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Original Article

Stereotactic MR-guided on-table adaptive radiation therapy (SMART) for borderline resectable and locally advanced pancreatic cancer: A multi-center, open-label phase 2 study

Michael D. Chuong [a,*], Percy Lee [b], Daniel A. Low [c], Joshua Kim [d], Kathryn E. Mittauer [a], Michael F. Bassetti [e], Carri K. Glide-Hurst [e], Ann C. Raldow [f], Yingli Yang [f], Lorraine Portelance [g], Kyle R. Padgett [g], Bassem Zaki [h], Rongxiao Zhang [h], Hyun Kim [i], Lauren E. Henke [i], Alex T. Price [i], Joseph D. Mancias [j], Christopher L. Williams [j], John Ng [k], Ryan Pennell [k], M. Raphael Pfeffer [l], Daphne Levin [l], Adam C. Mueller [m], Karen E. Mooney [m], Patrick Kelly [n], Amish P. Shah [n], Luca Boldrini [o], Lorenzo Placidi [o], Martin Fuss [p], Parag Jitendra Parikh [d]

[a] *Miami Cancer Institute, Baptist Health South Florida, Miami, FL, United States*
[b] *City of Hope National Medical Center, Los Angeles, CA, United States*
[c] *UCLA Department of Radiation Oncology, Los Angeles, CA, United States*
[d] *Henry Ford Health - Cancer, Detroit, MI, United States*
[e] *University of Wisconsin—Madison, Department of Human Oncology, Madison, WI, United States*
[f] *Department of Radiation Oncology, UCLA David Geffen School of Medicine, Los Angeles, CA, United States*
[g] *Sylvester Comprehensive Cancer Center, Miller School of Medicine, Miami, FL, United States*
[h] *Section of Radiation Oncology Dartmouth-Hitchcock Medical Center, Lebanon, NH, United States*
[i] *Washington University School of Medicine in St. Louis, St. Louis, MO, United States*
[j] *Brigham and Women's Hospital, Department of Radiation Oncology, Dana-Farber Cancer Institute, Department of Radiation Oncology, Harvard Medical School, Boston, MA, United States*
[k] *Weill Cornell Medicine Sandra and Edward Meyer Cancer Center, New York, NY, United States*
[l] *Assuta Medical Center, Tel Aviv, IL, United States*
[m] *Department of Radiation Oncology, Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA, United States*
[n] *Orlando Health Cancer Institute, Orlando, FL, United States*
[o] *Department of Radiology, Radiation Oncology and Hematology, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Rome, Italy*
[p] *ViewRay, Inc, Denver, CO, United States*

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ABSTRACT

Background and purpose: Radiation dose escalation may improve local control (LC) and overall survival (OS) in select pancreatic ductal adenocarcinoma (PDAC) patients. We prospectively evaluated the safety and efficacy of ablative stereotactic magnetic resonance (MR)-guided adaptive radiation therapy (SMART) for borderline resectable (BRPC) and locally advanced pancreas cancer (LAPC). The primary endpoint of acute grade $\geq$ 3 gastrointestinal (GI) toxicity definitely related to SMART was previously published with median follow-up (FU) 8.8 months from SMART. We now present more mature outcomes including OS and late toxicity.

Materials and methods: This prospective, multi-center, single-arm open-label phase 2 trial (NCT03621644) enrolled 136 patients (LAPC 56.6 %; BRPC 43.4 %) after $\geq$ 3 months of any chemotherapy without distant progression and CA19-9 $\leq$ 500 U/mL. SMART was delivered on a 0.35 T MR-guided system prescribed to 50 Gy in 5 fractions (biologically effective dose$_{10}$ [BED$_{10}$] = 100 Gy). Elective coverage was optional. Surgery and chemotherapy were permitted after SMART.

Results: Mean age was 65.7 years (range, 36–85), induction FOLFIRINOX was common (81.7 %), most received elective coverage (57.4 %), and 34.6 % had surgery after SMART. Median FU was 22.9 months from diagnosis and 14.2 months from SMART, respectively. 2-year OS from diagnosis and SMART were 53.6 % and 40.5 %, respectively. Late grade $\geq$ 3 toxicity definitely, probably, or possibly attributed to SMART were observed in 0 %, 4.6 %, and 11.5 % patients, respectively.

* Corresponding author at: Miami Cancer Institute, Dept of Radiation Oncology 8900 N Kendall Dr Miami, FL 33176, United States.
E-mail address: michaelchu@baptisthealth.net (M.D. Chuong).

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Conclusions: Long-term outcomes from the phase 2 SMART trial demonstrate encouraging OS and limited severe toxicity. Additional prospective evaluation of this novel strategy is warranted.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a leading cause of cancer death [1]. Surgery is the only known curative treatment, although most newly diagnosed patients are not surgical candidates due to locally extensive and/or distant metastatic disease. Radiation therapy (RT) may benefit patients with advanced PDAC by improving local control (LC) [2], reducing pain [3], and enhancing quality-of-life (QoL) [4]. However, non-ablative RT does not provide an overall survival (OS) advantage over chemotherapy alone for borderline resectable (BRPC) [5] or locally advanced pancreas cancer (LAPC) [2].

Tumors in favorable anatomic locations such as the peripheral lung can safely be treated with ablative radiation dose that achieves a high rate of local control (LC) [6]. On the other hand, much lower dose is routine for tumors in anatomically challenging sites such as the pancreas to prioritize patient safety and resulting in only modest long-term LC [7]. Ensuring that the prescribed dose is confined to the tumor and not inadvertently delivered to nearby organs is limited by the suboptimal soft tissue image quality of cone-beam computerized tomography (CBCT) coupled with the inability of most conventional linear accelerators to account for changes in the stomach and bowel position by "adapting" the radiation dose distribution as needed on each treatment day [8]. If these challenges could be overcome then there would be rationale to further explore the benefits of ablative RT for PDAC, which may include longer OS as suggested by retrospective studies from MD Anderson Cancer Cancer [9] and Rudra et al [10].

Stereotactic magnetic resonance (MR)-guided adaptive radiation therapy (SMART) has emerged as a technique that may achieve safe dose escalation for tumors in unfavorable locations within the chest, abdomen, and pelvis [11–14]. SMART delivered with a 0.35 Tesla (T) MR-guided system overcomes the challenges of conventional CBCT-guided stereotactic body radiation therapy (SBRT) by 1) using the superior soft tissue contrast of MR imaging acquired before and continuously during treatment delivery, 2) automatically pausing treatment if the tumor is displaced out of the correct position, and 3) daily on-table treatment plan adaptation to account for interfraction anatomic changes [15]. We conducted a multi-center single-arm phase 2 trial of SMART prescribed to 50 Gy in 5 fractions delivered on a 0.35 T MR-guided system for patients with BRPC or LAPC. With median follow-up of 8.8 months from SMART, the primary endpoint of acute grade $\geq$ 3 GI toxicity definitely related to SMART was met (0 %) as previously published [16]. We now report more mature study results including OS and late toxicity.

Materials and methods

Study design and participants

This multi-center open-label single arm phase 2 trial was completed across 13 sites in 3 countries (United States, Israel, Italy). The study received institutional review board at each site, all participants provided written informed consent prior to study therapy, and it was registered on ClinicalTrials.gov (NCT03621644).

Patients were enrolled after completing $\geq$ 3 months of any induction chemotherapy without distant progression. Additional key eligibility criteria were previously published and included $\geq$ 18 years of age, adenocarcinoma of the pancreas classified as either BRPC or LAPC as per institutional definition, and CA19-9 $\leq$ 500 U/mL after induction chemotherapy [16]. There was no restriction on tumor size.

SMART

All patients were treated on a 0.35 T MR-guided radiation delivery system (ViewRay Inc., MRIdian®, Oakwood Village, OH, USA) using either cobalt-60 (MR-cobalt) or x-rays (MR-linac). Daily image guidance was performed using a breath-hold volumetric 0.35 T MR scan. The treatment approach was previously described [16]. Briefly, a total dose of 50 Gy in 5 fractions (biologically effective dose $(BED)_{10} = 100$ Gy) was prescribed to the PTV. A clinical target volume (CTV) was not initially permitted although became optional after a protocol amendment in April 2019. An internal target volume (ITV) was not utilized because intrafraction soft tissue tracking and automatic beam gating were mandatory. On-table adaptive replanning was required when the predicted dosimetry indicated: 1) violation of any GI organ-at-risk (OAR) constraint, 2) $<$ 85 % coverage of the GTV by the 95 % isodose line, 3) favorable anatomic shift between the GTV and OARs such that adaptive replanning would improve target coverage. OAR constraints included V33 $\leq$ 0.5 cm^3 each for the duodenum, stomach, small bowel, and large bowel, respectively [17]. Prospective central quality assurance (QA) review was not required of the plans or contours prior to treatment. SMART was not delivered with concurrent systemic therapy.

Therapy after SMART

Therapy after SMART including chemotherapy and/or surgery were permitted at the discretion of the treating physician. No specific chemotherapy regimen or duration was required. Additionally, there was no restriction on the type of surgery or the interval from SMART to surgery.

Patient assessments

Patient assessments were required every 3 months ($\pm$ 28 days) after SMART for the first year, then every 6 months ($\pm$ 28 days) until 5 years had elapsed after SMART. Adverse effects were also assessed at least once during SMART and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Acute adverse effects were defined as occurring within 90 days of initiating SMART while late adverse effects were those occurring thereafter. Patient-reported QoL was measured using the FACT FHSI-18 survey instrument at baseline, 3 months post-SMART, and 12 months post-SMART.

Study data were reviewed at least annually by a Data Safety Monitoring Board (DSMB). A separate Clinical Events Committee (CEC) was responsible for reviewing and adjudicating all grade $\geq$ GI adverse events as being possibly, probably, or definitely related to SMART. Members of both committees had expertise in management of PDAC, did not participate in both the DSMB and CEC, did not work at a center with a 0.35 T MR-guided RT system, and otherwise were not involved in the design or conduct of this study.

Statistical analysis

The primary endpoint was acute grade $\geq$ 3 GI toxicity definitely related to SMART. Secondary endpoints included: 1) 2-year OS after PDAC diagnosis, 2) 6-month distant progression free survival (DPFS) after SMART, 3) and QoL at 3 and 12 months after SMART. Local control (LC) was evaluated in the current analysis although was not a formal study endpoint.

OS was defined as the time to death from any cause or otherwise date

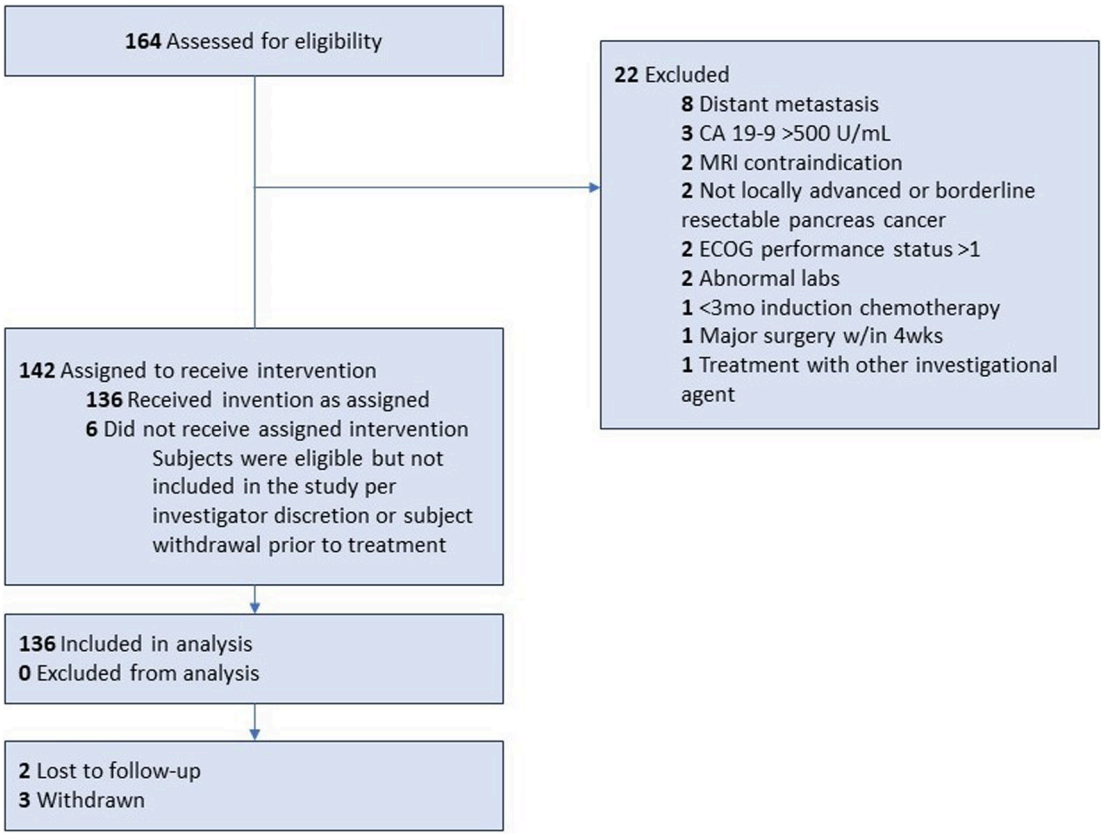

Fig. 1. Consort Diagram.

of last follow-up. DPFS was defined as the time to the date of distant progression or otherwise last follow-up. Since LC was not a formal study endpoint, the definition of LC was not included in the study protocol and was reported at the discretion of the treating physician.

Using a historical incidence of acute grade $\geq$ 3 GI toxicity of 15.8 %, a sample size of 113 patients was determined to provide 80 % power to detect a statistically significant and clinically meaningful difference assuming that the observed incidence in this study would be no greater than 8 %. The sample size calculation was performed using PASS 14 (NCSS, Kaysville, Utah). Target accrual was 133 patients assuming 15 % patient attrition. SAS (version 9.4, SAS Institute, Cary, NC) was used for all statistical analyses. A p-value of < 0.05 was statistically significant and an observed value of the one-sided upper 95 % confidence bound was used. OS, DPFS, and LC were evaluated using the Kaplan Meier method.

Results

A total of 136 patients were enrolled between January 2019 and January 2022 (Fig. 1) across 13 institutions in the United States (n = 11), Italy (n = 1), and Israel (n = 1). More than half (n = 78; 57.4 %) were enrolled by 4 institutions (30.8 %). Baseline patient and tumor characteristics are summarized in Table 1. Mean patient age was 65.7 years (range, 36–85 years). Most tumors were classified as LAPC (n = 77; 56.6 %) versus BPRC (n = 59; 43.4 %) and the majority were in the head of the pancreas (n = 95; 69.9 %). Mean CA19-9 at diagnosis was 537.5 U/mL (range, 1.0–9,600.0 U/mL) compared to 71.7 U/mL (range, 0.0–468.0 U/mL) after induction chemotherapy.

Patients received induction chemotherapy for a mean 4.5 months (range, 2.0–16.4 months), predominantly FOLFIRINOX +/- other regimens (n = 111; 81.7 %). Nearly all were treated on a 0.35 T MR-linac (n = 134; 98.5 %) vs. 0.35 T MR-cobalt system (n = 2; 1.5 %). Despite the need to adapt nearly all fractions (633/680; 93.1 %) typically due to predicted GI OAR constraint violations, the average GTV D_{90} across the initial and adapted plans was 48.9 (BED_{10} = 96.7)± 5.9 Gy and 48.6 (BED_{10} = 95.8)± 7.0 Gy, respectively. The average GTV maximum dose across initial and adapted plans was 63.6 Gy (BED_{10} = 144.5 Gy) and 66.4 Gy (BED_{10} = 154.5), respectively (Table 2).

Chemotherapy after SMART was given to 33 patients (24.3 %) although details regarding regimen or duration are unknown for most patients. Surgery was performed after SMART in 47 patients (34.6 %) more often among those with smaller primary tumor (mean 2.8 vs. 3.3 cm; p = 0.031), T1-3 vs. T4 stage (71.6 % vs. 36.2 %; p < 0.001), BRPC vs. LAPC (74.5 % vs. 25.5 %; p < 0.001), lower CA19-9 after induction chemotherapy (mean 52.9 vs. 81.7; p = 0.083). Surgical outcomes are summarized in Supplementary Table 1. Margin-negative (R0) resection was achieved in 38 patients (80.9 %). Among the 7 patients (14.9 %) with a positive margin most had BRPC (n = 6), received induction FOLFIRINOX (n = 5), and underwent venous (n = 1) or arterial resection (n = 3) including the celiac artery in 2 patients. Pathologic response rates included ypT0, ypT1, ypT2, ypT3, and ypT4 of 6.4 %, 31.9 %, 38.3 %, 4.3 %, and 6.4 %, respectively.

Median follow-up from diagnosis and SMART was 22.9 months (range, 8.0–51.5 months) and 14.2 months (range, 1.2–47.4 months), respectively. Sixty-two patients (45.6 %) were alive at the time of analysis while the others had died (n = 69), were lost to follow-up (n = 3), withdrew consent (n = 1), or were withdrawn by the investigator (n = 1) (see Fig. 2a).

Median OS from diagnosis and SMART was 22.8 months and 14.2 months, respectively. 2-year OS for the entire cohort from diagnosis (Fig. 2a) and SMART (Fig. 2b) was 53.6 % and 40.5 %, respectively. On multivariable analysis (MVA), lower 2-year OS from diagnosis was associated with head vs. body/tail tumor (hazard ratio [HR] 2.045, 95 % confidence interval [CI], 1.090–3.838; p = 0.026) and CA19-9 increase after SMART (HR 2.525, 95 % CI, 1.111–5.742; p = 0.027) while surgery was associated with higher 2-year OS (HR 0.218, 95 % CI, 0.104–0.454;

Table 1
Baseline patient and tumor characteristics.

Characteristic	N (range)
Total number of patients	136
Age (years), mean	65.7 (36–85)
Gender	69
Male	(50.7 %) 67
Female	(49.3 %)
Race	118
White	(86.8 %) 10
Black or African American	(7.3 %) 4
Asian	(2.9 %) 1
American Indian or Alaska Native	(0.7 %) 1
Other	(0.7 %) 2
Unknown	(1.5 %)
ECOG performance status	62
0	(45.6 %) 74
1	(54.4 %)
Histology	135
Adenocarcinoma	(99.3 %) 1
Adenosquamous carcinoma	(0.7 %)
Tumor location	96
Head/neck	(70.6 %) 25
Body	(18.4 %) 4
Head/body	(2.9 %) 10
Body/tail	(7.4 %) 1
Tail	(0.7 %)
Largest tumor size (cm), mean	3.1 (0.6–6.6)
Resectability	77
Locally advanced	(56.6 %) 59
Borderline resectable	(43.4 %)
Clinical T stage	5
T1	(3.7 %) 33
T2	(24.3 %) 17
T3	(12.5 %) 80
T4	(58.8 %) 1
Unknown	(0.7 %)
Clinical N stage	93
N0	(68.4 %) 33
N1	(24.3 %) 10
NX	(7.3 %)
Clinical M stage	136
M0	(100 %)
CA 19–9 (U/mL), mean	537.5
At diagnosis	(1–9,600) 71.7
Before SMART	(0–468)
Induction chemotherapy regimens	89
FOLFIRINOX only	(65.4 %) 22
FOLFIRINOX then other regimen	(16.2 %) 23
Gemcitabine/nab-paclitaxel	(16.9 %) 1
Gemcitabine only	(0.7 %) 1
Other	(0.7 %)
Induction chemotherapy duration (months), mean	4.5 (2.0–16.4)

$p < 0.0001$); 2-year estimated OS for resected vs. unresected patients from SMART was 67 % vs. 26 % ($p < 0.001$), respectively (Supplementary Table 2). 2-year LC from diagnosis and SMART for the entire cohort was 77.7 % and 78.2 % (Fig. 2c), respectively, and was higher for resected vs. unresected patients (90 % vs. 71 %; $p = 0.019$). 6-month DPFS from SMART was 72.0 %. 2-year DPFS from diagnosis and SMART for the entire cohort was 39.5 % and 28.5 % (Fig. 2d), respectively, and was higher for resected vs. unresected patients (67 % vs. 22 %; $p < 0.001$) (see Figs. 2d–2g).

The number of patients with worst acute and late ≥ 3 GI toxicities is summarized in Table 3 with specific adverse events described in Supplementary Table 3. As previously reported, the incidence of acute grade ≥ 3 GI toxicity definitely, probably, or possibly related to SMART was 0 %, 2.2 %, and 6.6 %, respectively [16]. Late grade ≥ 3 GI toxicity definitely, probably, or possibly related to SMART was reported in 0 %, 5.3 % (7/131), and 14.5 % (19/131) of patients, respectively. One late grade 5 event was adjudicated to being possibly related to SMART in a patient with local failure at the site of a bleeding malignant ulcer.

QoL assessment was completed at baseline, 3 months post-SMART, and 12 months post-SMART by 133 (97.8 %), 107 (83.0 %), and 55 (64.7 %) enrolled patients, respectively. QoL outcomes will be published separately.

Discussion

The phase 2 SMART trial is the first prospective study of ablative 5-fraction SMART for BRPC/LAPC and, to the best of our knowledge, is also the largest SBRT trial for PDAC of any stage. The development of the SMART trial was inspired by several retrospective studies that suggested radiation dose escalation benefits patients with inoperable PDAC (see Table 4) [9,10]. A phase 1 trial published by Henke et al. was the first to prospectively demonstrate the feasibility of SMART prescribed to 50 Gy in 5 fractions (biologically effective dose [BED_{10}] = 100 Gy) to unresectable abdominal tumors including several in the pancreas [11]. A multi-center analysis of inoperable PDAC patients treated on a 0.35 T MR-cobalt device in 5–28 fractions reported 2-year OS of 49 % vs. 30 % ($p = 0.03$) among those prescribed a BED_{10} of > 70 Gy vs. ≤ 70 Gy; no grade 3 or higher toxicity was reported in the high dose cohort [10]. MD Anderson Cancer Center also reported that LAPC patients prescribed a $BED_{10} > 70$ Gy with CT guidance usually in 28 fractions had higher median OS than those prescribed lower dose [9].

While radiation dose escalation may be feasible at experienced centers and for patients with more favorable anatomy when delivered in up to 28 fractions using CT guidance [9,18], prior attempts to safely dose escalate in up to 5 fractions have been unsuccessful [19,20]. A phase 2 trial from Denmark that enrolled 22 LAPC patients who were prescribed 45 Gy in 3 fractions ($BED_{10} = 112.5$ Gy) resulted in most patients experiencing acute grade ≥ 3 toxicity within 14 days of treatment including pain, nausea, diarrhea, and/or a decline in performance status [19]. Courtney and colleagues published phase 1 trial outcomes of SBRT prescribed up to 50 Gy in 5 fractions using CBCT that included "nontrivial rates of severe late GI toxicity" including multiple grade 4 and 5 adverse events [20]. As such, non-ablative SBRT (e.g., 33 Gy in 5 fractions; $BED_{10} = 54.8$ Gy) is a standard of care to optimize safety, but potentially at the expense of efficacy.

The SMART trial was designed with the hypothesis that the advanced imaging and delivery capabilities of a 0.35 T MR-guided system could overcome historical limitations in achieving safe radiation dose escalation [21]. Given that no prospective study had demonstrated the feasibility of ablative ultra-hypofractionated RT for PDAC, the SMART trial was principally designed to assess safety, and also evaluate long-term treatment efficacy. We previously reported that with median follow-up of 8.8 months from SMART the primary endpoint of acute grade ≥ 3 GI toxicity definitely related to SMART was met [16]. The current analysis presents mature study outcomes with median follow-up of 22.9 months from diagnosis and 14.2 months from SMART.

Treatment was well tolerated during and after SMART with most patients being followed at least 12–18 months. The incidence of late grade ≥ 3 GI toxicity definitely (0 %) or probably (4.6 %) related to SMART was similar to what has been reported after non-ablative SBRT [7,22]. The clinical significance of several late adverse events, especially some adjudicated to be possibly related to SMART, is unclear given that they occurred in the context of disease progression (e.g., "abdominal distention" and "ascites" in patients with peritoneal metastasis) or surgery (e.g., "abdominal infection"). Moreover, late GI bleeding possibly related to SMART (including 1 grade 5 event) was documented in several patients with local tumor progression into the stomach or bowel.

Ablative SMART was feasible despite our mean PTV volume of 133.4 cm^3 (range, 32.8–444.2 cm^3) being the largest in any pancreas SBRT trial to the best of our knowledge (Table 3). The median PTV in a trial by Courtney et al. [20] was 37 cm^3 (range, 4.4–187 cm^3) and was 71.4 cm^3 (range, 31.9–225.2 cm^3) in a study from Herman and colleagues [7]; neither permitted elective coverage. The generous PTV volume in our study was influenced by > 50 % of patients being treated to not only gross tumor but also areas of potential microscopic disease, which we

Table 2
Target dose metrics of initial versus adapted plans.

	Initial Plans			Adapted Plans		
	Mean Dose ± SD (Gy)	Mean BED_{10} (Gy)	Range (Gy)	Mean Dose ± SD (Gy)	Mean BED_{10} (Gy)	Range (Gy)
GTV D_{95}	45.3 ± 7.1	86.3	28.9–62.4	45.0 ± 8.0	85.5	21.4–61.5
CTV D_{95}	43.5 ± 7.2	81.4	28.5–57.5	43.6 ± 7.4	81.6	21.5–59.8
PTV D_{95}	37.1 ± 7.0	64.6	21.9–54.1	36.7 ± 7.6	63.6	6.1–54.2
GTV D_{90}	48.9 ± 5.9	96.7	32.4–63.4	48.6 ± 7.0	95.8	24.4–63.8
CTV D_{90}	47.3 ± 6.2	92.1	31.8–58.2	47.7 ± 5.9	93.2	25.1–61.0
PTV D_{90}	42.4 ± 6.8	78.4	25.1–55.6	42.2 ± 7.1	77.8	11.2–56.0
GTV D_{80}	52.4 ± 4.5	107.3	38.2–64.4	52.5 ± 5.4	107.6	30.2–66.0
CTV D_{80}	51.3 ± 4.5	103.9	36.6–59.8	51.4 ± 3.9	104.2	31.1–62.1
PTV D_{80}	47.9 ± 5.0	93.8	29.6–56.9	47.9 ± 5.1	93.8	23.9–58.8
GTV maximum dose	63.6 ± 4.2	144.5	51.9–75.5	66.4 ± 4.8	154.5	49.9–79.4
CTV maximum dose	65.0 ± 4.7	149.5	51.9–75.5	64.9 ± 4.8	149.1	50.3–79.4
PTV maximum dose	64.0 ± 4.1	145.9	52.0–75.5	65.0 ± 4.8	149.5	50.3–79.4
GTV mean dose	55.2 ± 3.7	116.1	47.5–66.3	56.2 ± 4.0	119.3	36.9–67.2
CTV mean dose	54.7 ± 3.3	114.5	47.4–63.4	54.2 ± 3.3	112.9	37.5–63.9
PTV mean dose	52.1 ± 2.9	106.3	42.8–60.0	52.0 ± 3.3	106.0	33.5–61.7
GTV minimum dose	29.4 ± 9.0	46.7	15.2–56.5	31.0 ± 9.3	50.2	11.3–57.0
CTV minimum dose	27.3 ± 7.0	42.2	15.9–49.9	25.4 ± 6.4	38.3	8.5–49.0
PTV minimum dose	20.2 ± 5.7	28.4	10.2–41.8	19.8 ± 5.4	27.6	3.0–34.8

GTV = gross tumor volume; CTV = clinical target volume; PTV = planning target volume; BED = biologically effective dose; SD = standard deviation.

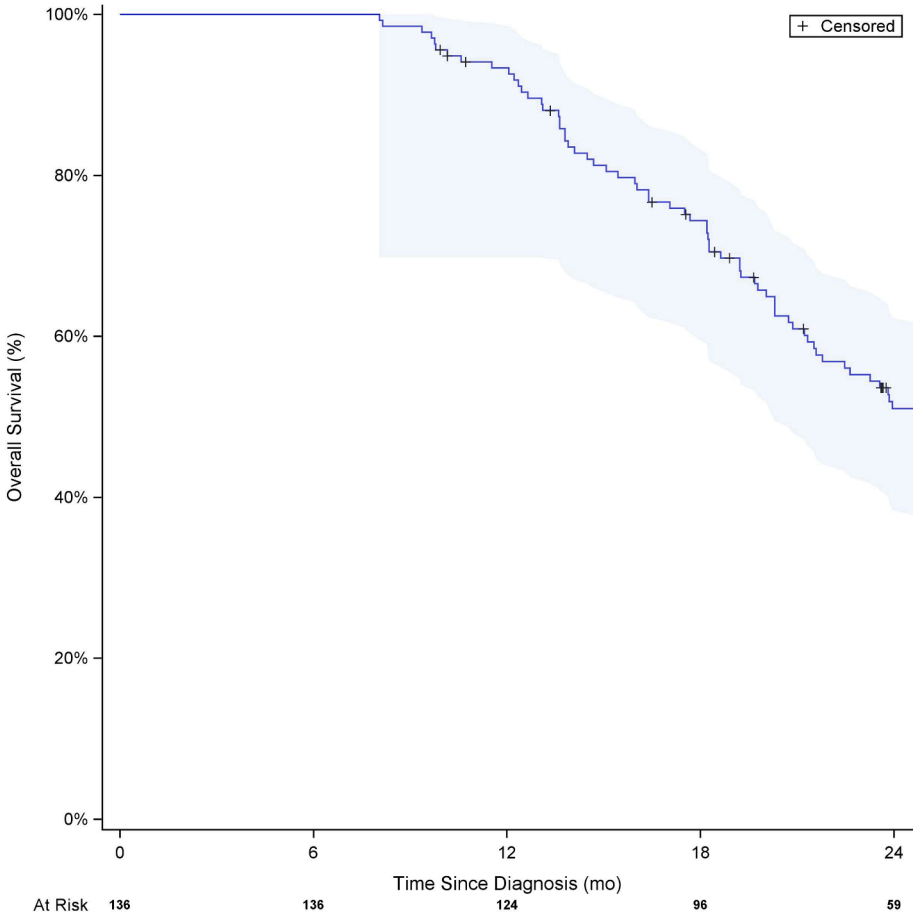

Fig. 2a. Overall Survival from Diagnosis.

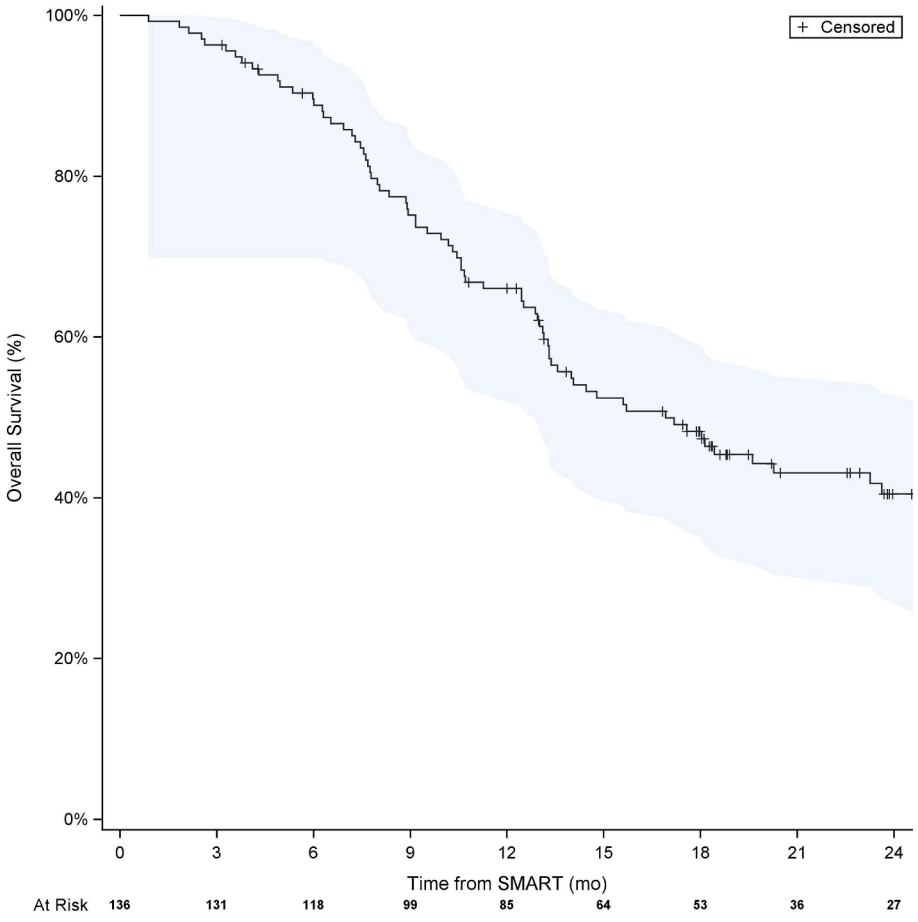

Fig. 2b. Overall Survival from SMART.

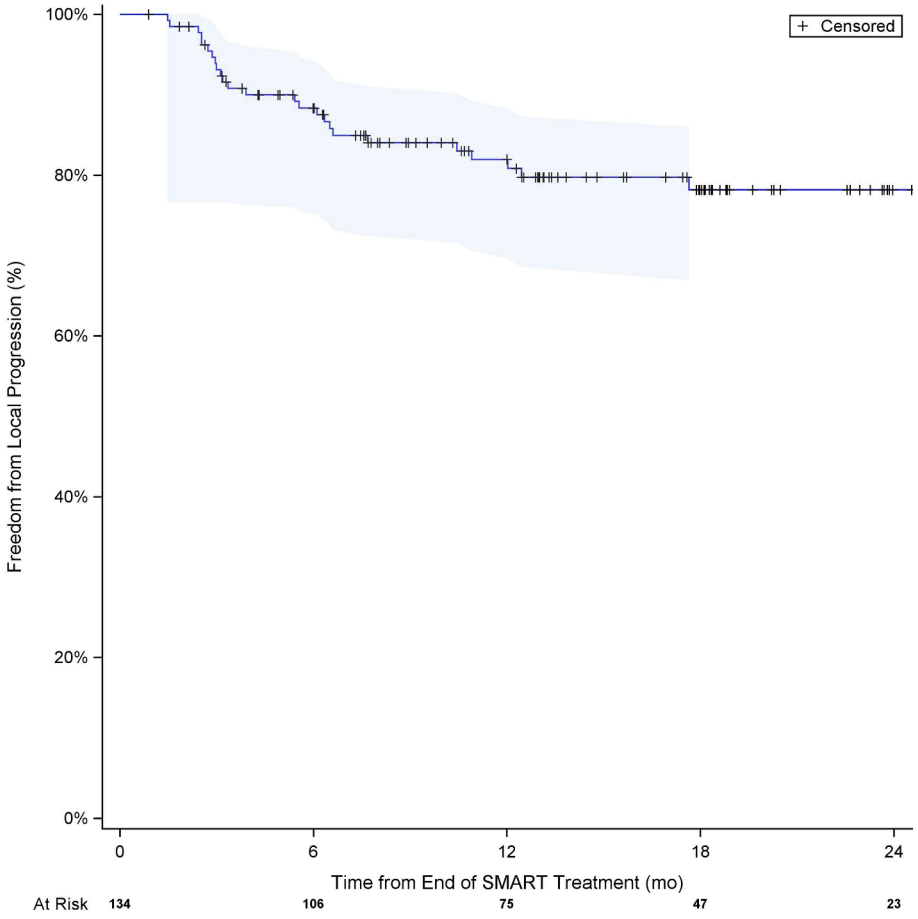

Fig. 2c. Local Control from SMART.

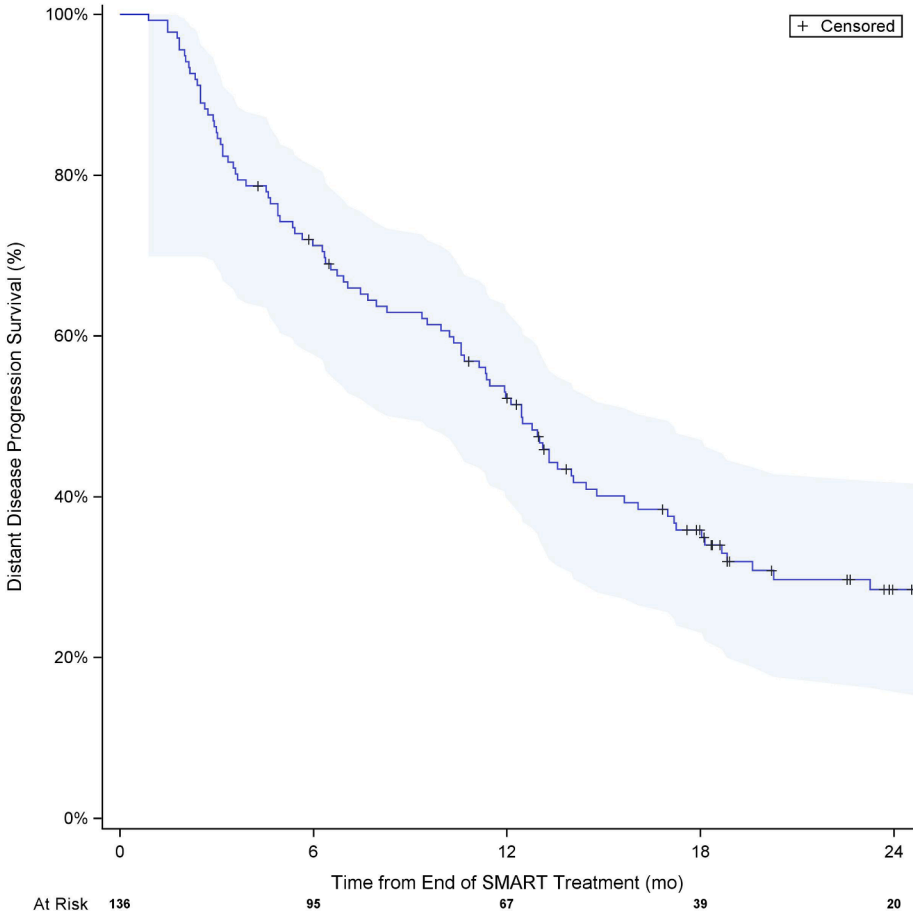

Fig. 2d. Distant Disease Progression Free Survival from SMART.

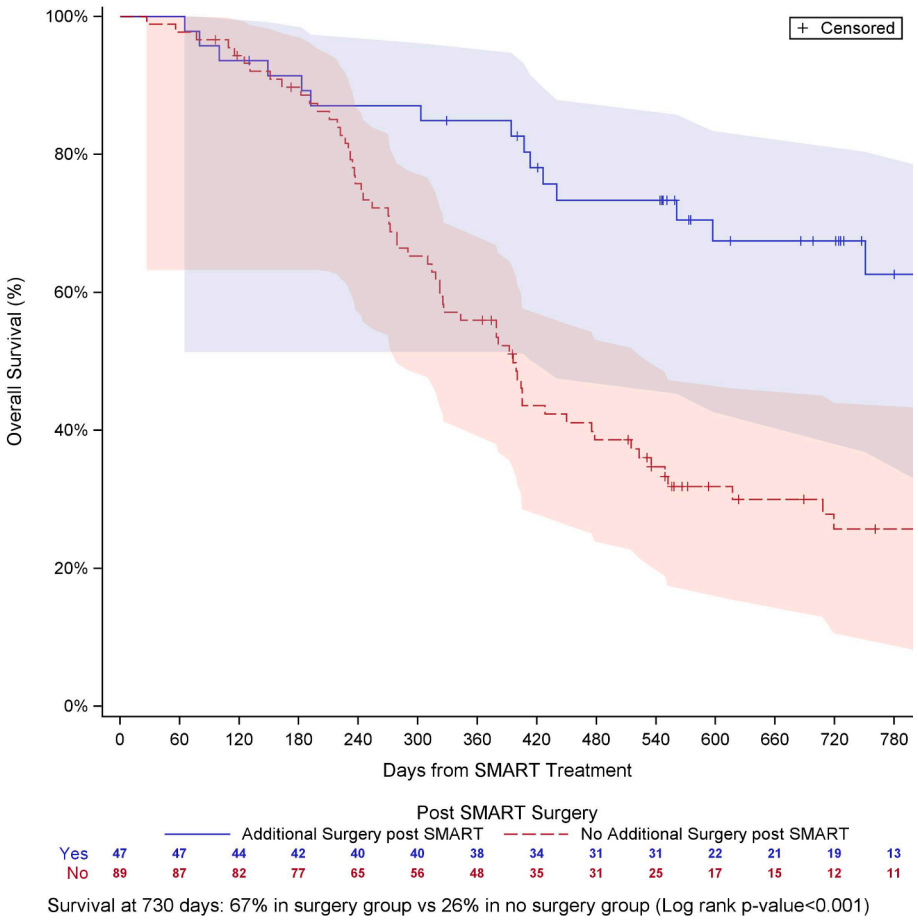

Fig. 2e. Resected Patients vs Non-Resected Patients Overall Survival from SMART.

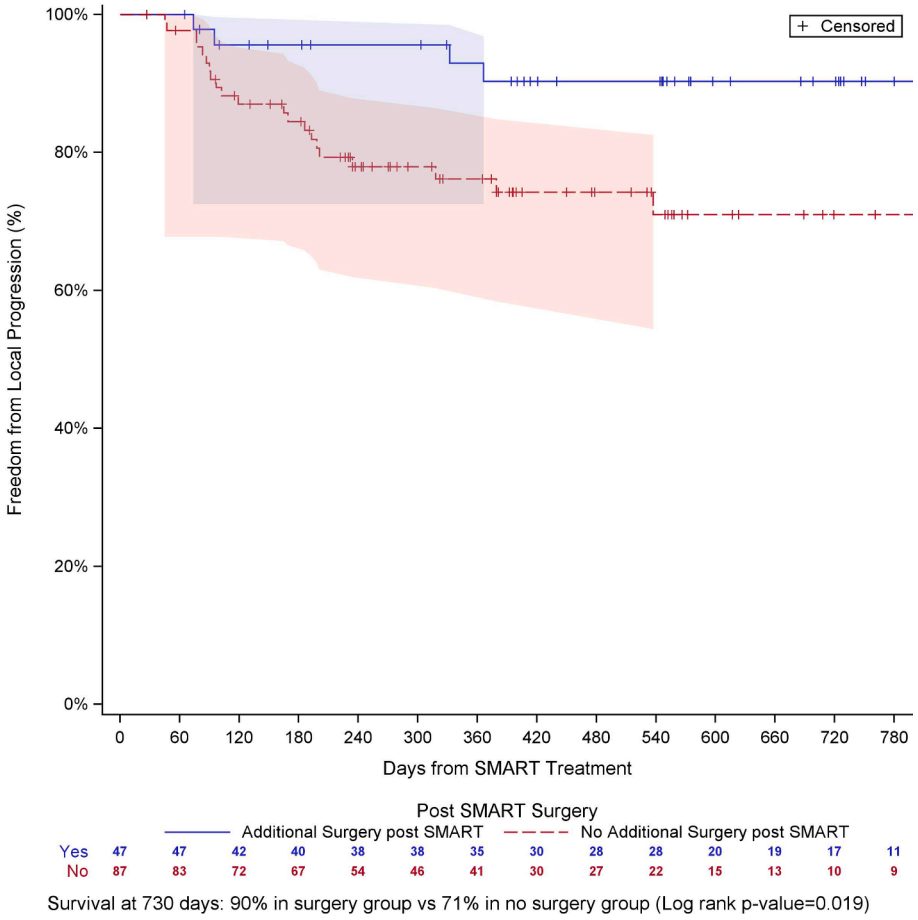

Fig. 2f. Resected Patients vs Non-Resected Patients Local Control from SMART.

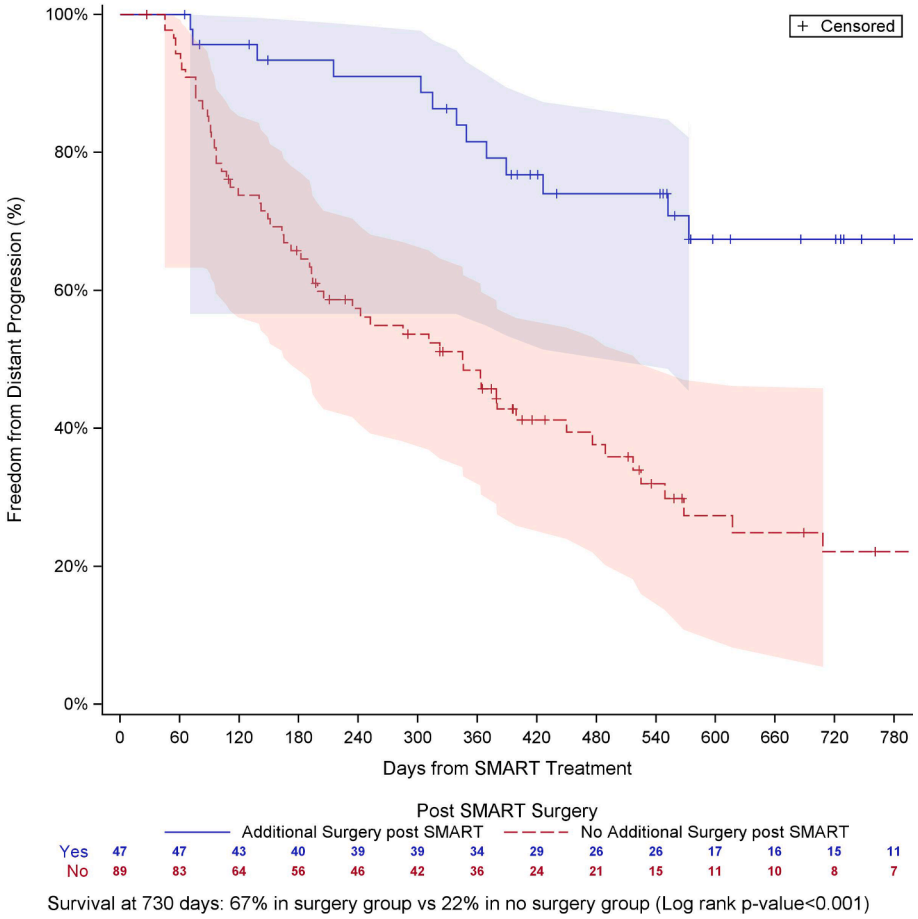

Fig. 2g. Resected Patients vs Non-Resected Patients Distant Disease Progression Free Survival from SMART.

Table 3
Patients with worst acute and late grade 3 or higher adverse events possibly, probably, or definitely attributed to SMART.

Acute (≤ 90 days from SMART)	
Definitely related to SMART	
Grade 3	0/136 (0 %)
Grade 4	0/136 (0 %)
Grade 5	0/136 (0 %)
Grade ≥ 3	0/136 (0 %)
Probably related to SMART	
Grade 3	3/136 (2.2 %)
Grade 4	0/136 (0 %)
Grade 5	0/136 (0 %)
Grade ≥ 3	3/136 (2.2 %)
Possibly related to SMART	
Grade 3	5/136 (3.7 %)
Grade 4	2/136 (1.5 %)
Grade 5	2/136 (1.5 %)
Grade ≥ 3	9/136 (6.6 %)
Late (>90 days from SMART)	
Definitely related to SMART	
Grade 3	0/131 (0 %)
Grade 4	0/131 (0 %)
Grade 5	0/131 (0 %)
Grade ≥ 3	0/131 (0 %)
Probably related to SMART	
Grade 3	1/131 (0.8 %)
Grade 4	5/131 (3.8 %)
Grade 5	0/131 (0 %)
Grade ≥ 3	6/131 (4.6 %)
Possibly related to SMART	
Grade 3	13/131 (9.9 %)
Grade 4	1/131 (0.8 %)
Grade 5	1/131 (0.8 %)
Grade ≥ 3	15/131 (11.5 %)

recognize is controversial [23,24]. Lastly, elective regions were prescribed the same dose as gross disease although while this may be feasible, a lower elective dose (e.g., 25–33 Gy) may decrease toxicity while maintaining efficacy [25,26].

The 2-year OS rates from diagnosis and SMART was 53.6 % and 40.5 %, respectively, which are notably higher than what has been reported after non-ablative SBRT (Table 3). We acknowledge that evaluating the effect of ablative dose on OS is complicated by enrolling not only LAPC but also BRPC patients and permitting surgery after SMART. Resected patients had more favorable baseline characteristics including less advanced disease, and therefore is not surprising that treatment outcomes including DPFS and OS were superior to those of the unresected patients. It is unknown whether we would have achieved higher OS outcomes if inclusion criteria were more restrictive. However, only 1 patient received single-agent chemotherapy and the median CA19-9 after chemotherapy was relatively low at 71.7 U/mL although ranged up to 468 U/mL.

Why might OS be improved in select patients who receive ablative radiation dose? Local failure may cause not only morbidity, but also mortality in nearly one-third of PDAC patients even in the presence of limited distant metastatic disease, as reported by a rapid autopsy study from Johns Hopkins University [27]. As such, significantly delaying or preventing local progression in well selected patients could not only at least maintain QoL, but also potentially improve OS. A retrospective analysis from the Miami Cancer Institute was the first to suggest that improved durable LC achieved by ablative 5-fraction SMART may decrease the likelihood of death due to local progression [28]. 2-year LC in the current study from SMART was 78.2 %, which is higher than historical SBRT outcomes and may be related to the ablative prescribed dose as per a HyTEC analysis demonstrating a dose–response relationship for LC among unresectable PDAC patients [29]. The amount of the target covered by ablative dose may impact LC and can be enhanced with on-table adaptive replanning compared to non-adaptive workflows [30,31]. Target volume coverage by at least the prescribed dose was substantial not only in the initial but also adapted SMART trial plans.

Study limitations include enrolling both BRPC and LAPC patients, and that institutional resectability criteria were permitted instead of a standardized definition. Any induction chemotherapy regimen was permitted although nearly all patients received FOLFIRINOX and/or gemcitabine/nab-paclitaxel. Although the primary study endpoint was related to patient safety, OS may have been influenced by permitting CA19-9 up to 500 U/mL after induction chemotherapy. The lack of a standardized LC definition complicates comparison of our results with other studies. Prospective centralized plan and contour QA review was not required and prior PDAC RT trials have shown that study deviations are common, especially regarding contouring and treatment planning [32], which may influence OS [33].

In summary, this updated analysis of the phase 2 SMART trial demonstrates that ablative 5-fraction SMART is safe and results in favorable long-term OS for BRPC and LAPC patients. A phase 3 randomized trial evaluating whether OS is improved with addition of ablative SMART to chemotherapy versus chemotherapy alone for LAPC is warranted.

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CRediT authorship contribution statement

Michael D. Chuong: Conceptualization, Data curation, Writing – original draft, Methodology, Supervision, Writing – review & editing. **Percy Lee:** Conceptualization, Data curation, Writing – review & editing, Supervision. **Daniel A. Low:** Writing – review & editing. **Joshua Kim:** Writing – review & editing. **Kathryn E. Mittauer:** Writing – review & editing. **Michael F. Bassetti:** Conceptualization, Writing – review & editing. **Carri K. Glide-Hurst:** Writing – review & editing. **Ann C. Raldow:** Writing – review & editing. **Yingli Yang:** Writing – review & editing. **Lorraine Portelance:** Conceptualization, Writing – review & editing. **Kyle R. Padgett:** Writing – review & editing. **Bassem Zaki:** Writing – review & editing. **Rongxiao Zhang:** Writing – review & editing. **Hyun Kim:** Writing – review & editing. **Lauren E. Henke:** Writing – review & editing. **Alex T. Price:** Writing – review & editing. **Joseph D. Mancias:** Writing – review & editing. **Christopher L. Williams:** Writing – review & editing. **John Ng:** Writing – review & editing. **Ryan Pennell:** Writing – review & editing. **M. Raphael Pfeffer:** Writing – review & editing. **Daphne Levin:** Writing – review & editing. **Adam C. Mueller:** Writing – review & editing. **Karen E. Mooney:** Writing – review & editing. **Patrick Kelly:** Writing – review & editing. **Amish P. Shah:** Writing – review & editing. **Luca Boldrini:** Writing – review & editing. **Lorenzo Placidi:** Writing – review & editing. **Martin Fuss:** Conceptualization, Writing – review & editing. **Parag Jitendra Parikh:** Conceptualization, Data curation, Writing – review & editing, Supervision.

Table 4
Select radiation therapy studies for borderline resectable and locally advanced pancreas cancer.

Study	N	Imaging	Resectability	IC duration (mo)	IC regimen	RT Dose	BED_{10} (Gy)	Elective coverage	PTV volume	Surgery after RT	Median FU (mo)	LC	DPFS	OS	Grade 3 + toxicity
LAP07 trial (phase 3)	133 (CRT)	x-ray	LA 100 %	median 4.0	G +/- E (100 %)	54 Gy / 30 fx	63.7	No	NR	3 (2.3 %)	46.2 (CRT arm, from 1st randomization)	NR	NR	median: 15.2 months (CRT arm, from 1st randomization)	CRT/G (19.8 % non-heme) CRT/G-E (23.1 % non-heme)
CONKO-007 trial (phase 3)	168 (CRT)	x-ray	LA 100 %	median 3.0	FFX (81.2 %) G (18.8 %)	50.4 Gy/28 fx	59.5	No	NR	61 (36.3 % of CRT patients)	16.0 (from randomization)	NR	NR	2-yr: 34.8 % (CRT patients after randomization)	14 %
Hoyer et al. (phase 2)	22	x-ray	LA 100 %	N/A	None (100 %)	45 Gy/3 fx	112.4	No	GTV: 32 cc	0 %	NR	6-mo: 57 %	NR	1-yr: 5 %	Acute grade 2+: 79 % Late grade 2+: 94 %
Herman et al. (phase 2)	49	x-ray, CBCT	LA 100 %	NR	G (100 %)	33 Gy/5 fx	54.8	No	71.4	4 (8.2 %)	13.9 (from dx)	1-yr: 78 % 2-yr: NR	NR	1-yr: 59 % 2-yr: 18 %	Grade 2+: 11 %
Teriaca et al. (phase 2)	39	CBCT	LA 100 %	NR	FFX (1005)	40 Gy/8 fx	72.0	No	NR	7 (17.9 %)	13 (from dx)	2-yr: ~60 % (from dx)	NR	2-yr: ~20 % (from dx)	Acute: 0 % Late: 10 %
Comito et al (phase 2)	45	CBCT	LA 100 %		GEMOX (38 %) G (1.5 %) Other (1 %) None (29 %)	45 Gy/6 fx	78.8	No	median 64.7 cc	3 (6.7 %)	13.5 (from RT)	2-yr: 87 % (from RT)	NR	2-yr: 33 % (from dx) 2-yr: 18 % (from RT)	Acute: 0 % Late: 0 %
Krishnan et al. (retro)	47	CBCT, CT-on-rails	LA 100 %	median 3.5	G-based (68.1 %) FFX (31.9 %)	63 Gy/28 fx (29.8 %) 70 Gy/28 fx (23.4 %) 67.5 Gy/15 fx (14.9 %) 60 Gy/10 fx (2.1 %) 50 Gy/5 fx (2.1 %) 51.3–70.4 Gy/13–39 fx (29.7 %)	77.2 87.5 97.9 96.0 100.0 70.4–84.3	No	NR	2 (4.3 %)	9.6 (from RT)	2-yr: 17 % (from RT)	2-yr: NR	2-yr: 22 % (from RT)	Acute: 2 % Late: NR
Reyngold et al. (retro)	119	CBCT	LA 100 %	median 4.0	FFX (55 %) G/A (31 %) Other (11 %) None (2.5 %)	67.5 Gy/15 fx (19 %) 75 Gy/25 fx (81 %)	97.9 97.5	Yes (100 %)	median GTV 31 cc	0 %	24.5 (from dx) 18.4 (from RT)	2-yr: 67.2 % (from RT)	NR	2-yr: 38 % (from RT)	Acute/late: 13.4 %
Rudra et al. (retro)	25	0.35 T MR	LA 75 % BR 16.7 %	median 3.9	FFX (37.5 %) FOLFOX	40–52 Gy/5 fx (64 %) 50–67.5	median 77.6	Yes (% NR)	median 73.3 cc	2 (8.3 %)	17 (from RT)	2-yr: 77 %	1.5-yr: 24 %	2-yr: 49 % (from RT)	Acute: 0 % Late: 0 %

(*continued on next page*)

Table 4 (*continued*)

Study	N	Imaging	Resectability	IC duration (mo)	IC regimen	RT Dose	BED_{10} (Gy)	Elective coverage	PTV volume	Surgery after RT	Median FU (mo)	LC	DPFS	OS	Grade 3 + toxicity
					(4.2 % Other (16.7 %) None (8.3 %)	Gy/10–15 fx (36 %)	median 82.7					(from RT)	(from RT)		
Hassanzadeh et al. (retro)	44	0.35 T MR	LA 64 % BR 14 %	median 5.8	FFX (36.4 %) G/A (34.1 %) G alone (6.8 %) A alone (4.5 %) None (18.2 %)	50 Gy/5 fx	100.0	No	median 109 cc	3 (6.8 %)	16 (from dx)	2-yr 59.3 % (from dx)	2-yr 37.8 % (from dx)	2-yr: 37.9 % (from dx)	Acute: 0 % Late: 0 %
Chuong et al. (retro)	62	0.35 T MR	LA 72.6 % BR 22.6 %	median 4.2	FFX (69.4 %) G/A (24.2 %) G (6.4 %)	50 Gy/5 fx (88.7 %) 45 Gy/5 fx (8.1 %) 40 Gy/5 fx (3.2 %)	100.0 85.5 72.0	Yes (80.6 %)	NR	6 (9.7 %)	18.6 (from dx) 11.0 (from RT)	2-yr: 68.8 % (from RT)	2-yr: 23.7 % (from RT)	2-yr: 27.7 % (from RT)	Acute: 4.8 % Late: 4.8 %
SMART trial (phase 2)	136	0.35 T MR	LA 56.6 % BR 43.4 %	mean 4.5	FFX (65.4 %) FFX + other (16.2 %) G/A (16.9 %) G (0.7 %) Other (0.7 %)	50 Gy/5 fx	100.0	Yes (54.4 %)	mean 133.4 cc	47 (34.6 %)	22.9 (from dx) 14.2 (from RT)	2-yr: 77.7 % (from dx) 2-yr: 78.2 % (from RT)	2-yr: 39.5 % (from dx) 2-yr 28.5 % (from RT)	2-yr: 53.6 % (from dx) 2-yr: 40.5 % (from RT)	Acute: 0 % definitely, 2.2 % probably, 6.6 % possibly related Late: 0 % definitely, 4.6 % probably, 11.5 % possibly related

Retro = retrospective; CRT = chemoradiation; CBCT = cone-beam computerized tomography; MR = magnetic resonance; LA = locally advanced; BR = borderline resectable; FFX = 5-fluorouracil, leucovorin, oxaliplatin, irinotecan; FOLFOX = 5-fluorouracil, leucovorin, oxaliplatin; G = gemcitabine; A = nab-paclitaxel; E = erlotinib; GEMOX = gemcitabine, oxaliplatin; fx = fraction; dx = diagnosis; RT = radiation therapy; NR = not reported.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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ViewRay Inc., was involved in the design and conduct of the study and review and approval of the manuscript.

Appendix A. Supplementary data

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References

[1] Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin 2023;73:17–48.
[2] Hammel P, Huguet F, van Laethem JL, Goldstein D, Glimelius B, Artru P, et al. Effect of Chemoradiotherapy vs Chemotherapy on Survival in Patients With Locally Advanced Pancreatic Cancer Controlled After 4 Months of Gemcitabine With or Without Erlotinib: The LAP07 Randomized Clinical Trial. J Am Med Assoc 2016;315:1844–53.
[3] Hammer L, Hausner D, Ben-Ayun M, Shacham-Shmueli E, Morag O, Margalit O, et al. Single-Fraction Celiac Plexus Radiosurgery: A Preliminary Proof-of-Concept Phase 2 Clinical Trial. Int J Radiat Oncol Biol Phys 2022;113:588–93.
[4] Vornhulz M, Anton S, Eross B, Szakacs Z, Hegyi P, Regel I, et al. Role of stereotactic body radiation in the enhancement of the quality of life in locally advanced pancreatic adenocarcinoma: a systematic review. Radiat Oncol 2022;17:108.
[5] Katz MHG, Shi Q, Meyers J, Herman JM, Chuong M, Wolpin BM, et al. Efficacy of Preoperative mFOLFIRINOX vs mFOLFIRINOX Plus Hypofractionated Radiotherapy for Borderline Resectable Adenocarcinoma of the Pancreas: The A021501 Phase 2 Randomized Clinical Trial. JAMA Oncol 2022;8:1263–70.
[6] Timmerman RD, Paulus R, Pass HI, Gore EM, Edelman MJ, Galvin J, et al. Stereotactic Body Radiation Therapy for Operable Early-Stage Lung Cancer: Findings From the NRG Oncology RTOG 0618 Trial. JAMA Oncol 2018;4:1263–6.
[7] Herman JM, Chang DT, Goodman KA, Dholakia AS, Raman SP, Hacker-Prietz A, et al. Phase 2 multi-institutional trial evaluating gemcitabine and stereotactic body radiotherapy for patients with locally advanced unresectable pancreatic adenocarcinoma. Cancer 2015;121:1128–37.
[8] Green OL, Henke LE, Hugo GD. Practical Clinical Workflows for Online and Offline Adaptive Radiation Therapy. Semin Radiat Oncol 2019;29:219–27.
[9] Krishnan S, Chadha AS, Suh Y, Chen HC, Rao A, Das P, et al. Focal Radiation Therapy Dose Escalation Improves Overall Survival in Locally Advanced Pancreatic Cancer Patients Receiving Induction Chemotherapy and Consolidative Chemoradiation. Int J Radiat Oncol Biol Phys 2016;94:755–65.
[10] Rudra S, Jiang N, Rosenberg SA, Olsen JR, Roach MC, Wan L, et al. Using adaptive magnetic resonance image-guided radiation therapy for treatment of inoperable pancreatic cancer. Cancer Med 2019;8:2123–32.
[11] Henke L, Kashani R, Robinson C, Curcuru A, DeWees T, Bradley J, et al. Phase I trial of stereotactic MR-guided online adaptive radiation therapy (SMART) for the treatment of oligometastatic or unresectable primary malignancies of the abdomen. Radiother Oncol 2018;126:519–26.
[12] Henke LE, Olsen JR, Contreras JA, Curcuru A, DeWees TA, Green OL, et al. Stereotactic MR-Guided Online Adaptive Radiation Therapy (SMART) for Ultracentral Thorax Malignancies: Results of a Phase 1 Trial. Adv Radiat Oncol 2019;4:201–9.
[13] Henke LE, Stanley JA, Robinson C, Srivastava A, Contreras JA, Curcuru A, et al. Phase I Trial of Stereotactic MRI-Guided Online Adaptive Radiation Therapy (SMART) for the Treatment of Oligometastatic Ovarian Cancer. Int J Radiat Oncol Biol Phys 2021.
[14] Chuong MD, Clark MA, Henke LE, Kishan AU, Portelance L, Parikh PJ, et al. Patterns of utilization and clinical adoption of 0.35 Tesla MR-guided radiation therapy in the United States - Understanding the transition to adaptive, ultra-hypofractionated treatments. Clin Transl. Radiat Oncol 2023;38:161–8.
[15] Chuong MD, Palm RF, Tjong MC, Hyer DE, Kishan AU. Advances in MRI-Guided Radiation Therapy. Surg Oncol Clin N Am 2023;32:599–615.
[16] Parikh PJ, Lee P, Low DA, Kim J, Mittauer KE, Bassetti MF, et al. 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. Int J Radiat Oncol Biol Phys 2023.
[17] Palta M, Godfrey D, Goodman KA, Hoffe S, Dawson LA, Dessert D, et al. Radiation Therapy for Pancreatic Cancer: Executive Summary of an ASTRO Clinical Practice Guideline. Pract Radiat Oncol 2019;9:322–32.
[18] Reyngold M, O'Reilly EM, Varghese AM, Fiasconaro M, Zinovoy M, Romesser PB, et al. Association of Ablative Radiation Therapy With Survival Among Patients With Inoperable Pancreatic Cancer. JAMA Oncol 2021.
[19] Hoyer M, Roed H, Sengelov L, Traberg A, Ohlhuis L, Pedersen J, et al. Phase-II study on stereotactic radiotherapy of locally advanced pancreatic carcinoma. Radiother Oncol 2005;76:48–53.
[20] Courtney PT, Paravati AJ, Atwood TF, Raja N, Zimmerman CT, Fanta PT, et al. Phase I Trial of Stereotactic Body Radiation Therapy Dose Escalation in Pancreatic Cancer. Int J Radiat Oncol Biol Phys 2021;110:1003–12.
[21] Hall WA, Small C, Paulson E, Koay EJ, Crane C, Intven M, et al. Magnetic Resonance Guided Radiation Therapy for Pancreatic Adenocarcinoma, Advantages, Challenges, Current Approaches, and Future Directions. Front Oncol 2021;11:628155.
[22] Teriaca MA, Loi M, Suker M, Eskens F, van Eijck CHJ, Nuyttens JJ. A phase II study of stereotactic radiotherapy after FOLFIRINOX for locally advanced pancreatic cancer (LAPC-1 trial): Long-term outcome. Radiother Oncol 2021;155:232–6.
[23] Kharofa J, Mierzwa M, Olowokure O, Sussman J, Latif T, Gupta A, et al. Pattern of Marginal Local Failure in a Phase II Trial of Neoadjuvant Chemotherapy and Stereotactic Body Radiation Therapy for Resectable and Borderline Resectable Pancreas Cancer. Am J Clin Oncol 2019;42:247–52.
[24] Zhu X, Ju X, Cao Y, Shen Y, Cao F, Qing S, et al. Patterns of Local Failure After Stereotactic Body Radiation Therapy and Sequential Chemotherapy as Initial Treatment for Pancreatic Cancer: Implications of Target Volume Design. Int J Radiat Oncol Biol Phys 2019;104:101–10.
[25] Miller JA, Toesca DAS, Baclay JRM, Vitzthum LK, Dubrowski P, Pollom EL, et al. Pancreatic Stereotactic Body Radiation Therapy With or Without Hypofractionated Elective Nodal Irradiation. Int J Radiat Oncol Biol Phys 2022;112:131–42.
[26] Chuong MD, Kharofa J, Sanford NN. Elective Target Coverage for Pancreatic Cancer: When Less Does Not Clearly Achieve More. Int J Radiat Oncol Biol Phys 2022;112:143–5.
[27] Iacobuzio-Donahue CA, Fu B, Yachida S, Luo M, Abe H, Henderson CM, et al. DPC4 gene status of the primary carcinoma correlates with patterns of failure in patients with pancreatic cancer. J Clin Oncol 2009;27:1806–13.
[28] Chuong MD, Herrera R, Ucar A, Aparo S, De Zarraga F, Asbun H, et al. Causes of death among initially inoperable pancreas cancer patients after induction chemotherapy and ablative 5-fraction stereotactic magnetic resonance image-guided adaptive radiation therapy. Advances in Radiation Oncology.
[29] Mahadevan A, Moningi S, Grimm J, Li XA, Forster KM, Palta M, et al. Maximizing Tumor Control and Limiting Complications With Stereotactic Body Radiation Therapy for Pancreatic Cancer. Int J Radiat Oncol Biol Phys 2021;110:206–16.
[30] Rhee DJ, Beddar S, Jaoude JA, Sawakuchi G, Martin R, Perles L, et al. Dose Escalation for Pancreas SBRT: Potential and Limitations of using Daily Online Adaptive Radiation Therapy and an Iterative Isotoxicity Automated Planning Approach. Adv Radiat Oncol 2023;8:101164.
[31] Chuong MD, Bryant J, Mittauer KE, Hall M, Kotecha R, Alvarez D, et al. Ablative 5-Fraction Stereotactic Magnetic Resonance-Guided Radiation Therapy With On-Table Adaptive Replanning and Elective Nodal Irradiation for Inoperable Pancreas Cancer. Pract Radiat Oncol 2021;11:134–47.
[32] Tchelebi LT, Winter KA, Abrams RA, Safran HP, Regine WF, McNulty S, et al. Analysis of radiation therapy quality assurance in NRG Oncology RTOG 0848. Int J Radiat Oncol Biol Phys 2023.
[33] Giraud P, Racadot S, Vernerey D, Goldstein D, Glimelius B, Van Houtte P, et al. Investigation of Relation of Radiation Therapy Quality With Toxicity and Survival in LAP07 Phase 3 Trial for Locally Advanced Pancreatic Carcinoma. Int J Radiat Oncol Biol Phys 2021;110:993–1002.