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Original Article

Adaptive MRI-guided stereotactic body radiation therapy for locally advanced pancreatic cancer – A phase II study

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ABSTRACT

Purpose: Stereotactic body radiotherapy (SBRT) has emerged as a promising new modality for locally advanced pancreatic cancer (LAPC). The current study evaluated the efficacy and toxicity of SBRT in patients with LAPC (NCT03648632).

Methods: This prospective single institution phase II study recruited patients with histologically or cytologically proven adenocarcinoma of the pancreas after more than two months of combination chemotherapy with no sign of progressive disease. Patients were prescribed 50–60 Gy in 5–8 fractions. Patients were initially treated on a standard linac (n = 4). Since 2019, patients were treated using online magnetic resonance (MR) image-guidance on a 1.5 T MRI-linac, where the treatment plan was adapted to the anatomy of the day. The primary endpoint was resection rate.

Results: Twenty-eight patients were enrolled between August 2018 and March 2022. All patients had non-resectable disease at time of diagnosis. Median follow-up from inclusion was 28.3 months (95 % CI 24.0-NR). Median progression-free and overall survival from inclusion were 7.8 months (95 % CI 5.0–14.8) and 16.5 months (95 % CI 10.7–22.6), respectively. Six patients experienced grade III treatment-related adverse events (jaundice, nausea, vomiting and/or constipation). One of the initial four patients receiving treatment on a standard linac experienced a grade IV perforation of the duodenum. Six patients (21 %) underwent resection. A further one patient was offered resection but declined.

Conclusion: This study demonstrates that SBRT in patients with LAPC was associated with promising overall survival and resection rates. Furthermore, SBRT was safe and well tolerated, with limited severe toxicities.

Introduction

The number of patients with pancreatic cancer (PC) is increasing globally, and PC is projected to become the second most common cause of cancer-related mortality by 2025 [1–3]. Patients are staged according to the cTNM classification based on imaging, but in clinical practice, patients are more often divided into four major clinical groups: Resectable PC (rPC), borderline resectable PC (brPC), locally advanced PC (LAPC), or metastatic PC (mPC) [4–6]. The expected median overall survival (mOS) for patients with LAPC is 12–15 months, based on randomised study data [7–9].

LAPC is characterised by the incasement of the major blood vessels such as the superior mesenteric artery (SMA), coeliac trunk (TC), common hepatic artery (CHA), and perhaps other adjacent organs, making upfront radical resection difficult or even impossible. The definition of LAPC varies slightly among medical professionals and institutions

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[10–12]. Imaging techniques, such as computed tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasound (EUS), or laparoscopy with laparoscopic ultrasound (LUS) combined with frozen section if needed are commonly used to evaluate the extent of local involvement and thereby determine whether the tumour is resectable or not [10]. The exact staging and final treatment decision may also involve clinical assessment and multidisciplinary discussions among oncologists, surgeons, radiologists, and pathologists.

Patients with LAPC represent 20–30 % of all patients treated for PC. Traditionally, these patients are often treated as patients with mPC. However, research has shown that some of these patients can achieve tumour shrinkage after treatment, which allows subsequent curatively intended resection [13–16]. Currently, there is no definitive consensus on the role of radiotherapy in the treatment of pancreatic cancer. Also, the timing of radiotherapy is debated as historically conventional doses and fraction sizes were used, and radiotherapy is often regarded as a definitive strategy in patients with unresectable disease. Furthermore, several studies have failed to demonstrate a survival benefit [17]. However, stereotactic body radiotherapy (SBRT) has shown potential as a treatment option due to advancements in radiotherapy, as seen in recent studies demonstrating improved local control rates and less toxicity [18].

The goal of chemoradiotherapy (CRT) is to obtain or maintain response and tumour control after chemotherapy and to potentially induce sufficient shrinkage to down-size the tumour to allow resection with curative intent. Conventional fractionated CRT with biological equivalent doses (BEDs) of 50–54 Gy after chemotherapy have had minimal impact on survival for patients with LAPC [17,19–21]. BEDs around 50 Gy were originally established based on large fields and tolerability of adjacent organs at risk (OAR) (e.g. duodenum). The intrinsic radioresistance of PC cells may partly explain the lack of benefit. SBRT permits the precise application of high-dose radiation to a limited target volume in a few fractions, but relies on image guidance that clearly identifies targets and surrounding organs, allowing the use of inhomogeneous dose distribution. A clear definition of SBRT (also referred to as stereotactic ablative radiotherapy (SABR)), is not well established. In this study, we define SBRT by the above-mentioned characteristics and the ability to deliver a very high dose, e.g. a minimum BED of 70 Gy. Therefore, SBRT offers a potential advantage in PC because of the possibility of delivering ablative doses to overcome inherent radioresistance [22]. Many, but primarily retrospective studies, have shown promising outcomes for SBRT with local control rates of 50–100 % [17,23].

Online MRI-guided radiotherapy (MRIgRT) enables the delivery of intensity-modulated radiotherapy radiation in areas with movement due to, e.g. the digestive and respiratory systems, through better imaging and daily dose adaption. This technique may deliver ablative doses to the target while maintaining low doses to OAR, hopefully prolonging survival without inducing severe adverse events. Therefore, this study was initiated in 2018, at the time of the introduction of the MRI-Linac at Odense University Hospital (OUH), Denmark.

The current phase II study was designed to evaluate the efficacy and toxicity of SBRT in patients with LAPC.

Material and methods

This single institution phase II trial enrolled patients between August 2018 and March 2022 (NCT03648632). Patients were enrolled from different departments of oncology in Denmark, including OUH. Inclusion criteria were pathologically confirmed pancreatic ductal adenocarcinoma in patients with LAPC and an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2. All patients had LAPC as defined by NCCN guidelines. In brief, all patients must have had more than 180° encasement of SMA or TC. In addition, study participants should have received combination chemotherapy for at least two months before enrollment without any sign of progressive disease, unless contra-indicated. All patients were assessed by the multidisciplinary team conference at OUH, with the participation of upper HPB (Hepato-Pancreato-Biliary) surgeons, radiologists, pathologists and oncologists. Resectability was evaluated at the local multidisciplinary team conference or at a dedicated weekly national pancreatic tumour conference with the participation of surgeons, radiologists and oncologists from all four surgical departments performing pancreatic surgery in Denmark. All patients signed an informed consent form prior to treatment.

Imaging and treatment protocol

SBRT was performed at OUH. The first 4 included patients were treated on a conventional cone-beam CT (CBCT) based linear accelerator, but from September 2019, patients were treated on the MRI-Linac.

Patients were prescribed 50 Gy in five fractions or 60 Gy in eight fractions, depending on the target size, at the treating physician's discretion. Patients were planned to receive treatment over a period of 7–8 days or 10–13 day, depending on the number of fractions. The gross tumour volume (GTV) should preferentially be covered by the 95 % isodose line (GTV V95% $>$ 99 %), and the mean GTV dose should be greater than 100 % (GTV $D_{mean} \geq 100$ %). The planning target volume (PTV) should be covered by the 70 % isodose line (PTV V70% $>$ 99 %) if treated in five fractions or the 66 % isodose line (PTV66% $>$ 99 %) if treated in eight fractions. Elective node irradiation was not used. A compromise of the target coverage was enforced to meet hard dose constraints for OAR (see Supplementary Table S1). The simulation workflow is described in detail in the supplementary materials.

CBCT based image-guided radiotherapy using implanted fiducial markers for image registration was performed in breath-hold at Versa HD accelerators (Elekta Instrument AB, Sweden). Online MRIgRT using an adapt-to-shape (ATS) workflow was carried out on the Unity 1.5 T MRI-Linac (Elekta AB, Stockholm, Sweden) [24]. The patient was positioned on the MRI-Linac table at each adaptive treatment fraction, and a session 3D T2w scan was acquired. During both imaging and treatment, the patients were breathing freely or had breathing motion restricted by an abdominal compression belt [25]. Daily ATS workflow was used where the GTV, OAR, and density contours were propagated from the reference scan to the session scan and manually edited by present physician. To verify the target position, an additional 3D T2w position verification scan was acquired during plan adaptation and during beam delivery, the target position was monitored using cine images. A sample session MRI scan and adapted dose plan are shown in Fig. 1.

Follow-up and outcome assessment

The primary endpoint was the resection rate for all patients starting SBRT. Secondary endpoints were progression-free survival (PFS), OS, and adverse events. Adverse events were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

To determine acute toxicities from radiotherapy, patients were scheduled for a visit one week after SBRT. Afterwards, visits were scheduled five weeks after SBRT and every three months with a physical exam, blood samples, assessment of performance status, and CT imaging. Local or distant progression was characterised by follow-up imaging according to RECIST 1.1 criteria [26]. Acute toxicity was defined as events occurring within 28 days following the initial SBRT fraction, while late toxicity referred to events occurring after 28 days.

Statistical analysis

The sample size for this trial was based on Simon's two-stage Minimax design [27,28]. This was chosen to ensure early study termination if there was insufficient effect. A resection rate of less than 10 % after SBRT was considered not relevant clinically. Assuming a significance

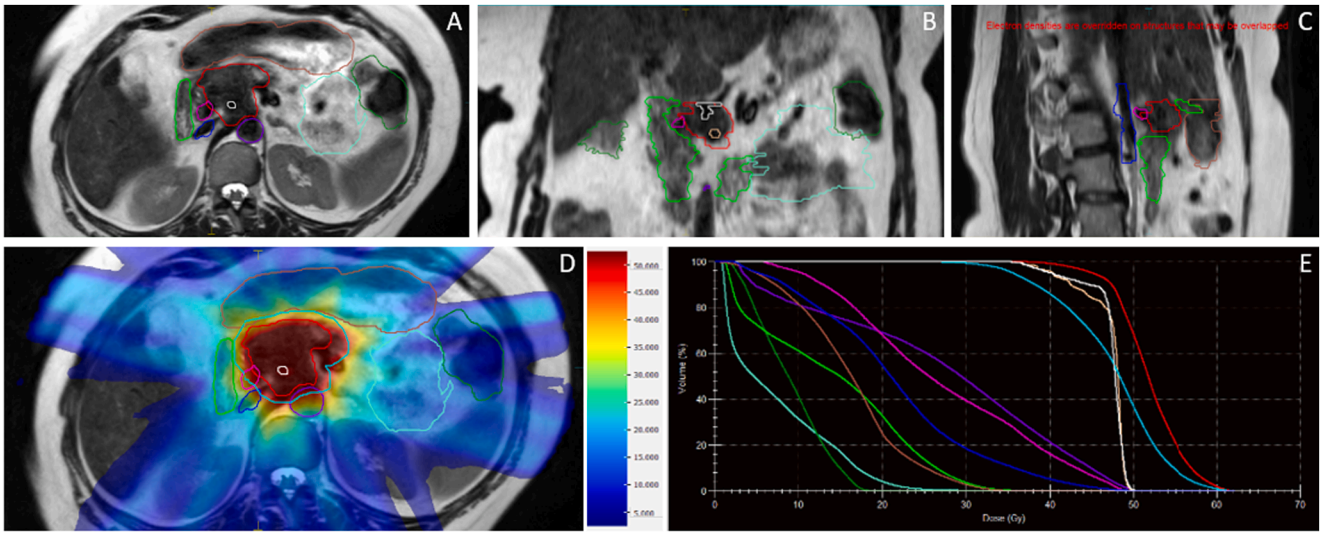

Fig. 1. A sample scan acquired on the magnetic resonance image linear accelerator and adapted dose plan. The patient is a 49-year-old woman with a 40 cm^3 tumour shown in the transversal (A), coronal (B), and sagittal plane (C). The gross tumour volume (GTV) is shown in red. The following organs at risk are shown: Stomach (dark brown), duodenum (light green), large bowel (dark green), small bowel (turquoise), biliary tract (pink), aorta (purple), vena cava (dark blue), celiac trunk (white), superior mesenteric artery (light brown). The target was prescribed 50 Gy in five fractions. A planning target volume (PTV) was created by expanding the GTV by 4 mm in the left–right and anterior-posterior directions and 6 mm in the superior-inferior directions. The PTV and a dose colour wash of the adapted treatment plan are provided (D). Dose-volume histograms for target volumes and organs at risk are shown (E). The relative volume of the GTV covered by 47.5 Gy was 89.4 %, and the mean dose was 51.8 Gy. The relative volume of the PTV covered by 35 Gy was 95.9 %. The patient was treated in September 2021 and was still alive at the cut-off date. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

level of 0.1 ($\alpha = 0.1$) and a power of 90 % ($\beta = 0.1$), it was estimated that 16 patients should be included in the first part of the study. The enrolment continued until 16 patients had completed SBRT and had been re-evaluated for resection by CT scan (and EUS and/or LUS with or without biopsy, if available). If only one or none of the first 16 consecutive patients had undergone resection, we would reject our hypothesis that SBRT ensures a satisfactory resection rate and close the study after the first stage of accrual. If two or more patients had undergone resection, an additional nine patients would be accrued in the second stage.

Nonparametric methods were used to calculate patient characteristics, side effects and disease control. Progression-free survival (PFS) was calculated from date of inclusion in the study until first occurrence of disease progression or death. Overall survival was calculated from the date of inclusion in the study to death of any cause. To ensure comprehensive analysis, patients whose events had not occurred by the end of the study were censored at their last follow-up date. Kaplan-Meier curves were utilised to visualise and estimate survival probabilities.

Results

A total of 33 patients were evaluated for eligibility based on the study criteria. Five patients were excluded from the study; one patient never started SBRT due to rapid progression, two had resectable disease at time of inclusion and two patients had recurrence (see supplementary Figure S1). Table 1 provides an overview of the baseline characteristics of the 28 patients who were included and began SBRT. The majority of patients (n = 26, 93 %) had an ECOG performance status of 0–1. All patients had radiological LAPC at the time of radiotherapy. Before undergoing SBRT, all patients but one had received chemotherapy, with a median duration of 6.0 months from diagnosis to the initiation of SBRT. Among the included 28 patients, the first four were treated using a conventional accelerator, while the remaining 24 patients received treatment using an MRI-Linac.

The median (range) GTV volume for the CBCT and MRI-Linac were 65 (16–80) and 95 (68–100) cm^3, respectively. The median PTV volume for both were 86 (84–97) and 96 (74–100) cm^3, respectively. Of the patients prescribed 50 Gy in five fractions, the median (range) GTV mean dose was 49 (42–49) and 53 (49–56) Gy for the standard linac and MRI-Linac, respectively. All fractions delivered, whether on a standard linac or MRI-Linac, met the constraints for the organs at risk, as demonstrated in Table 2.

All patients were evaluated for resection. Six patients (21 %) underwent resection, with four patients achieving an R0-resection. R0 resection being defined as no microscopic residual disease within ≤ 1 mm from the margin [29]. Five patients were resected with a Whipples procedure, and one patient with a total pancreatectomy. Of the six patients that underwent resection, three patients received adjuvant chemotherapy afterwards. One patient were offered resection but declined. The remaining 21 patients were re-assessed at the local MDT and deemed unresectable.

The median PFS and OS from inclusion was 7.8 months (95 % CI 5.0–14.8) and 16.5 months (95 % CI 10.7–21.6), respectively (Fig. 2). The median OS for patients that received resection from diagnosis and inclusion was 27.7 months (95 % CI 26.3-NR) and 23.9 months (95 % CI 21.2-NR), respectively. Six patients (6/28, 21 %) were still alive at the time of analysis, the cut-off date being July 1, 2023. One patient has recurrence/ and or progression. Five patients had no evidence of active disease. The median follow-up from inclusion was 28.3 months (95 % CI 24.0-NR). The median overall survival from diagnosis of pancreatic cancer was 20.8 months (95 % CI 17.8–26.6).

Twenty-six patients (93 %) completed the planned SBRT course. The two treatment discontinuations occurred because of hospitalisation due to pain in one case and a decline in performance status in the other, and both discontinuations were not likely to be related to SBRT. Treatment related adverse events (TRAE) are demonstrated in Table 3. Six patients experienced grade III TRAE (jaundice, nausea, vomiting and/or constipation). Five of the latter patients were treated with the MRI-Linac. The three patients that developed obstructive jaundice during treatment, were treated with endoscopic retrograde cholangiopancreatography (ERCP) and stenting as an inpatient treatment, enabling them to resume and complete SBRT. One of the initial four patients receiving treatment on a CBCT based linac had a grade IV TRAE, a perforation of the proximal duodenum near the tumour. The perforation did require surgery, and the patient survived. One patient developed upper

Table 1
Baseline and treatment characteristics of 28 patients with locally advanced pancreatic cancer treated with stereotactic body radiotherapy.

	N (%)
BASELINE	
Sex	
	12 (43%)
- Male	16 (57%)
- Female	
NCCN tumour stage	
	25 (89%)
- T4	3 (11%)
- Other[d]	
Performance status	
	10 (36%)
- ECOG 0	16 (57%)
- ECOG 1	2 (7%)
- ECOG 2	
Prior chemotherapy	
	1 (4%)
- No	27 (96%)
- Yes	18 (67%)
o FOLFIRINOX	5 (19%)
o Gem/Nab-P[a]	2 (7%)
o Gem/S1[b]	2 (7%)
o Gem[c]	
TREATMENT	
Radiation dose	
	26 (93%)
- 50 Gy / 5 Fx	2 (7%)
- 60 Gy / 8 Fx	
Duration of SBRT	8 days (7-12)
- Median, range (IQR)	
Time fromdiagnosis of LAPC to SBRT	
- Median, range (IQR)	6.0 months (5.2-7.6)
Resection	
	22 (78%)
- No	6 (22%)
- Yes	4 (67%)
o R0 resection	2 (33%)
o R1 resection	
Time from SBRT to resection	2.9 months (2.7-3.2)
- Median, range (IQR)	

[a] Gemcitabine/Nab-paclitaxel.
[b] Gemcitabine/Teysuno.
[c] Gemcitabine.
[d] These three patients had tumors that where deemed non-resectable by the local MDT.

Table 2
Target and organs at risk: Constraints and obtained values for the 26 patients prescribed 50 Gy in five fractions. Data is not shown for the two patients prescribed 60 Gy in eight fractions.

Structure	Constraint	Standard linac (n = 3)	MRI-linac (n = 23)	
			Pre-treatment	Adapted treatments
GTV V47.5 Gy [%]	V47.5 Gy > 99 %	65.2 (15.9—80.1)	97.2 (76.1—100)	95.0 (67.9—99.8)
GTV Dmean [Gy]	Dmean > 50 Gy	48.7 (42.4—48.8)	52.9 (49.5—56.8)	53.2 (49.4—56.2)
PTV V35Gy [%]	V35Gy > 99 %	85.6 (83.6—96.7)	96.8 (79.8—100)	96.4 (74.2—100)
Duodenum D1cc [Gy]	D1cc < 33 Gy	30.0 (27.6—32.1)	31.8 (21.1—33.2)	31.6 (20.3—33.0)
Stomach D1cc [Gy]	D1cc < 33 Gy	6.7 (1.0—15.9)	22.4 (0.4—33.1)	23.8 (0.4—32.8)
Large Bowel D1cc [Gy]	D1cc < 33 Gy	14.8 (12.3—17.4)	18.3 (8.2—31.5)	17.9 (6.2—31.6)
Small Bowel D1cc [Gy]	D1cc < 40 Gy	32.9 (30.5—35.3)	23.2 (2.9—37.7)	23.7 (5.0—36.1)
Right Kidney D40% [Gy]	D40% < 10 Gy	3.8 (1.0—5.1)	5.5 (0.7—8.2)	5.4 (0.7—8.3)
Left Kidney D40% [Gy]	D40% < 10 Gy	4.9 (0.8—9.2)	3.8 (0.6—9.1)	3.9 (0.6—9.2)

Population median and range is given. For the adaptive treatments, values were averaged over fractions before calculating the population values. Abbreviations: GTV = gross tumour volue; PTV = planning target volume; VxxGy = the volume receiving XX Gy or more; Dmean = mean dose; D1cc = the dose to the 1 cc recieving the highest dose.

gastrointestinal bleeding, was hospitalised and treated with endoscopy and interventional radiology (coiling). The aetiology of the bleeding was judged to be tumour progression by the treating physician and not likely to be related to SBRT. One patient experienced a grade II radiation-induced gastroduodenal paralysis. The condition resolved within a month of onset without treatment. There were no late toxicities defined as any TRAE developing later than 28 days.

Discussion

The current study represents one of the few prospective phase II studies evaluating SBRT in LAPC with an ablative dose, BED $\geq$ 100 Gy. The study was initiated simultaneously with the implementation of the MRI-Linac at OUH, although not contingent on the treatment being MRI-guided; treatment could also be offered on a standard accelerator. The intention of the study, as stated above, was to administer ablative doses to the tumor. The primary endpoint of this study was to evaluate efficacy by resection rate. While resection rate is not a common primary endpoint, we found it relevant in this study. Surgical resection is still the only option for cure in patients with LAPC and, therefore, has a significant impact on patient outcomes, including overall survival. In the current study, the first evaluation CT scan was scheduled for 4 weeks after completion of SBRT to increase the chance of swelling and tissue impact to subside, subsequently all patients were discussed at the local MDT. Twenty-one per cent (6/28) of the included patients underwent resection, similar to other recent studies.

Most patients in our study did not develop severe toxicity; seven (25 %) patients did experience grade III or IV acute toxicity. One patient developed an acute grade IV duodenal perforation, possibly due to SBRT. This patient was not treated on an MRI-Linac. Ablative doses from SBRT can cause the described toxicities, but the data is insufficient to draw clear conclusions. Due to the symptoms caused by the tumour itself, radiation-induced toxicity in patients with LAPC is challenging to determine.

The optimal treatment for patients with LAPC remains unclear despite advancements in systemic chemotherapy treatment options, such as FOLFIRINOX (fluorouracil, oxaliplatin, irinotecan, leucovorin) or gemcitabine/nab-paclitaxel, having significantly improved outcomes [30–32].

Radiotherapy as a treatment option in patients with LAPC remains controversial, but dose escalation has become possible with the arrival of more advanced radiation delivery techniques. The highly focused treatment delivers ablative radiation doses and has demonstrated promising results with longer survival and improved quality of life [33,34]. Though these recent studies support the benefit of ablative radiotherapy in LAPC, other older studies do not support radiotherapy in PC, leading to its limited implementation. As demonstrated in Table 4, several of the most recent studies, using BED of 70 Gy or more, reported 2-year survival rates that approximate the median 2-year survival rate after surgery with acceptable toxicity. Likewise, in the present study, toxicity is limited compared to earlier studies (Table 4).

One of the initial studies involving SBRT was a small Danish phase II study conducted to examine the application of ablative doses in LAPC and included 22 patients who underwent SBRT with a BED of 112 Gy. Unfortunately, the results were discouraging, showing an OS rate of

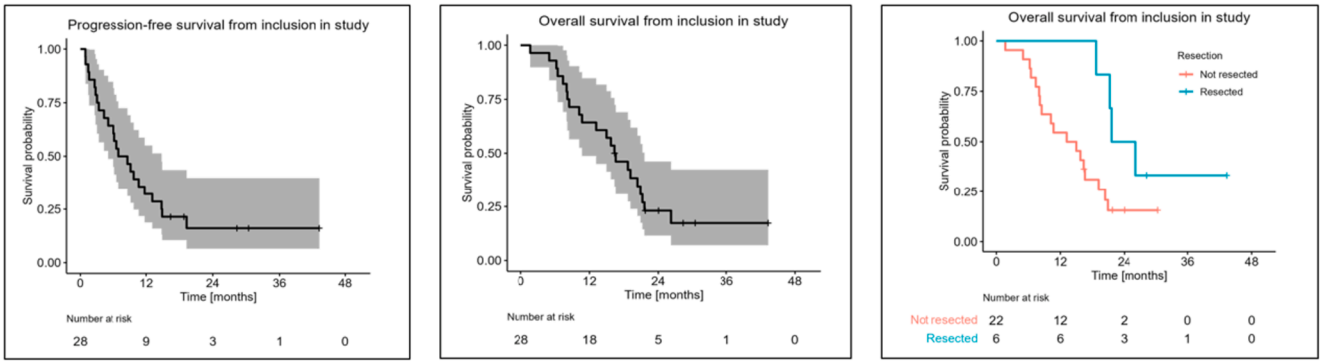

Fig. 2. Survival outcomes from inclusion in the study.

Table 3
Treatment related adverse events.

Patients, N (%)	Grade I	Grade II	Grade III	Grade IV	Grade V
Acute					
Nausea	9 (32 %)	1 (4 %)	2 (7 %)	0 (0 %)	0 (0 %)
Vomiting	3 (11 %)	0 (0 %)	1 (4 %)	0 (0 %)	0 (0 %)
Fatigue	7 (25 %)	2 (7 %)	0 (0 %)	0 (0 %)	0 (0 %)
Abdominal pain	5 (18 %)	2 (7 %)	0 (0 %)	0 (0 %)	0 (0 %)
Constipation	2 (7 %)	0 (0 %)	2 (7 %)	0 (0 %)	0 (0 %)
Diarrhea	4 (14 %)	2 (7 %)	0 (0 %)	0 (0 %)	0 (0 %)
Jaundice	0 (0 %)	0 (0 %)	3 (11 %)	0 (0 %)	0 (0 %)
Duodenal perforation	0 (0 %)	0 (0 %)	0 (0 %)	1 (4 %)	0 (0 %)
Late					
Any AE[a]	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)

[a] Adverse events.

merely 5.7 months and significant toxicity. Notably, the study was conducted prior to the implementation of conformal radiation techniques like IMRT and VMAT and several years before the implementation of MRI-Linacs, which partly can explain the substantial toxicity [35].

Prior to the development of MRI-Linacs, verification of the tumour location during SBRT of LAPC was mainly done by imaging implanted fiducial markers using onboard X-ray-based imaging systems, such as CBCT. Recent studies have shown improved outcome and reduced toxicity. In 2021, Teriaca et al. presented data from the LAPC-1 trial, a phase II study of SBRT after FOLFIRINOX for LAPC. Fifty patients were included in the study. All patients were to receive chemotherapy. Due to progression, only 39 patients were treated with SBRT (40 Gy in eight fractions). This study demonstrated a median OS of 18 months. Late grade III toxicity or more were reported in 10 %, all related to gastrointestinal obstruction or bleeding [36]. Another recent publication, is a phase II study from Choung et al. One-hundred thirty-six patients with either BrPC or LAPC were included in this study. The majority of patients received induction chemotherapy prior to MR-guided SBRT, with a prescription of 50 Gy in 5 fractions, resulting in a BED of 100 Gy. Acute gastrointestinal TRAEs within the first 90 days were observed in 8.8 % of the patients, potentially related to SBRT. Late toxicities attributed to SBRT were defined by grade 3 or more and was seen in up to 11.5 % of patients. The two-year survival from SBRT was 40.5 %. [33].

One of the current study's strengths is the strict inclusion criteria, limiting the population to LAPC and not a mixture including brPC, as seen in multiple previous studies. The limitations of this study include that it was non-randomised and, therefore, lacked a direct comparison group. In addition, there is a possible selection bias since the patients offered SBRT had been diagnosed in a median of approximately six months before radiotherapy. Furthermore, we initially defined acute toxicity as occurring within 28 days of SBRT. However, since the beginning of our study, other research has defined acute toxicity at 90 days after SBRT, which, in hindsight, appears to be a more suitable distinction between acute and late toxicity.

Our study supports that radiotherapy can benefit certain individuals with LAPC and may even extend the survival of carefully chosen patients. However, the current evidence supporting the use of radiotherapy as a standard treatment for LAPC is still scarce. Fortunately, several ongoing trials are testing the use of SBRT, which can provide valuable knowledge regarding patient selection and treatment effectiveness.

Conclusion

This phase II study demonstrates that SBRT in patients with locally advanced pancreatic cancer (LAPC) was associated with promising OS and resection rates. Furthermore, SBRT was safe and well tolerated, with limited severe toxicities. These data are consistent with other studies evaluating ablative radiotherapy.

This study warrants further studies to define when SBRT is a plausible intervention for patients with pancreatic cancer.

Table 4
Important trials with stereotactic body radiotherapy (BED > 70) of pancreatic cancer.

Author, year	Stage	Phase	Therapy	Gy / fx	BED_{10}	N	mOS months	2Y OS %	Toxicity Acute	Toxicity Late
Hoyer, 2005[35]	LAPC	II	SBRT	45/3	112	22	5.7	0	–	G3+: 22 %
Schellenberg, 2008[37]	LAPC	II	Gem[a] ⟹ SBRT ⟹ Gem	25/1	88	16	11.9	18	G2+: 19 %	G2+: 44 %
Schellenberg 2011[38]	LAPC	II	Gem ⟹ SBRT ⟹ Gem	25/1	88	20	11.8	20	–	G2+: 20 %
Teriaca, 2021[36]	LAPC	II	FOLFIRINOX ⟹ SBRT	40/5	72	39	18	26	–	G2+: 10 %
Bordeau, 2022[39]	LAPC brPC	II	CT ⟹ SBRT	50/5	100	52	15.2	36	G2+: 0 %	G2+: 1.4 %
Tringale, 2022[34]	(LAPC)		(CT) ⟹ SBRT	50/5	100	30	NR	70.8	G2+: 17 %	G2+: 0 %
Choung, 2024[33]	LAPC BrPC	II	CT ⟹ SBRT	50/5	100	160	14.2	40.5	G3+: 9 %	G3+: 17 %
Ejlsmark, 2023	LAPC	II	FOLFIRINOX ⟹ SBRT	50/5	100	31	16.4	20	G3+: 25 %	G2+: 0 %

[a] Gemcitabine, Chemotherapy.

CRediT authorship contribution statement

Mathilde Weisz Ejlsmark: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Visualization, Writing – original draft, Writing – review & editing. **Rana Bahij:** Investigation, Resources, Writing – review & editing. **Tine Schytte:** Investigation, Resources, Writing – review & editing. **Christian Rønn Hansen:** Resources, Writing – review & editing. **Anders Bertelsen:** Investigation, Resources, Writing – review & editing. **Faisal Mahmood:** Resources, Writing – review & editing. **Michael Bau Mortensen:** Resources, Writing – review & editing. **Sönke Detlefsen:** Resources, Writing – review & editing. **Britta Weber:** Resources, Writing – review & editing. **Uffe Bernchou:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing – review & editing. **Per Pfeiffer:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

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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Appendix A. Supplementary data

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