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Original Article

Stereotactic Magnetic Resonance-Guided Daily Adaptive SABR (SMART) for Localised Non-Metastatic Pancreatic Cancer: First Reported Clinical Outcomes From the UK

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Abstract

Aims: Prognosis of locally advanced pancreatic cancer (LAPC) remains poor with limited therapeutic options. Radiation therapy in pancreatic cancer has been restricted by the disease's proximity to radiosensitive organs at risk (OAR). However, stereotactic magnetic resonance-guided adaptive radiation therapy (SMART) has demonstrated promise in delivering ablative doses safely. We sought to report clinical outcomes from a UK-based Compassionate Access Programme that provided access to SMART to patients with LAPC.

Materials and methods: This was a registry retrospective study conducted at a single centre with access to SMART. Patients with LAPC were treated with prescription dose of 40 Gy in 5 fractions. The planning objective was that 98% of PTV received ≥95% of the prescribed dose, prioritising duodenal, stomach and bowel UK SABR consortium constraints. Daily online adaptation was performed using magnetic resonance guidance and on-table re-optimisation. 0–3 months and > 3-month post-treatment-related toxicities, local progression-free survival, metastatic-free survival and overall survival were evaluated.

Results: 55 patients were treated with SMART at our institution from 2020 to 2022. Median follow-up from date of diagnosis was 17 months (range 5–37 months). Median age was 69.87% of patients underwent induction chemotherapy. 71% of patients reported 0–1 grade acute toxicity only. No grade >3 acute toxicity was reported. 5 patients (9%) reported a grade 3 toxicity (fatigue, nausea, abdominal pain, duodenal stricture). No grade >3 toxicity after 3 months was reported. 6 (10%) of patients had grade 3 toxicity (fatigue, nausea, abdominal pain, duodenal haemorrhage). Median local PFS post diagnosis was 17 months (95% CI 15.3–18.7). Median OS post diagnosis was 19 months (95% CI 15.9–22.1). One-year local control post SMART was 65%.

Conclusion: This is the first UK-reported experience of MR-guided daily adaptive pancreatic SABR. SMART shows promise in delivering ablative doses with acceptable toxicity rates and good clinical outcomes.

Key words: Daily adaptive radiotherapy; MRI-Guided SABR; pancreatic cancer; SABR

Abbreviations: 0.35 T, 1.5 T, 3 T, 0.35, 1.5, 3 Tesla (magnetic field strength) BED, Biological equivalent dose; CRT, Chemotherapy and RT; CCO, Consultant Clinical Oncologist; CTCAE, Common Terminology Criteria for Adverse Events, Version 4.0; CT TAP, Computerised Tomography Thorax Abdomen and Pelvis; CTV, Clinical Target Volume; DART, Daily Adaptive RT; FOV, Field of view; GI, Gastrointestinal; GTV, Gross Tumour Volume; Gy, Gray (unit); HPB, Hepatobiliary; ICF, Informed Consent Form; MFS, Metastatic-free Survival; MR(I), Magnetic Resonance (Imaging); MRLinac, Viewray MRIdian MR Linac (in this publication); MRgRT, Magnetic Resonance guided RT; NHS, National Health Service (United Kingdom); OAR, Organs at risk; OS, Overall Survival; LANPC, Locally advanced non-metastatic pancreatic cancer; Local PFS, Local Progression-Free Survival; PET, Positron Emission Topography; PROMS, Patient reported outcome measures; PTV, Planned Target Volume; Px, Prescription; QA, Quality Assurance; QC, Quality Control; RT, Radiotherapy; SABR/SBRT, Stereotactic (ablative) body radiotherapy; SMART, Stereotactic MR-guided adaptive radiotherapy; TRUFISP, True fast imaging with steady-state free precession (MRI sequence).

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Introduction

Survival of patients with pancreatic cancer is poor. In the UK, there are approximately 10,500 new cases diagnosed each year with approximately 8000 deaths accounting for 6% of all cancer deaths [1]. Mortality from pancreatic cancer remains high with the majority of patients succumbing to their disease within 1 year [1]. Surgical resection offers the best chance of long-term survival; however, only ~20% of patients are operable at diagnosis. In contrast, 30–40% have locally advanced pancreatic cancer (LANPC) and another 40–50% have metastatic disease [2].

The optimum treatment of patients with LANPC is unclear. Historically, these patients are managed similar to patients with metastatic disease, under the premise that this is a systemic disease with a high propensity to metastasise [3]. However, tumour downstaging to facilitate complete R0 resection [3] and improving local control are becoming a more relevant aim thanks to improvements in systemic therapy. In this context, RT may have an important role in local disease management. In fact, CRT is often used after induction chemotherapy since the phase III GERCOR LAP 07 trial of chemotherapy with or without consolidation chemoradiotherapy (54Gy/30 fractions) showed a decrease in local progression (32% vs 46%, $p = 0.03$) and a delay in the onset of second-line chemotherapy [4].

SBRT, where an ablative dose of RT is delivered to a small volume in 1–5 fractions, has been shown to achieve 12-month local tumour control rates as high as 60–90% [5], compared to 68% reported in the LAP 07 trial [4]. There are several advantages to SBRT over CRT for LANPC patients. The increased conformality of SBRT increases normal tissue sparing, thus allowing dose escalation to a higher BED in these radioresistant tumours. Furthermore, reducing the number of hospital appointments for patients with a limited life expectancy by employing the much shorter SBRT treatment is another clear benefit. Several meta-analyses have shown favourable outcomes with SBRT. For example, a recently published series compared conventionally fractionated RT versus SBRT in LANPC. SBRT had a statistically improved 2-year OS with a reduced incidence of acute grade 3/4 toxicity [6]. Notably, 5-fraction SBRT regimens have recently been commissioned by NHS England, and are rapidly replacing conventional CRT as the preferred mode for consolidation therapy following 3–6 months of induction chemotherapy [7]. However, SBRT is not without side effects. Serious toxicity (grade 3+) including gastrointestinal toxicity (bleeding/ulceration/fistulation) has been reported in ~10% of patients with conventional CT-based SBRT [8].

Indeed, the proximity of the pancreas to adjacent critical and highly radiosensitive mobile organs (duodenum, stomach, and small bowel) that are poorly visualised on CT-based image guidance brings significant challenges to the safe delivery of SABR. SMART has emerged as a promising means by which to overcome these barriers. It brings several advancements to the delivery of ablative radiotherapy. Firstly, by utilising the enhanced soft tissue contrast of MR imaging, GTV and OAR contours and the radiotherapy dose delivery of each individual fraction can be adapted to the patient's daily anatomy. With both the MRIdian and Elekta Unity the pancreatic tumour position is tracked in real time coupled with beam gating that prevents treatment delivery if the target is outside the defined boundary. Whether the ability to account for both intra-fraction and inter-fraction motion could be used to dose escalate safely has been investigated by the SMART study [9]. They reported acute grade 3 and grade 4 GI toxicity definitely and probably related to SMART amongst the 136 patients treated with 50 Gy in 5 fractions (BED10 100 Gy) as 0% and 2.2% ($n = 3$), respectively. The study's 2-year overall survival of over 50%, suggesting a potential survival benefit which may embolden future trialists to investigate OS as a primary endpoint post-pancreas SMART for LANPC.

We report here the successful completion of a UK-based Compassionate Access Programme that provided SMART access to patients with borderline resectable (BRPC) and locally advanced non-metastatic (LAPC) pancreatic cancer. We report associated acute and late toxicity rates in addition to local PFS, MFS and OS outcomes post-pancreas SMART.

Methods

Study Design and Participants

This was a registry retrospective study conducted at a single centre with access to SMART. Eligible UK NHS patients with medically inoperable, borderline operable, locally advanced, and locally recurrent pancreatic cancer had access to pancreas SMART treatment through a *compassionate access programme*. Full inclusion and exclusion criteria and clinician referral pathways are included in Appendix A.

Systemic Chemotherapy

Induction chemotherapy was not mandated. Prior to SMART pancreas treatment, patients could undergo a referring clinician's choice of systemic chemotherapy. No systemic chemotherapy was mandated post-SABR treatment.

Radiotherapy Prescription

Patients with locally advanced, locally recurrent, or medically inoperable disease received a maximum dose of 40 Gy in 5 fractions, with 35 Gy in five fractions being used in the case of borderline resectable disease, or when the OAR constraints could not be met at 40 Gy. Treatment delivery was on alternative days.

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Radiotherapy Treatment Planning and Delivery

(See Appendix A for a detailed overview of the MRLinac simulation and image import registration, radiotherapy planning, adaption workflow, and treatment protocol).

Target Volume Delineation

All volumes of interest were outlined with all available diagnostic imaging considered. Tumour volume definition was discussed with a pancreatic/upper GI radiologist. Peer review of contours by another HPB site specialist was strongly recommended. The PTV margin was 3mm on GTV or CTV if used. (CTV= GTV + 2–5 mm, with CTV cropped to the visceral OARs). The duodenum, oesophagus, stomach, bowel, liver, kidneys, and spinal cord were contoured as organs at risk, where appropriate.

Treatment Planning

The PTV was divided into PTV_high and PTV_low so that any overlap of OAR and PTV still allowed achievable tolerance of OAR.

The planning objective was that 98% of PTV_high received ≥95% of the prescribed dose. If the mandatory duodenum, bowel, or stomach constraints could not be met, PTV_low coverage was reduced until the constraints were met.

Daily Adaptive Workflow

For each individual fraction, a new MRI TRUFISP sequence was acquired daily, and the GTV was matched to baseline plan. The contours (GTV and OARs) were adjusted to the patient's on-set presenting anatomy by a CCO. All delivered plans were re-optimised to adapted OAR volumes.

Patients Follow-up and Assessment

The endpoints of this study were acute (≤3 months) and late (>3 months) toxicities in addition to local PFS and MFS, based on radiological assessment, and OS. All patients who underwent SMART pancreas treatment through the compassionate access programme were offered enrolment in a patient registry database. Patients consented to information collection and storage regarding their clinical outcomes post-SABR treatment. Referring clinicians were contacted at prospectively agreed time points (baseline, 1, 3, 6, 12 months and at time of study censor) for specific patient clinical outcome details regarding both SABR-related toxicity and grade as assessed by the clinician according to CTCAE version 4.0 criteria and patient survival and disease progression.

Statistical Analysis

OS was evaluated from both the date of diagnosis and post-SMART pancreas treatment until death from any cause, or the date of last follow-up/date of study censor. Local PFS was calculated separately from both the date of diagnosis and post-SMART treatment to first local recurrence, date of death (without local recurrence), or the date of last clinical follow-up/date of study censor. MFS was calculated separately from both date of diagnosis and post SMART to the first distant recurrence, date of death (without metastatic spread), or the date of last clinical follow-up/data censor. The Kaplan-Meier method was used to estimate the median OS, local PFS, and MFS rates for both.

Multiple linear regression analyses were carried out to investigate the relationship between the independent variables: neoadjuvant chemotherapy, duration of chemotherapy (months), age, PS, time to SABR (months), PTV size (cc), min dose to PTV (Gy), metastatic progression and the individual dependents a) LPFS post SABR, b) LPFS post diagnosis, c) MFS post SABR, d) MFS post diagnosis, E) OS post SABR and F) OS post diagnosis. All statistical tests were two-sided and assessed for significance at the 0.05 level. Statistical analyses were carried out using IBM® SPSS® statistical software version 25.

Results

Patient Participants and Baseline Characteristics

Between July 2020 and December 2021, 58 patients underwent SMART pancreas treatment and were included in our retrospective registry study. Three patients were lost to follow-up. Patients were followed up until death or to date of study censor in December 2022. An overview of patient, tumour, and treatment characteristics of the 55 patients are outlined in Table 1. Median follow-up was 17 (range 5–31 months) and 9 months (range 4–27 months) from diagnosis and SMART respectively. Median age was 69. The median size of pancreatic tumour was 48 cc (14–126 cc) with 80% of tumours being located in the pancreatic head. 87% of patients underwent induction chemotherapy (FOLFIRINOX 67%) with a median duration of 13 weeks.

Acute Toxicity (≤3 Months)

All reported worst acute treatment-related toxicity grades that occurred in the first 3 months post SMART are summarised in Table 2. No grade >3 toxicity was reported with 71% of patients experiencing 0–1 grade toxicity only. 5 patients (9%) reported a grade 3 toxicity; 2 patients experienced G3 fatigue, of the G3 toxicity 5.4% (n = 3) was GI related; 1 patient experienced G3 nausea/anorexia, 1 patient experienced G3 abdominal pain and 1 patient was reported to develop a duodenal stricture in the acute setting which was managed conservatively with a watch-and-wait approach until resolution.

Late Toxicity (>3 Months)

Table 3 shows the worst late treatment-related toxicity reported post-pancreas SMART treatment. 33 (66%) of

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Table 1
Patient, tumour and treatment characteristics amongst patients who underwent pancreas SMART

Variable		N = 55	(%)
(a) Patient			
Age, years at diagnosis			
<40		0	0
40–49		1	2
50–59		11	20
60–69		16	29
70–79		22	40
80+		5	9
Sex			
Male		34	62
Female		21	38
Performance status			
0		19	35
1		32	58
2		4	7
3		0	0
(b) Tumour			
Site			
Head		44	80
Body		5	9
Tail		2	4
Recurrent		4	7
Tumour stage			
Operable (Medically unfit)		4	7
Borderline resectable		3	6
Locally advanced		44	80
Recurrent		4	7
Tumour size			
GTV cc *(median, range)*	48 (14–126)		
PTV cc *(median, range)*	99 (36–359)		
(c) Treatment			
Months from diagnosis to SABR *(median)*	7		
Radiotherapy dose fractionation			
40 Gy in 5 fractions		49	89
35 Gy in 5 fractions		6	11
Induction chemotherapy			
No		7	13
Yes-		48	87
FOLFIRINOX		37	67
Gemcitabine		5	9
Gemcitabine/capecitabine		3	5
Gemcitabine/abraxane		2	4
Oxaliplatin/capecitabine		1	2
Chemotherapy duration in weeks *(median)*	13		
Prior Surgery			
No		51	93
Yes-	Whipple procedure	4	7
All Patients		**55**	**100**

patients reported no late toxicity during the follow-up period. No grade >3 delayed toxicity was reported. 6 (10%) of patients had grade 3 (G3) toxicity which was reported; 1 patient was reported to have G3 fatigue, 1 patient experienced G3 nausea/anorexia, 3 patients reported G3 abdominal pain and 1 patient was reported to have had a G3 duodenal haemorrhage that was medically managed with complete resolution.

Oncological Outcomes (Local PFS, OS, MFS)

Table 4 summarises local progression events, metastatic events (no local progression) and death within the first 12 months of SMART. Initial local tumour control at 3 months was 80% (Appendix Figure B1). Median local PFS post diagnosis was 17 months (95% CI 15.3–18.7) with 65% of

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Table 2
Reported CTCAE acute toxicity assessments post-pancreas SMART

CTCAE acute (≤3 months) toxicity assessments					
	None	Grade 1	Grade 2	Grade 3	Grade 4
Any	17 (31%)	22 (40%)	10 (18%)	5 (9%)	0 (0%)
Fatigue	-	8	3	2	0
Nausea/Anorexia	-	6	2	1	0
Abdominal pain	-	7	3	1	0
Diarrhoea	-	1	1	0	0
Duodenal stricture	-	0	0	1	0
Biliary obstruction	-	0	1	0	0

Table 3
Reported CTCAE late toxicity assessments post-pancreas SMART

CTCAE late (>3 months) toxicity assessments					
	None	Grade 1	Grade 2	Grade 3	Grade 4
Any	33 (60%)	8 (15%)	2 (4%)	6 (10%)	0 (0%)
Fatigue	-	4	1	1	0
Nausea/Anorexia	-	1	0	1	0
Abdominal pain	-	3	1	3	0
Diarrhoea	-	0	0	0	0
Duodenal haemorrhage	-	0	0	1	0
Biliary obstruction	-	0	0	0	0

patients maintaining local control at 1 year post SMART. Local PFS post SMART was 8 months (95% CI 5.3–10.7) (Appendix Figure B3 and Figure 1). Median OS post diagnosis was 19 months (95% CI 15.9–22.1) and 12 months (95% CI 9.5–14.5) (Appendix Figure B4 and Figure 2) post SMART. Median MFS post diagnosis was 15 months (95% CI 13.1–17.2) and 6 months (95% CI 4.7–7.3) post SMART (Appendix Figure B5 and Figure 3), with liver (36%), peritoneum (30%) and lung (28%) being the most common sites for first distant failure (Figure B2). OS, LPFS and MFS were higher in patients who underwent neoadjuvant chemotherapy prior to radiotherapy; OS 21 months with neoadjuvant chemotherapy versus 16 months with SABR alone ($p = 0.02$), LPFS 17 months with neoadjuvant chemotherapy versus 14 months with SABR alone ($p = 0.08$) and MFS 16 months with neoadjuvant chemotherapy versus 14 months with SABR alone ($p = 0.14$) (Figures B6, B7 and B8).

Table 4
Summary of local progression, metastatic and death events within 12 months of pancreas SMART

Events within 12 months of SABR	SABR n = 55
No Events	7 (13%)
Local progression (with or without metastasis)	19 (35%)
Deaths:	23 (42%)
- Evidence of local progression (with or without metastasis)	10
- No local progression	13

Multiple Linear Regression Analyses

There was no statistically significant relationship found in the analysis except between minimum dose to PTV and MFS post diagnosis, with the higher the minimum dose to PTV, the longer MFS ($p = 0.038$, B=+0.4).

Discussion

The management of pancreatic cancer is an ever-evolving paradigm. There are numerous complexities facing radiation oncologists, surgeons, and medical oncologists for its optimal treatment. Pancreatic cancers not only have a high propensity to metastasise early, leading to high mortality rates, but their anatomical location adjacent to vascular and digestive luminal structures presents numerous challenges for improving clinical outcomes. Surgical resection offers the best chance of cure with OS being improved with the addition of adjuvant FOLFIRINOX [10]. Unresected patients have a particularly poor outcome with most patients succumbing to their disease within 12 months [11]. Chemotherapy has improved clinical outcomes in LANPC patients with Gemcitabine, FOLFIRINOX and Nab paclitaxel all demonstrating an improved OS benefit [10,12,13]. In the neoadjuvant pre-operative setting the Alliance A021501 trial could not find a benefit for the

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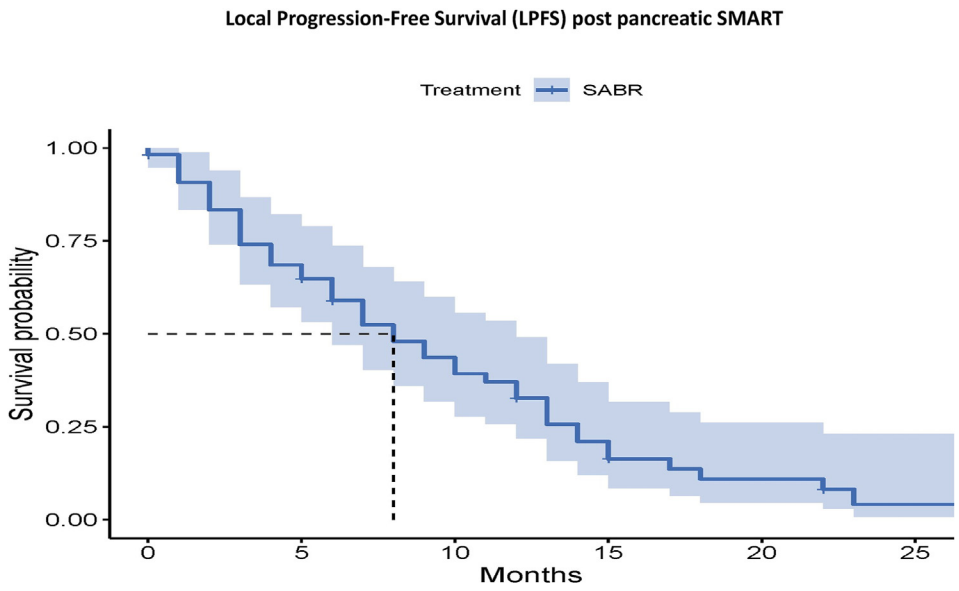

Fig 1. Local progression-free survival post-pancreatic SMART.

addition of hypofractionated radiation post mFOLFIRINOX regimen [14]. The role of radiotherapy and its integration and combination with chemotherapy needs to be defined. One randomised study of chemotherapy plus or minus consolidation chemoradiotherapy (54Gy/30 fractions) showed a decrease in local progression (32% vs 46%, p = 0.03) but not an OS benefit [4]. More recently, SBRT has been using advances in precision radiotherapy to deliver ablative doses of RT to a small volume in 1–5 fractions. This modality improves normal tissue sparing of adjacent OARs whilst ensuring excellent coverage of the tumour. These much shorter courses of treatment are also very attractive for patients with limited life expectancy. With SABR, local control rates can be as high as 60–90% [5] compared to 68% with CRT [4] (Appendix Table B2.1).

There have been several meta-analyses looking at patient outcomes with SBRT. A recently published meta-analysis including 1147 patients across 21 studies comparing conventionally fractionated radiation therapy (CFRT) versus SBRT in LANPC showed favourable outcomes for SBRT [6]. The random effects estimate for 2-year OS was 26.9% (95%CI, 20.6%–33.6%) for SBRT vs 13.7% (95%CI, 8.9–19.3%) for CFRT. The most common dose for SBRT was 30Gy in 5 fractions (BED10 = 48Gy). Most patients received SBRT using CBCT image guidance and fiducials. The random effects estimate for grade 3/4 toxicity was 5.6% (95%CI, 0.0%–20%) for SBRT vs 37.7% (95% CI, 24.0-% -52.5%) for CFRT. Indeed, with this evidence, NHS England has now commissioned SABR as an alternative option to CRT for consolidation treatment post 3–6 months of chemotherapy

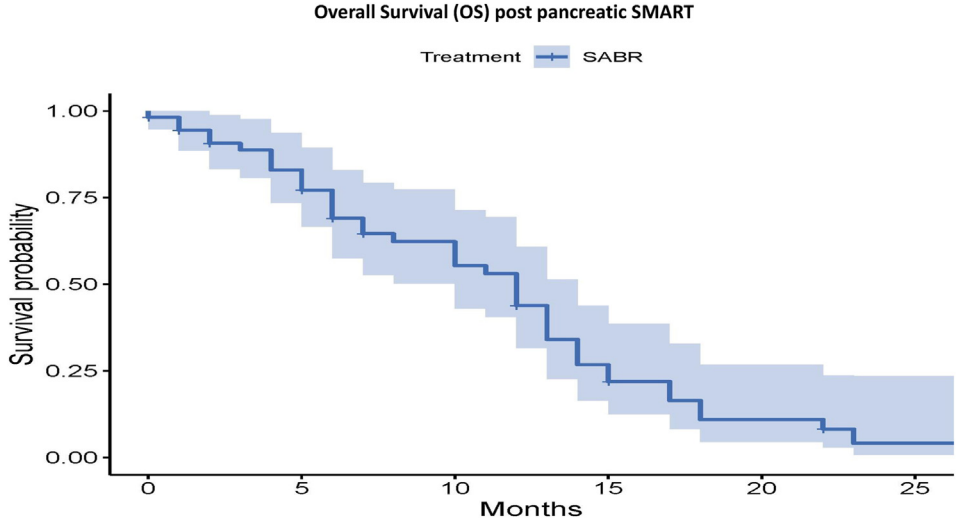

Fig 2. Overall survival post-pancreatic SMART.

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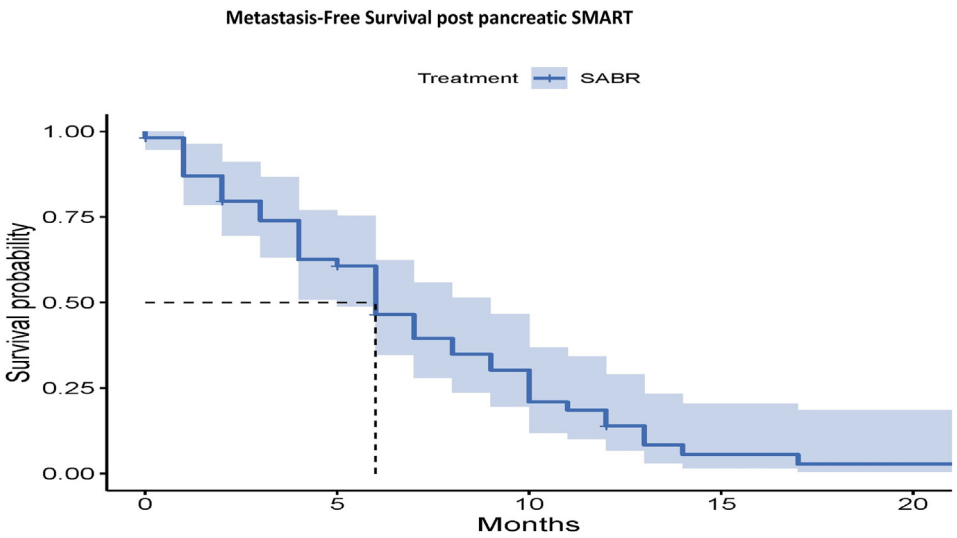

Fig 3. Metastatic-free survival post-pancreatic SMART.

[7]. However, pancreatic SABR is not without its side effects. Serious toxicity (grade 3+) including gastrointestinal toxicity (bleeding/ulceration/fistulation) was reported exceeding 10% of patients during the initial experience with SABR [8] (Appendix B2.2).

SMART is relatively a new modality of treatment in precision pancreatic radiotherapy. It provides an opportunity to spare dose to the very proximal and highly radiosensitive duodenum, stomach, and small bowel. A number of planning and clinical studies have now shown that dose escalation whilst adhering to OAR constraints is possible with an MR Linac [15,16]. The 0.35T system on which this study was conducted remains in widespread clinical, and technical advances in the 1.5T MR-linac system that is currently commercially available now facilitate beam gating as well as improved soft-tissue definition and adaptive recontouring, meaning that these results are likely to be applicable on a platform-agnostic basis. There have been several series that have shown this dosimetric improvement has translated into reduced toxicity, even with dose escalation. For example, Chuong *et al.* [17] reported on 62 patients who underwent 50 Gy in 5 fractions after induction chemotherapy with acute and late grade 3+ toxicity rates of 4.8% and 4.8%, respectively; Hassanzadeh *et al.* [18] reported on a single centre experience of 44 patients with a late toxicity incidence of 4.6% grade 3 (gastrointestinal ulcers) and 6.8% grade 2 toxicities (duodenal perforation, antral ulcer, and gastric bleed) post 50 Gy in 5 fractions SMART. Another series from Michalet *et al.* reported no acute or late grade >2 toxicity in their 30 patients. Toxicity data from a trial setting has now been recently published from the USA-based SMART trial [9]. This trial reported an incidence of acute grade 3 and grade 4 GI toxicity definitely and probably related to SMART of 0% and 2.2% amongst 136 patients who underwent 50 Gy in 5 fractions. Our results are concordant with this, we report no grade 3+ toxicity in the acute and late setting. Our acute grade 3 GI toxicity was 5.4% (n = 3) and late grade 3 GI toxicity was 9% (n = 5) with abdominal pain being the most common late effect. When reviewing the milder toxicities, there may be an opportunity to optimise patients' supportive medications. As reported by Michalet *et al.* the most common milder toxicities (G1-2) were nausea and abdominal pain suggesting that creating an anti-emetic and analgesia protocol post SMART may improve patient's experience.

We report a median local PFS post diagnosis of 17 months with 65% of patients maintaining local control at 1-year post-SMART. Although it is important to note that the vast majority of patients (87%) underwent chemotherapy and there may be an immortal time bias for patients that were ultimately referred to our centre for SMART. Median Local PFS post SMART was 8 months. Median OS post diagnosis was 19 months and 12 months post SMART. Our results are similar to the current literature. Hassanzadeh *et al.* [18] reported median overall survival of 15.7 months, while 1-year and 2-year overall survival rates were 68.2% and 37.9%, respectively. One-year local control was 84.3%. The median progression-free survival (PFS), and overall survival (OS) from diagnosis were reported by Chuong *et al.* [17] as 20 months, and 23 months, respectively, whilst the SMART Trial [9] reported a 1-year LC and DPFS from SMART at 82.9% and 50.6%, respectively. Their 1-year OS was 93.9% from diagnosis and 65.0% from SMART. Our median MFS was short at 6 months reflecting pancreatic cancers' high propensity to metastasise. We did not mandate chemotherapy after SABR but with such a rapid distal failure rate it may suggest a potential role for maintenance chemotherapy in selected patients. Our OS and PFS survival must be interpreted in the context of the n-SARS-CoV-2 pandemic with most of our patients being treated during its peak, which may have affected mortality amongst our cohort [19] that we could not adjust for. Our choice of prescription is another important factor to consider when interpreting our results. As this was our initial experience with SMART pancreas SABR, we opted for 40 Gy in 5 fractions (BED10 72 Gy). However, there is some evidence for a dose response

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suggesting that dose escalation to 50 Gy in 5 may be superior. A study by Rudra *et al.* [20] demonstrated that increasing the BED10 to >70 Gy impacted survival. Patients who received a BED10 >70 Gy had a 2-year OS of 49% versus 30% in patients who received a BED10 <70 Gy. The higher LC and OS rates seen in the SMART trial compared to our data suggest that dose escalation to 50 Gy in 5 fractions may be superior. Our multivariate analysis did not reveal any statistically significant relationship between treatment and dosimetric outcomes except between MFS and the minimum dose to PTV, suggesting that dose response and local control may influence metastatic events.

There are some limitations to our study. Our data is from a single centre with modest numbers; however, this is in the context of SMART being a novel treatment with limited availability. Our inclusion criteria did not specify criteria for operability, with the decision left to the surgical teams. Most surgeons in the UK follow the NCCN guidelines. However, clinical resource pressures from n-SARS-CoV-2 pandemic may have influenced decisions for surgical management. Our follow-up is limited and our results will need to be confirmed with a more extended follow-up period.

Our study has several strengths. Prior to the commencement of our pancreatic SMART programme, we set out a protocol for patient selection, planning treatment and delivery, and created a prospective patient registry that facilitated retrospective collection of clinical outcomes. All target volume delineation and plans were peer reviewed by two experienced clinicians.

The safety of further dose escalation and hypofractionation is the endpoint of the UK Emerald trial [21] that opened in 2022. This phase I/expansion trial is investigating the safety of 50 Gy in 5 fractions (BED10: 100 Gy), 39Gy in 3 fractions (BED10: 90 Gy) and 25 Gy in 1 fraction (BED10: 88 Gy).

Conclusion

SMART for pancreatic cancer is feasible and safe with low rates of acute and late toxicity. It allows ablative doses with promising outcomes whilst minimising toxicity. Future trials exploring dose escalation and the best integration of SMART with systemic treatment are recommended.

Ethics

All patients underwent a written consent to participate in the programme and for their clinical outcome data to be collected and reported.

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Author Contribution

1 Guarantor of integrity of the entire study KN ST JG.
2 Study concepts and design JG TM SM ST.
3 Literature research KN.
4 Clinical studies KN ST.
5 Experimental studies/data analysis KN ST.
6 Statistical analysis KN.
7 Manuscript preparation All authors contributed.
8 Manuscript editing All authors contributed.

Conflicts of Interest

The authors declare no conflict of interest.

Data Availability

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2024.05.012.

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