a mean 51.4 ± 52.8 days from SMART (range, 13-349 days). Twenty-three patients (52%) who received surgery required vascular resection. Vascular resection was venous only (n = 15; 65%), arterial only (n = 3; 13%), or arterial and venous (n = 5; 22%).

Median follow-up from diagnosis and SMART was 16.4 months (8.0, 40.3) and 8.8 months (1.2, 36.1), respectively. One-year DPFS, LC, and OS from SMART (Fig. 1) were 50.6%, 82.9%, and 65.0%, respectively. One-year DPFS, LC, and OS from diagnosis were 80.1%, 90.0%, and 93.9%, respectively. One-year DPFS, LC, and OS from SMART in resected versus unresected patients were 82% versus 46%, 93% versus 78%, and 85% versus 56%, respectively.

Twelve patients (8.8%) had treatment-related acute (<90 days) GI grade 3 or higher toxicities (Table 4), including abdominal pain (n = 6), bleeding (n = 4), diarrhea (n = 1), and chyle leak after surgery (n = 1). All were determined to be possibly related to SMART except for 3 incidents of abdominal pain that were adjudicated as probably related.

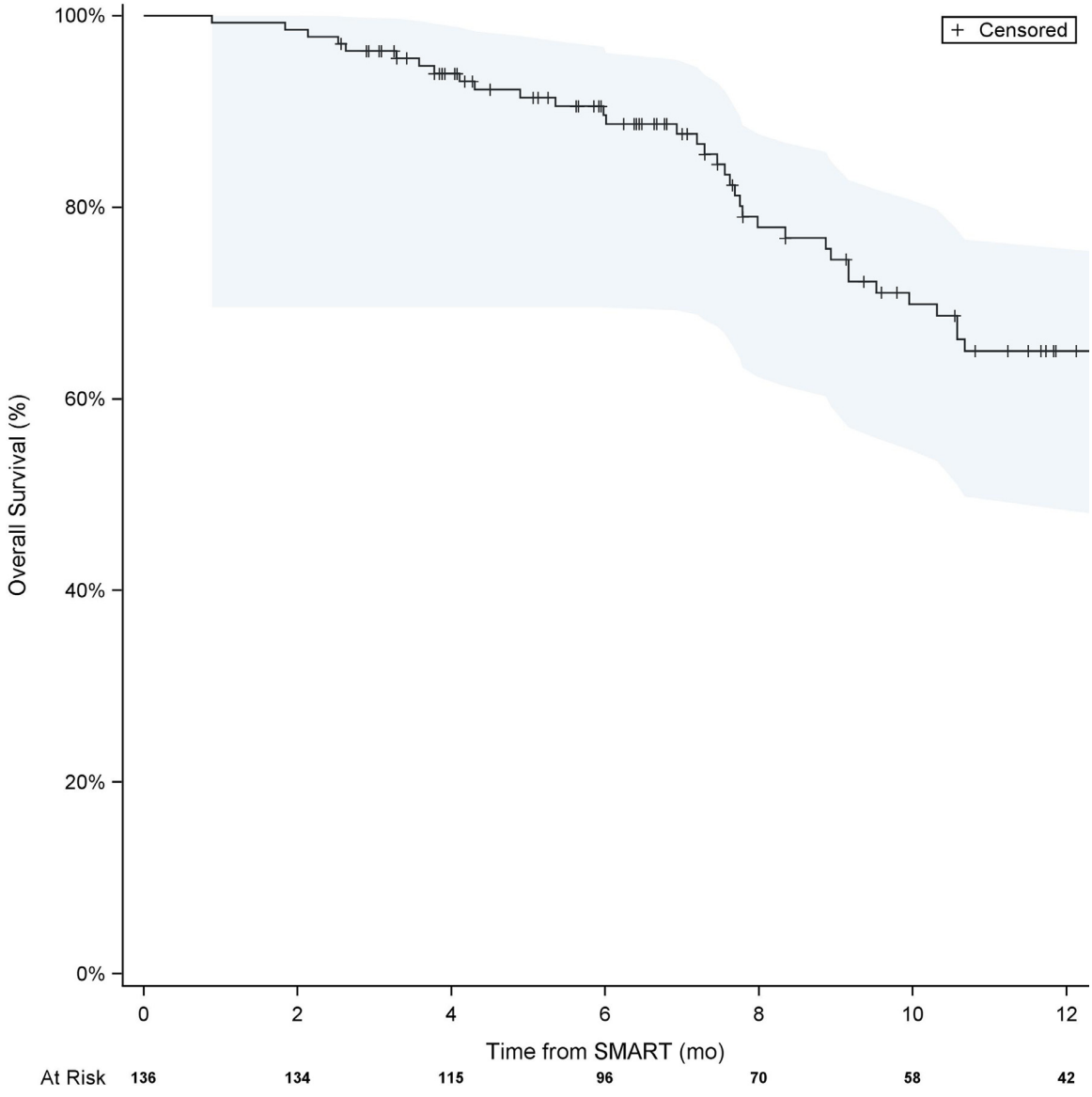

Fig. 1. Overall survival from stereotactic magnetic resonance-guided adaptive radiation therapy.

Each was determined to be grade 3 except for 2 grade 4 events (abdominal pain occurring 10 days after surgery with intraoperative irreversible electroporation; duodenal bleeding with evidence of tumor invasion into the duodenum) and 2 grade 5 events (gastroduodenal artery bleed 5 weeks after surgery and 11 weeks from SMART; bleeding during surgery performed 8 weeks after SMART). Both grade 5 events were determined to be possibly related to SMART and occurred in patients with BRPC who underwent portal vein resection and reconstruction. There were 4 additional deaths within 90 days of SMART not attributed to SMART and instead either disease progression (n = 3) or suicide (n = 1).

Clavien-Dindo grade 3 or higher surgical complications occurred in 9/44 (20.5%) resected patients. In addition to the 2 patients whose surgical complications were related to SMART, there was 1 patient who had surgery 129 days after SMART and died of postoperative complications adjudicated as being unrelated to SMART. All 3 postoperative deaths occurred in patients who had a vascular resection >5 weeks from SMART (39, 60, 129 days, respectively). The most common Clavien-Dindo grade 3 or higher complications after surgery included abdominal pain (23.1%), wound infection (23.1%), and hemorrhage (23.1%).

Discussion

Radiation therapy for inoperable PDAC is typically delivered using nonablative doses, with higher dose being avoided in order not to exceed the radiation tolerance of nearby GI luminal organs. Common nonablative regimens for BRPC/LAPC include 50.4 Gy in 28 fractions

Table 4 Gastrointestinal toxicity attributed to radiation therapy

Characteristic	Total events*	Participants with events (by worst event)
0-90 d		
Treatment-related GI toxicity†		
Grade 3	10	5.9% (8/136)
Grade 4	2	1.5% (2/136)
Grade 5	2	1.5% (2/136)
Grade ≥3	14	8.8% (12/136)
Treatment-related GI toxicity: definitely related		
Grade 3	0	0.0% (0/136)
Grade 4	0	0.0% (0/136)
Grade 5	0	0.0% (0/136)
Grade ≥3	0	0.0% (0/136)
Treatment-related GI toxicity: probably related		
Grade 3	3	2.2% (3/136)
Grade 4	0	0.0% (0/136)
Grade 5	0	0.0% (0/136)
Grade ≥3	3	2.2% (3/136)
Treatment-related GI toxicity: possibly related		
Grade 3	7	3.7% (5/136)
Grade 4	2	1.5% (2/136)
Grade 5	2	1.5% (2/136)
Grade ≥3	11	6.6% (9/136)

Values are percentages (counts/sample size) unless otherwise stated. Table contains CEC-adjudicated data.

Abbreviations: CEC = Clinical Events Committee; GI = gastrointestinal.

* One participant may have more than 1 event.

† Definitely, probably, or possibly related.

(BED_{10} = 59.5 Gy) and 33 Gy in 5 fractions (BED_{10} = 54.8 Gy). Published data demonstrate that higher prescribed BED_{10} is expected to improve local tumor control, especially for patients with PDAC who do not ultimately undergo surgery.[15] The concept that ablative radiation dose ($BED_{10} \geq$ 100 Gy) improves tumor control probability has been clearly demonstrated for other cancers such as stage I non-small cell lung cancer.[16]

Significant radiation dose escalation has not been pursued for PDAC because of technological limitations in visualizing and avoiding radiation to the mobile and radiosensitive stomach and small intestine at the time of treatment delivery. Standard LINACs that use on-board cone beam computed tomography (CT) for daily image guidance are unable to image the tumor and surrounding OARs during treatment with high resolution and do not have an on-table adaptive workflow to modify dose distributions before each fraction to account for substantial interfraction anatomic changes. Outcomes of a phase 1 trial of cone beam CT–guided, dose-escalated, 5-fraction pancreas stereotactic body RT (40, 45, 50 Gy) had 2 patients (6.7%) who experienced late grade 4 or 5 GI bleeding in the 45 Gy group.[17] A phase 2 pancreas stereotactic body RT trial that prescribed 45 Gy in 3 fractions (BED_{10} = 112.5 Gy) with 2-dimentional x-ray guidance reported acute grade 3 to 4 toxicities in most patients.[18] Reyngold et al[6] published a retrospective analysis of 15- to 25-fraction CT-guided ablative RT for LAPC that demonstrated favorable 2-year OS; a relatively low incidence (12.6%) of grade 3 toxicity was reported, most commonly upper GI bleeding. Although our study included patients who had surgery after SMART, no patients in the study by Reyngold et al were reported to have surgery.

Our trial represents the first prospective, multi-institutional evaluation of SMART delivered in 5 fractions with an ablative prescription dose of 50 Gy (BED_{10} = 100 Gy). The primary objective of the study was met, which was to demonstrate that the incidence of acute grade 3 or higher GI toxicity definitely related to SMART would be <15.8%, and the observed incidence was 0%. The incidence of acute grade 3 or higher GI toxicity at least possibly related to SMART was 8.8%, similar to what is expected from nonablative CT-guided RT.[17] This confirms findings from several published phase 1 trials using dose-escalated 5-fraction SMART on a 0.35T MRgRT system delivered to various targets in the abdomen and pelvis with minimal toxicity,[19,20] as well as multiple retrospective studies with similar findings.[7-10] Table 5 summarizes toxicities reported in other RT studies.

Although most patients in the current study did not have severe toxicity, a small number did experience grade 4 to 5 events. Although we cannot exclude the possibility that SMART may have contributed, the available data are not sufficient to draw meaningful conclusions regarding SMART and the causality of these events. Two patients experienced acute grade 4 toxicity possibly due to SMART; 1 resected patient had abdominal pain in the immediate postoperative period and another had bleeding with endoscopic evidence of duodenal invasion by tumor. Two patients with BRPC who underwent surgery with vascular reconstruction died because of bleeding complications within 90 days, 1 intraoperatively and 1 just under 3 months after surgery. One BRPC patient who had surgery with venous resection 129 days after SMART died 20 days postoperatively from spontaneous GI bleed.

Minimizing the risk of treatment-related toxicities should always be a priority, although despite best efforts to do so, some patients with BRPC or LAPC treated with or without RT will experience severe morbidity and even mortality. The probability of such events is not trivial, especially

Table 5 Toxicity outcomes from select studies of RT for inoperable pancreatic cancer

Reference	Study design	No.	Image guidance	Prescribed radiation dose/ fractions	Prescribed BED_{10}	Median follow-up	Toxicity
Herman et al[11]	Phase 2	49	CBCT	33 Gy/5 fractions	54.8 Gy	13.9 mo from diagnosis	Acute G2+ GI: 2%; late G2+ GI: 11%
Quan et al[26]	Phase 2	35	CBCT	36 Gy/3 fractions	79.2 Gy	15.4 mo from diagnosis	Acute G3+ GI: 0%; late G3+ GI: 0%
Comito et al[27]	Phase 2	45	CBCT	45 Gy/6 fractions	78.8 Gy	13.5 mo from diagnosis	Acute G3+ GI: 0%; late G3+ GI: 0%
Rudra et al[8]	Retrospective	44	0.35T MRI	Various	Various	17 mo from diagnosis	Acute G3+ GI: 0% (BED_{10} > 70 Gy); late NR
Hassanzadeh et al[7]	Retrospective	44	0.35T MRI	50 Gy/5 fractions	100 Gy	16 mo from diagnosis	Acute G3+ GI: 0%; late G3+ GI: 4.6%
Chuong et al[9]	Retrospective	62	0.35T MRI	Median, 50 Gy/5 fractions	Median, 100 Gy	18.6 mo from diagnosis; 11.0 mo from RT	Acute G3+ GI: 4.8%; late G3+ GI: 4.8%
Present study	Phase 2	136	0.35T MRI	50 Gy/5 fractions	100 Gy	8.8 mo from RT	Acute G3+ GI: 0% definitely related, 8.8% possibly/ probably related

Abbreviations: BED = biologically effective dose; CBCT = cone beam computed tomography; G = grade; GI = gastrointestinal; MRI = magnetic resonance imaging; RT = radiation therapy; NR= not reported.

among patients who undergo surgery after preoperative therapy, especially when vascular resection is performed. The observed Clavien-Dindo grade ≥3 complication rate in our study was 20.5%, which is similar to outcomes from a recent retrospective study of postoperative outcomes after ablative 5-fraction SMART from Moffitt Cancer Center.[21] We highlight that the rates of severe surgical complications from both studies are similar to historical surgical studies that did not include preoperative RT. Caruso et al[22] reported outcomes of 65 consecutive patients with LAPC who did not receive preoperative RT and had surgery with venous resection at 3 high volume centers in Spain; the Clavien-Dindo grade 3 perioperative morbidity rate was 21.5%. An analysis of 14 retrospective cohort studies including 7604 patients who underwent resection for PDAC without preoperative RT reported Clavien-Dindo grade ≥3 complication rates up to 31%.[23] A single institution analysis of 1056 pancreaticoduodenectomies reported a Clavien-Dindo grade ≥3 complication rate of 15.3%.[24] An international multicenter retrospective cohort study of 423 patients with PDAC who had preoperative FOLFIRINOX and then surgery found that postoperative major morbidity occurred in 20.8% and 90-day mortality was 2.8%.[25]

Although the incidence of grade 3 or higher postoperative complications in our study is not overtly higher than historical surgical outcomes without SMART, there is still much that is unknown about the effect of ablative radiation dose on surgery. We recommend proceeding cautiously when pursuing surgery, especially if vascular resection is required after ablative RT, and patients should be informed of potential surgical risks. Future studies are needed to better understand the effect of SMART on surgical outcomes and approaches, including the optimal timing of surgery after SMART; the postoperative deaths in our study occurred when surgery with vascular resection was performed ≥8 weeks after SMART. Lastly, we recommend that resections be performed by a surgeon with experience operating after ablative RT.

Strengths of this study are its prospective nature, use of a novel radiation delivery technology, detailed radiation planning guidelines, and the use of an independent clinical events review committee separate from the study investigators. This study was not limited to quaternary cancer referral centers and included both public and private institutions across multiple countries, thereby allowing the study results to be more generalizable to a spectrum of clinical practices.

There are several study limitations, which include enrolling both BRPC and LAPC that had different prognoses; LAPC or BPRC was determined based on institutional resectability criteria; variability in chemotherapy permitted before study enrollment, including single agent regimens; single-arm trial design; and variability in additional therapies given after SMART. At present, follow-up after SMART is limited, although our early results are encouraging and warrant additional evaluation of this novel treatment strategy. Longer follow-up is planned to better understand late toxicity outcomes and treatment efficacy results especially beyond 1 to 2 years from SMART. Lastly, we do not present patient-reported QoL outcomes in this article because not all data were available at the time of analysis; these outcomes will be presented in the future.

Based on the encouraging early results from this phase 2 trial, we plan to conduct an international, multi-institutional, phase 3 randomized trial for LAPC of chemotherapy alone versus chemotherapy followed by 5-fraction ablative SMART delivered on a 0.35T MR-LINAC with primary endpoint of 2-year OS (NCT05585554).

Conclusion

This is the first prospective evaluation of 5-fraction ablative SMART delivered on a 0.35T MR-guided radiation delivery system. Acute treatment-related grade 3 or higher toxicity was rare and the primary endpoint was met. Although it is unclear whether SMART contributed to postoperative toxicity, we recommend caution when pursuing surgery, especially with vascular resection. Further investigation is needed regarding the safety of surgery after SMART. Additional prospective evaluation of this novel treatment strategy is planned, with focus on long-term treatment efficacy.

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