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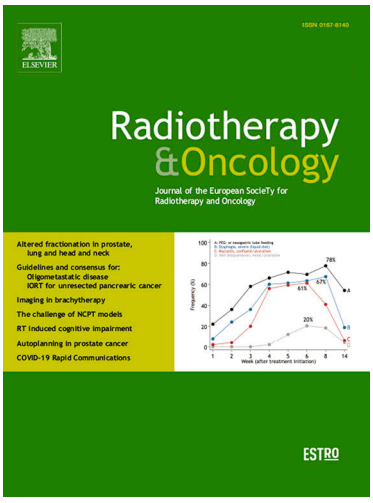

Original Article

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SPARC, a phase-I trial of pre-operative, margin intensified, stereotactic body radiation therapy for pancreatic cancer

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SPARC, a phase-I trial of pre-operative, margin intensified, stereotactic body radiation therapy for pancreatic cancer

Abstract

Background and purpose

Following resection of pancreatic cancer, risk of positive margins and local recurrence remain high, especially for borderline-resectable pancreatic cancer (BRPC). We aimed to establish the maximum tolerated dose of a margin-intensified five-fraction stereotactic body radiotherapy (SBRT) regimen designed to treat the region at risk.

Materials and methods

We conducted a prospective multicentre phase-1 rolling-six dose-escalation study. BRPC patients received pre-operative SBRT, with one dose to the primary tumour and an integrated boost to the region where tumour was in contact with vasculature. Four dose-levels were proposed, with starting dose 30 Gy to primary PTV and 45 Gy to boost volume (PTV_R), in five daily fractions. Primary endpoint was maximum tolerated dose (MTD), defined as highest dose where zero of three or one of six patients experienced dose-limiting toxicity (DLT).

Results

Twelve patients were registered, eleven received SBRT. Radiotherapy was well tolerated with all treatment completed as scheduled. Dose was escalated one level up from starting dose without encountering any DLT (prescribed 32.5 Gy PTV, 47.5 Gy PTV_R). Nine serious adverse reactions or events occurred (seven CTCAE Grade 3, two Grade 4). Two patients went on to have surgical resection. Median overall survival for SBRT patients was 8.1 months. The study closed early when it was unable to recruit to schedule.

Conclusion

Toxicity of SBRT was low for the two dose-levels that were tested, but MTD was not established. Few patients subsequently underwent resection of pancreatic tumour after SBRT, and it is difficult to draw conclusions regarding the safety or toxicity of these therapies in combination.

Introduction

Surgical resection aims to achieve long-term disease control in pancreatic cancer, but even when adjuvant chemotherapy is prescribed, 50% of patients will suffer local recurrence [1] and improvement in multi-modal therapy is therefore required. For patients with positive surgical resection margins, survival outcomes are similar to those for patients who present with unresectable disease [2-4], and despite centralisation of surgery and improved pre-operative investigations, positive margins are reported in around 35-60% of UK patients [5, 6].

Borderline-resectable pancreatic cancer (BRPC) is a radiological definition of a tumour with likely requirement for vascular reconstruction [7] and a particular risk of positive margins following excision (>60% in the UK) [8]. Around 15% of pancreas cancers are borderline resectable at presentation, among whom median overall survival is around two years, with those resected having significantly longer survival (28.8 months, IQR 20.3–43.9) than those not (14.5 months, IQR, 10.7–20.7, $p < 0.001$) [9]. The most widely accepted BRPC definition is published by the National Comprehensive Cancer Network [10], [11], while an alternative definition proposed by the MD Anderson Cancer Centre is not as widely recognised [12]. Whichever definition is used, a multidisciplinary team should assess every patient [12, 13].

The management of BRPC is controversial, and there is increasing interest in multimodal preoperative treatments [14], which are standard for some tumour sites, but not yet in pancreatic cancer [15]. Potential drawbacks include possible over-treatment, and the need for biopsy and biliary stent while awaiting surgery. Benefits include possible downstaging - for patients with unresectable tumours, chemoradiotherapy can induce sufficient regression to achieve resection in around 35% [16]. These patients can have high rates of clear margins [17, 18] and low rates of local recurrence [19, 20].

Stereotactic body radiation therapy (SBRT) uses precision targeting to safely deliver higher biological doses than standard radiotherapy, offering higher likelihood of disease control. SBRT has been shown to be effective in unresectable pancreatic cancer, with high rates of local control [21-24]. Treatment split into three to five fractions causes lower rates of toxicity while maintaining efficacy [25-31], and remains safe when used after induction chemotherapy [31, 32].

We designed a clinical trial of margin-intensified SBRT. Intensity-Modulated Radiation Therapy (IMRT) principles are used to deliver an integrated boost to the regions of tumour abutting adjacent structures (Figure 1) which show high risk of positive surgical margins [33]. This concept aims to improve local control without increasing toxicity, as the boost region tends not to overlap with the major dose-limiting organ at risk (duodenum). A five-fraction schedule intended to balance short duration and tumouricidal dose with acceptable risk of late normal-tissue injury. Prospective dose escalation aimed to establish the maximum tolerated dose (MTD), for subsequent definitive assessment of efficacy.

Materials and methods

We performed a prospective multi-centre ethics-board approved phase-I dose escalation study (ISRCTN14138956) using a rolling-six single-arm open-label design [34].

Full eligibility criteria have been published [39] and are included in supplementary Table 3. Eligible patients were 18 years or older, with newly-diagnosed, biopsy confirmed BRPC as assessed by hepato-pancreato-biliary (HPB) surgical MDT, Eastern Cooperative Oncology Group (ECOG), performance status

0-1, and with absolute neutrophil count >1.5 x 10^9/, platelet count >100 x 10^9/l, serum bilirubin <50 µmol/l, and ALT and/ or AST ≤3.0 times upper limit of normal.

Chemotherapy prior to enrolment was initially not permitted, but a protocol amendment was made to reflect evolving clinical practice and permit it, with a 2-week wash-out prior to SBRT. Other prior treatment for pancreatic cancer was not permitted.

Patients underwent contrast-enhanced CT and 4DCT at radiotherapy planning, with online volumetric (CT) image verification and motion mitigation (gating or abdominal compression) mandated if tumour motion was over 5 mm. GTV was defined as visible tumour on imaging, and margin from GTV to PTV was 3 mm. The target region for the margin-directed boost (PTV_R) was defined following discussion with radiologists and/or HPB surgeons to identify vascular structures responsible for the tumour being classified as borderline resectable [10], with no additional margin. In the event of overlap between target structures and organs at risk, the organs-at-risk constraints (Table 4) were prioritised, even if compromising target coverage [35].

SBRT dose was started at level one (Table 1). As the trial recruited, dose was escalated as permitted by observed toxicity. All radiotherapy comprised five daily fractions. A comprehensive radiotherapy quality assurance (RTQA) programme used tools previously shown to reduce target definition variation [36-38]. Web-conference review of RT planning enabled prompt feedback and revision [39]. All patients underwent CT restaging between SBRT and surgery.

The primary endpoint was the MTD, defined as the highest level of SBRT at which no more than one of six patients, or zero of three patients, experiences a dose-limiting toxicity (DLT). The definition of DLT and other adverse events is included in the supplementary material (Table 5). Secondary outcomes included

resection rate, resection margin status, pathological complete response, late toxicity, and long-term safety. Survival and disease control (progression-free survival) were calculated by log-rank. For both, survival time was counted from registration and patients were censored at 27 January 2019, or end of trial participation if sooner.

Results

The trial opened in April 2015. Across four UK centres, 84 patients were screened, as per the CONSORT diagram (Figure 2). Twelve patients were registered, of whom eleven received SBRT (one patient suffered progressive disease before SBRT, and has been omitted from analyses). The study was closed early by the trial management group when it was unable to recruit to schedule and further funding was not available.

Demographic and baseline staging information for the treated patients is shown in Table 2. All remained performance status 0–1 throughout. The modal Charlson comorbidity index was five (range three to six).

SBRT was delivered as intended for all patients, with no protocol violations and no delays, modifications or dose-reductions. Five patients were treated at dose-level one, and six at dose-level two. No DLT or suspected unexpected serious adverse reactions were observed in SPARC, and no patient deaths were thought to have been caused by SBRT.

Patient imaging took place prior to and (?CECT only) after SBRT. The T-stage remained stable for all but two patients, where for one patient it rose from T3 to T4, and for one patient the reverse occurred. Metastatic spread was found at this point in four patients.

Ten of the eleven patients who received SBRT are known to have died. Median overall survival was 8.2 months (247 days). Median progression-free survival was 2.4 months (71 days). Median follow-up was 6.2 months (190 days).

Sixty-seven adverse events were reported, including six serious adverse events and three serious adverse reactions, affecting six patients (55%). One patient completed their participation in the study without any documented adverse events. Of the nine serious adverse outcomes, seven were classified as CTCAE Grade 3, and two were Grade 4. One Grade 4 SAE was post-operative bacteraemia, considered unrelated to SBRT, and one was post-surgical skin/soft-tissue wound dehiscence, considered to be 'Probably related' to trial therapy. Two adverse events (one Grade 1 anorexia, and one Grade 1 nausea) but no SAE were

classified as 'Definitely related [to SBRT]'. One occurrence of Grade 3 anorexia and one Grade 3 GI haemorrhage were each classified as 'Possibly related'. No late SBRT toxicity was reported.

The cumulative incidence of side effects considered to be part of the spectrum of upper GI radiotherapy toxicity (nausea, vomiting, anorexia, weight loss, abdominal pain, indigestion/heartburn) was 45% (5/11 patients), and of Grade ≥ 2 events was 18% (2/11). The specific events are detailed in supplementary material, Table 6.

Two patients underwent tumour resection following SBRT (18%). Both had initially received chemotherapy. Five patients were unresectable due to disease progression at CT, and for three patients surgery was attempted but the tumour was found to be too locally advanced (for one of these patients liver metastases were also evident intra-operatively). Only one of these eight patients had received prior chemotherapy. One patient did not proceed with surgery due to anaesthetic safety concerns, though he had received chemotherapy and radiotherapy.

The first resected patient underwent a pancreaticoduodenectomy, 52 days after radiotherapy. Histopathology confirmed pancreatic ductal adenocarcinoma (PDAC) with clear resection margins. Substantial response to neoadjuvant treatment was seen, with estimated 80% resolution of viable tumour, and 0/25 lymph nodes were involved (stage ypT3N0 R0).

The second operated patient had surgery 40 days post-SBRT. Restaging CT after SBRT had shown increased soft tissue surrounding the pancreatic head, though this was thought to indicate radiotherapy changes rather than tumour progression. During surgery, fibrotic tissue was evident, but was negative for tumour on intra-operative frozen section. The tissues were found friable and haemorrhagic, and the operation was prolonged by difficulty in completing satisfactory vascular reconstruction. Unfortunately,

the patient did not recover from surgery and died 49 days later. Histopathology confirmed PDAC, with perineural and lymphovascular invasion. Tumour was found within 0.5 mm of the pancreatic vascular groove, and within the wall of the portal vein, extending to the longitudinal transected ends. There was evidence of treatment response (College of American Pathologists Grade 2), but 1/24 lymph nodes was involved, (ypT3N1, R1).

Overall the rate of positive resection margins was therefore 50%, and the rate of complete pathological response was 0%.

Five patients received FOLFIRINOX (folinic acid, 5-FU, irinotecan, and oxaliplatin) chemotherapy prior to registration for SPARC (6-7 cycles). Four patients had stable disease after chemotherapy, while one suffered progressive disease, and this patient was registered for the study but did not proceed to SBRT. One patient received systemic therapy after SBRT (FOLFIRINOX).

None of the patients who showed metastases between SBRT and surgery had received induction chemotherapy prior to joining the study, and none of the patients who **did** receive induction chemotherapy were found to have metastatic disease at this point.

Discussion

The SPARC trial has shown several key findings despite the study closing early. Firstly, it is evident that few patients with BRPC on initial screening can ultimately be recruited to trials of neoadjuvant therapy, due to comorbidity and disease progression. However, this was the first clinical trial of pancreatic stereotactic radiotherapy in the UK and has demonstrated that recruiting patients to such a multi-centre

trial is feasible, though challenging. The observed recruitment can be used to inform planning for future studies.

Toxicity was low at the dose levels that have been tested: there were no dose-limiting toxicity events and all patients completed treatment as planned. However, the trial management group felt radiotherapy was likely to be a contributing factor to the surgical challenges and therefore also to the related complications suffered by the patient who died following surgery. Following this case recruitment was more difficult due to loss of clinical equipoise, and as such the primary endpoint, formal definition of MTD was not reached.

Objective response to radiotherapy in SPARC was limited, and no major change in tumour size or stage was observed. As only two patients underwent resection, it is not possible to make conclusions regarding histological changes in the treated tumour. Published data show that even when a tumour appears inoperable after induction therapy, in some cases the additional tissue is found to not contain viable tumour cells, and may reflect sterilised tumour or a host reaction to the radiotherapy [40, 41]. At present it is not clear how clinicians may preoperatively differentiate between true progression and fibrotic tissue, and it would greatly support future work if an imaging modality could achieve this.

Neoadjuvant treatment has previously been shown to be deliverable and effective in BRPC, such as in a series of 160 patients described by Katz et al., among whom 78% completed preoperative therapy and restaging and 41% underwent pancreatectomy, with a 94% rate of clear margins [42]. The recent PREOPANC study of relatively low-dose fractionated preoperative chemoradiotherapy (15 fractions of 2.4 Gy) showed improved disease control outcomes (R0 rate, and PFS), compared to initial surgery followed by adjuvant chemotherapy [43]. In a pre-planned subgroup analysis, patients with BRPC (45%) also

benefited from better overall survival (median OS, 17.6 vs 13.2 months, HR 0.62 (0.40 to 0.95), p = 0.029) though this effect was not significant for the study population as a whole.

Retrospective data on the use of SBRT in BRPC has been published [44, 45] , but prospective studies have not been completed to date. Retrospective institutional studies have demonstrated the feasibility of a margin-intensified approach, in conventional [46, 47] or moderately hypofractionated radiotherapy [31, 45, 48].

Two single-institution retrospective reviews are published describing the use of SBRT in patients with BRPC. These have shown high rates of surgical resection with clear margins [44, 45]. Rajagopalan et al. [44] report on twelve resected patients, of which seven were deemed BRPC, and most received gemcitabine. The SBRT consisted of 24-36 Gy in three fractions, surgery took place at a median 3.3 months (range 1.5–6.6 months) and 11/12 patients had an R0 resection. Chuong et al. [45] treated 73 patients with gemcitabine and 5-fraction SBRT. Median dose was 35 Gy to the tumour margin, and 25 Gy to the tumour. Of 57 BRPC cases, 44 underwent exploratory surgery and 31/32 resected cases had an R0 resection. No acute toxicity of Grade > 3 occurred and 5.3% (4 patients with locally advanced inoperable disease) experienced late Grade 3 toxicity (3 GI bleeding and 1 anorexia). The median overall survival was 16.4 months in all BRPC patients, with median overall survival of 19.3 months in resected patients. Radiological evidence of response to treatment (ie tumour shrinkage or downstaging) is not often seen [49], but the disappointing overall survival rates relative to good rates of local control may be attributed to variable provision of optimal systemic treatment.

Full results are awaited from two prospective studies. In the Alliance A021501 study in patients with BRPC received systemic therapy (FOLFIRINOX) with or without SBRT [50]. It is understood this study may not

meet its primary endpoint, but the outcomes may yet inform future studies [51]. The UK national multi-centre study ESPAC-5F has recently published results in abstract form, having established the feasibility of recruiting 90 patients with BRPC to be randomised, between two pre-operative chemotherapy regimens (GEMCAP and FOLFIRINOX), pre-operative chemoradiotherapy, and standard of care (surgery followed by adjuvant chemotherapy) [52]. There was shown to be an advantage for neoadjuvant therapy as a whole compared with immediate surgery, but no difference between the different preoperative therapy options [53].

There is growing evidence for activity of multi-agent chemotherapy in treating advanced pancreatic cancer, including gemcitabine combinations [54][55] and more recently FOLFIRINOX [56]. With the increase in efficacy, there has been increasing popularity of neoadjuvant chemotherapy in localised pancreatic cancer [57]. It is striking that of the patients in SPARC who first showed metastatic disease after SBRT, **none** had received induction chemotherapy, while of those who did receive induction chemotherapy before SBRT, **none** were diagnosed with metastatic disease between SBRT and surgery (though one had local progression and one was medically unfit for surgery). It may be important that none of the patients in SPARC underwent FDG-PET staging at baseline or prior to surgery. Two patients had liver MRI between radiotherapy and surgery, and both showed liver metastases. The lack of multimodality imaging will have underestimated the disease burden and has resulted in a low resection rate and poor overall survival due to progressive systemic disease. Furthermore not all patients received induction chemo which may also be a contributory factor (ref. m FFX neoadj studies?)

This study has also highlighted the challenge in recruiting in pancreatic cancer, and the proportion of patients successfully treated, relative to those screened, is lower than for many clinical trials (average is

around 47%, range 2-98%) [58]. The high attrition rate is partly due to poor patient performance status and high frequency of comorbidities in this disease setting.

The current optimal preoperative therapy in pancreatic cancer has therefore not yet been identified, and could involve chemotherapy, radiotherapy or both [59]. This study adds to the evidence that neoadjuvant radiotherapy is likely to be as a part of a multi-modality approach with systemic chemotherapy used to address the risk of early metastatic progression.

Implementing this study safely required establishment of a network of oncologist, surgeons, and radiotherapy technicians able to adopt innovative techniques and solutions, and the expertise and experience accrued can be applied to further investigation of these techniques [60]. Pre-operative stereotactic radiotherapy remains under investigation in several UK and international clinical trials, and its role in the treatment of resectable pancreatic cancer remains undefined. With increased adoption of FDG-PET and liver MRI in pre-operative staging to better exclude patients with early metastatic disease, an improvement in outcomes for patients that do reach surgery will be observed, and there will be increased attention paid to local control.

In conclusion, we have conducted a national phase-1 trial of pre-operative margin-intensified stereotactic radiotherapy for localised pancreatic cancer, however the study closed without reaching its primary endpoint of establishing the maximum tolerated dose.

The toxicity of SBRT was low for the two dose-levels that were tested. Unfortunately, few patients underwent resection of their pancreatic tumour after SBRT, and it is difficult to draw any conclusions regarding the safety or toxicity of these therapies in combination.

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References

1. Oettle, H., et al., *Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial.* JAMA, 2013. **310**(14): p. 1473-81.
2. Howard, T.J., et al., *A margin-negative R0 resection accomplished with minimal postoperative complications is the surgeon's contribution to long-term survival in pancreatic cancer.* J Gastrointest Surg, 2006. **10**(10): p. 1338-45; discussion 1345-6.
3. Ghaneh, P., E. Costello, and J.P. Neoptolemos, *Biology and management of pancreatic cancer.* Gut, 2007. **56**(8): p. 1134-52.
4. Sohn, T.A., et al., *Resected adenocarcinoma of the pancreas-616 patients: results, outcomes, and prognostic indicators.* J Gastrointest Surg, 2000. **4**(6): p. 567-79.
5. Neoptolemos, J.P., et al., *Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial.* JAMA, 2010. **304**(10): p. 1073-81.
6. Neoptolemos, J.P., et al., *Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial.* The Lancet, 2017. **389**(10073): p. 1011-1024.
7. Callery, M.P., et al., *Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement.* Ann Surg Oncol, 2009. **16**(7): p. 1727-33.
8. Ravikumar, R., et al., *Portal vein resection in borderline resectable pancreatic cancer: a United Kingdom multicenter study.* J Am Coll Surg, 2014. **218**(3): p. 401-11.
9. Javed, A.A., et al., *Outcome of Patients with Borderline Resectable Pancreatic Cancer in the Contemporary Era of Neoadjuvant Chemotherapy.* Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract, 2019. **23**(1): p. 112-121.
10. National Comprehensive Cancer Network, *Pancreatic Adenocarcinoma Version 2.2015.* 2015.
11. Mehta, V.K., et al., *Preoperative chemoradiation for marginally resectable adenocarcinoma of the pancreas.* J Gastrointest Surg, 2001. **5**(1): p. 27-35.
12. Varadhachary, G.R., et al., *Borderline resectable pancreatic cancer: definitions, management, and role of preoperative therapy.* Ann Surg Oncol, 2006. **13**(8): p. 1035-46.
13. Talamonti, M., *Borderline resectable pancreatic cancer: a new classification for an old challenge.* Ann Surg Oncol, 2006. **13**(8): p. 1019-20.
14. Heestand, G.M., J.D. Murphy, and A.M. Lowy, *Approach to patients with pancreatic cancer without detectable metastases.* J Clin Oncol, 2015. **33**(16): p. 1770-8.
15. Stessin, A.M., J.E. Meyer, and D.L. Sherr, *Neoadjuvant radiation is associated with improved survival in patients with resectable pancreatic cancer: an analysis of data from the surveillance, epidemiology, and end results (SEER) registry.* Int J Radiat Oncol Biol Phys, 2008. **72**(4): p. 1128-33.
16. Gillen, S., et al., *Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages.* PLoS Med, 2010. **7**(4): p. e1000267.
17. Sasson, A.R., et al., *Neoadjuvant chemoradiotherapy for adenocarcinoma of the pancreas: Analysis of histopathology and outcome.* International Journal of Gastrointestinal Cancer, 2004. **34**(2-3): p. 121-127.
18. White, R.R., et al., *Significance of histological response to preoperative chemoradiotherapy for pancreatic cancer.* Ann Surg Oncol, 2005. **12**(3): p. 214-21.

19. Breslin, T.M., et al., *Neoadjuvant chemoradiotherapy for adenocarcinoma of the pancreas: treatment variables and survival duration.* Ann Surg Oncol, 2001. **8**(2): p. 123-32.
20. Greer, S.E., et al., *Effect of neoadjuvant therapy on local recurrence after resection of pancreatic adenocarcinoma.* J Am Coll Surg, 2008. **206**(3): p. 451-7.
21. Koong, A.C., et al., *Phase I study of stereotactic radiosurgery in patients with locally advanced pancreatic cancer.* Int J Radiat Oncol Biol Phys, 2004. **58**(4): p. 1017-21.
22. Koong, A.C., et al., *Phase II study to assess the efficacy of conventionally fractionated radiotherapy followed by a stereotactic radiosurgery boost in patients with locally advanced pancreatic cancer.* Int J Radiat Oncol Biol Phys, 2005. **63**(2): p. 320-3.
23. Schellenberg, D., et al., *Gemcitabine chemotherapy and single-fraction stereotactic body radiotherapy for locally advanced pancreatic cancer.* Int J Radiat Oncol Biol Phys, 2008. **72**(3): p. 678-86.
24. Schellenberg, D., et al., *Single-fraction stereotactic body radiation therapy and sequential gemcitabine for the treatment of locally advanced pancreatic cancer.* Int J Radiat Oncol Biol Phys, 2011. **81**(1): p. 181-8.
25. Polistina, F., et al., *Unresectable locally advanced pancreatic cancer: a multimodal treatment using neoadjuvant chemoradiotherapy (gemcitabine plus stereotactic radiosurgery) and subsequent surgical exploration.* Ann Surg Oncol, 2010. **17**(8): p. 2092-101.
26. Mahadevan, A., et al., *Induction gemcitabine and stereotactic body radiotherapy for locally advanced nonmetastatic pancreas cancer.* Int J Radiat Oncol Biol Phys, 2011. **81**(4): p. e615-22.
27. Lominska, C.E., et al., *Stereotactic body radiation therapy for reirradiation of localized adenocarcinoma of the pancreas.* Radiat Oncol, 2012. **7**(1): p. 74.
28. Tozzi, A., et al., *SBRT in unresectable advanced pancreatic cancer: preliminary results of a mono-institutional experience.* Radiat Oncol, 2013. **8**(1): p. 148.
29. Gurka, M.K., et al., *Stereotactic Body Radiation Therapy (SBRT) Combined With Chemotherapy for Unresected Pancreatic Adenocarcinoma.* Am J Clin Oncol, 2014.
30. Herman, J.M., et al., *Phase 2 multi-institutional trial evaluating gemcitabine and stereotactic body radiotherapy for patients with locally advanced unresectable pancreatic adenocarcinoma.* Cancer, 2015. **121**(7): p. 1128-37.
31. Mellon, E.A., et al., *Long-term outcomes of induction chemotherapy and neoadjuvant stereotactic body radiotherapy for borderline resectable and locally advanced pancreatic adenocarcinoma.* Acta Oncologica, 2015. **54**(7): p. 979-985.
32. Shaib, W.L., et al., *A Phase 1 Study of Stereotactic Body Radiation Therapy Dose Escalation for Borderline Resectable Pancreatic Cancer After Modified FOLFIRINOX (NCT01446458).* Int J Radiat Oncol Biol Phys, 2016. **96**(2): p. 296-303.
33. Dholakia, A.S., et al., *Mapping patterns of local failure following pancreaticoduodenectomy for pancreatic cancer: A new approach to adjuvant radiation fields.* International Journal of Radiation Oncology Biology Physics, 2013. **1)**: p. S87.
34. Skolnik, J.M., et al., *Shortening the timeline of pediatric phase I trials: the rolling six design.* J Clin Oncol, 2008. **26**(2): p. 190-5.
35. Brunner, T.B., et al., *Simultaneous integrated protection : A new concept for high-precision radiation therapy.* Strahlenther Onkol, 2016. **192**(12): p. 886-894.
36. Nijkamp, J., et al., *Target volume delineation variation in radiotherapy for early stage rectal cancer in the Netherlands.* Radiother Oncol, 2012. **102**(1): p. 14-21.
37. Khoo, E.L., et al., *Prostate contouring variation: can it be fixed?* Int J Radiat Oncol Biol Phys, 2012. **82**(5): p. 1923-9.
38. Dewas, S., et al., *Delineation in thoracic oncology: a prospective study of the effect of training on contour variability and dosimetric consequences.* Radiat Oncol, 2011. **6**(1): p. 118.

39. Holyoake, D., et al., *Analysis of On-trial Quality Assurance for the SPARC Clinical Trial using Novel Peer-review Methodology.* Clinical Oncology, 2018. **30**(6): p. e60.
40. Ferrone, C.R., et al., *Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer.* Ann Surg, 2015. **261**(1): p. 12-7.
41. Katz, M.H., et al., *Preoperative Modified FOLFIRINOX Treatment Followed by Capecitabine-Based Chemoradiation for Borderline Resectable Pancreatic Cancer: Alliance for Clinical Trials in Oncology Trial A021101.* JAMA Surg, 2016: p. e161137.
42. Katz, M.H., et al., *Borderline resectable pancreatic cancer: the importance of this emerging stage of disease.* J Am Coll Surg, 2008. **206**(5): p. 833-46; discussion 846-8.
43. Versteijne, E., et al., *Preoperative Chemoradiotherapy Versus Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Results of the Dutch Randomized Phase III PREOPANC Trial.* Journal of Clinical Oncology, 2020: p. JCO.19.02274.
44. Rajagopalan, M.S., et al., *Pathologic response with neoadjuvant chemotherapy and stereotactic body radiotherapy for borderline resectable and locally-advanced pancreatic cancer.* Radiat Oncol, 2013. **8**(1): p. 254.
45. Chuong, M.D., et al., *Stereotactic body radiation therapy for locally advanced and borderline resectable pancreatic cancer is effective and well tolerated.* Int J Radiat Oncol Biol Phys, 2013. **86**(3): p. 516-22.
46. Passoni, P., et al., *Hypofractionated image-guided IMRT in advanced pancreatic cancer with simultaneous integrated boost to infiltrated vessels concomitant with capecitabine: a phase I study.* Int J Radiat Oncol Biol Phys, 2013. **87**(5): p. 1000-6.
47. Hirata, T., et al., *Histopathological effects of preoperative chemoradiotherapy for pancreatic cancer: an analysis for the impact of radiation and gemcitabine doses.* Radiother Oncol, 2015. **114**(1): p. 122-7.
48. Wang, L.S., et al., *Dose escalation with a vessel boost in pancreatic adenocarcinoma treated with neoadjuvant chemoradiation.* Pract Radiat Oncol, 2015. **5**(5): p. e457-63.
49. Katz, M.H.G., et al., *Response of borderline resectable pancreatic cancer to neoadjuvant therapy is not reflected by radiographic indicators.* Cancer, 2012. **118**(23): p. 5749-5756.
50. Katz, M.H.G., et al., *Alliance for clinical trials in oncology (ALLIANCE) trial A021501: preoperative extended chemotherapy vs. chemotherapy plus hypofractionated radiation therapy for borderline resectable adenocarcinoma of the head of the pancreas.* BMC Cancer, 2017. **17**(1): p. 505.
51. Perri, G., L.R. Prakash, and M.H.G. Katz, *Response to Preoperative Therapy in Localized Pancreatic Cancer.* Front Oncol, 2020. **10**(516): p. 516.
52. Ghaneh, P. *ESPAC - 5F: European Study Group for Pancreatic Cancer - Trial 5F: four arm, prospective, multicentre, randomised feasibility trial of immediate surgery compared with neoadjuvant chemotherapies and neoadjuvant chemoradiotherapy*. 2015; Available from: http://www.isrctn.com/ISRCTN89500674.
53. Ghaneh, P., et al., *ESPAC-5F: Four-arm, prospective, multicenter, international randomized phase II trial of immediate surgery compared with neoadjuvant gemcitabine plus capecitabine (GEMCAP) or FOLFIRINOX or chemoradiotherapy (CRT) in patients with borderline resectable pancreatic cancer.* Journal of Clinical Oncology, 2020. **38**.
54. Cunningham, D., et al., *Phase III Randomized Comparison of Gemcitabine Versus Gemcitabine Plus Capecitabine in Patients With Advanced Pancreatic Cancer.* Journal of Clinical Oncology, 2009. **27**(33): p. 5513-5518.
55. Von Hoff, D.D., et al., *Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine.* N Engl J Med, 2013. **369**(18): p. 1691-703.

56. Conroy, T., et al., *FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer.* N Engl J Med, 2011. **364**(19): p. 1817-25.
57. Suker, M., et al., *FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis.* Lancet Oncol, 2016. **17**(6): p. 801-10.
58. Harris-Brown, et al., *Reporting of pre-enrolment screening with randomized clinical trials: A small item that could impact a big difference*. Perspectives in Clinical Research, 2015. 6(3): p. 139-143.
59. Grose, D., et al., *The role of induction chemotherapy + chemoradiotherapy in localised pancreatic cancer: initial experience in Scotland.* J Gastrointest Oncol, 2017. **8**(4): p. 683-695.
60. Holyoake, D.L.P., et al., *Conformity analysis to demonstrate reproducibility of target volumes for Margin-Intense Stereotactic Radiotherapy for borderline-resectable pancreatic cancer.* Radiotherapy and Oncology, 2016. **121**(1): p. 86-91.

Tables

Radiotherapy dose level	Tumour (PTV)				Area at risk of R1 (PTV_R)			
	Dose/# [Gy]	Total dose [Gy]	BED [Gy_{10}]	EQD_2 [Gy]	Dose/# [Gy]	Total dose [Gy]	BED [Gy_{10}]	EQD_2 [Gy]
Level -1	6	30	50	40	8	40	72	60
Level 1	6	30	50	40	9	45	88	71.5
Level 2	6.5	32.5	56	45	9.5	47.5	92	77.2
Level 3	7	35	62	50	10	50	100	83.3

Table 1. Radiotherapy dose levels for the SPARC trial. BED [Gy10] = biologically effective dose for acute reacting tissues (α/β = 10), EQD2 = equivalent dose in 2-Gy fractions, # = fraction, R1 = microscopic positive margin status

Age (years)	Median 69 (IQR 58–73)
Sex	6 male, 5 female
Age, according to sex	Median 71 (IQR 67–72) vs 63 (57–72)
Weight (kg)	Median 73 (IQR 67–82)
Performance status	PS 0 = 4 patients, PS 1 = 7 patients
T stage	
T1	0
T2	3 (27%)
T3	6 (55%)
T4	2 (18%)
N Stage	
N0	8 (73%)
N1	3 (27%)
Tumour diameter,	Mean 29 mm (range 14–40 mm)
Neoadjuvant chemotherapy (FOLFIRINOX)	4 (36%)

Table 2. Baseline information for SPARC patients treated with SBRT (n = 11)

Figures

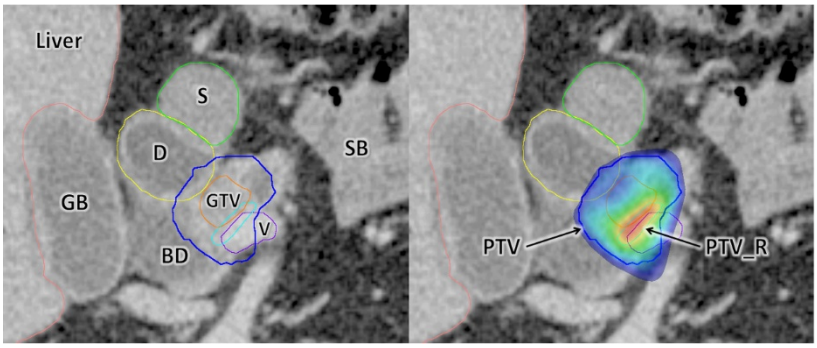

Figure 1. Axial contrast-enhanced CT of patient with borderline-resectable pancreatic cancer demonstrating SPARC radiotherapy planning. Left-hand image – delineated structures: (clockwise from left) GB = gall bladder, D = duodenum, S = stomach, SB = small bowel, V = vessel in contact with tumour, GTV = Gross Tumour Volume, BD = bile duct. Right-hand image – radiotherapy plan dose colourwash demonstrating dose levels delivered to PTV_R (boost volume, light blue contour), PTV (dark blue) and PTV overlapping with duodenum.

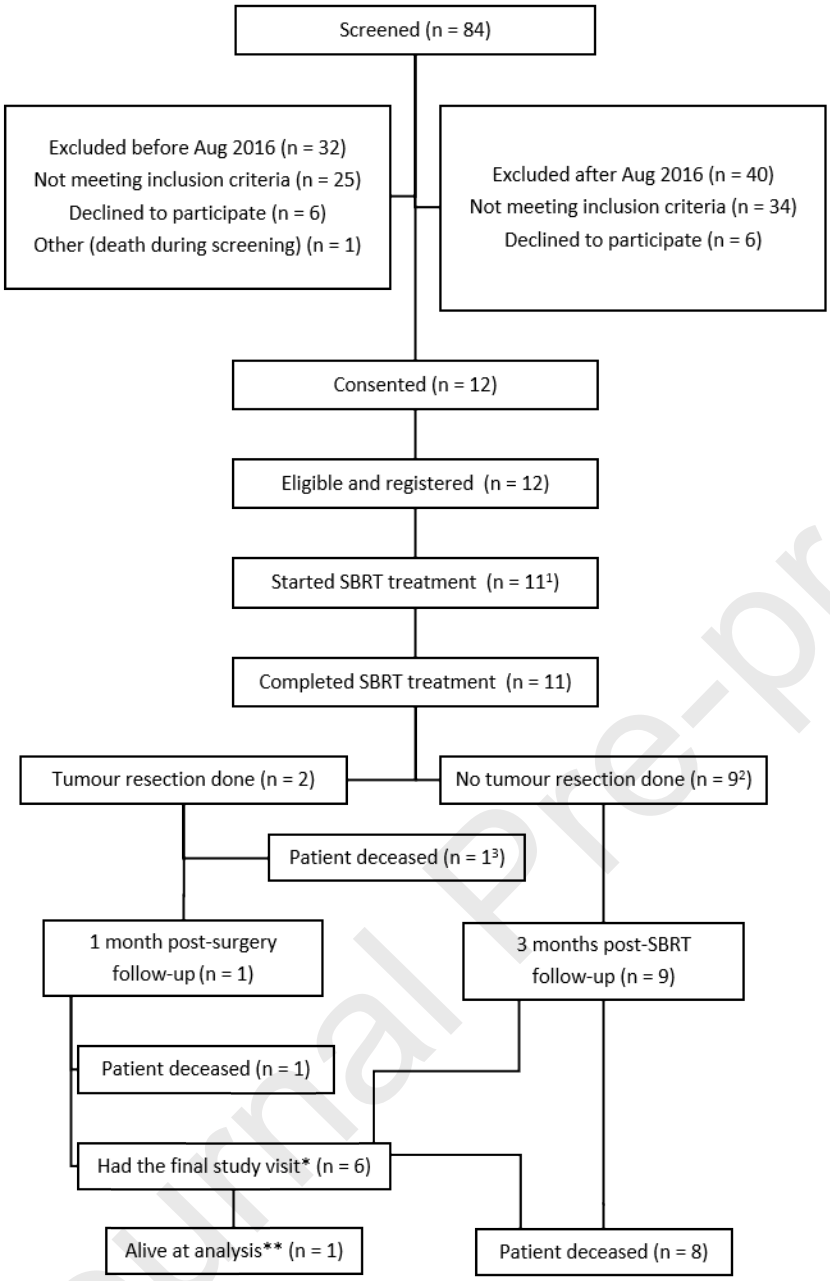

Figure 2. CONSORT diagram showing patient throughput among the 84 patients screened.

[1] Patient SP-C2-109 withdrew before commencing SBRT treatment

[2] SP-C1-102 went on surgery but no tumour removed. SP-C2-106 tumour found to be adhered to IVC during surgery, no tumour removed

[3] SP-C2-111 was unable to complete trial visits post-surgery due to complications, patient died nine weeks after surgery.

*Final study visit defined as 6 months post-surgery (or 6 months post SBRT if no surgery performed)

**Analysis date 27th Jan 2019

Figure 3. Kaplan-Meier survival plots demonstrating (a) overall survival (OS) and (b) progression-free survival (PFS). Time was recorded from date of registration and patients were censored at data lock, or at end of trial participation if sooner.

Appendix – Supplementary tables and data

Inclusion criteria	Exclusion criteria
1. Borderline resectable localised tumour of the pancreatic head/uncinate process/body as per NCCN Guidelines (tumours of the tail of pancreas are not eligible for inclusion) or operable tumour in contact with vessels increasing the risk of positive margin as defined by CT ± MRI ± PET criteria within 28 ± 7 days prior to trial entry, de novo or following systemic treatment. 2. Histologically proven pancreatic ductal adenocarcinoma or cytological proven pancreatic malignancy 3. Able to undergo biliary drainage using a stent 4. Deemed fit and suitable for surgical resection. 5. No overt metastases or uncertain status with investigations suspicious of possible metastatic disease (eg small equivocal pulmonary nodule(s)). 6. Male or female, Age ≥16 years 7. Life expectancy of at least 6 months 8. ECOG performance status 0–1 9. The patient is willing and able to comply with the protocol for the duration of the study, and scheduled follow-up visits and examinations 10. Written (signed and dated) informed consent and be capable of co-operating with protocol 11. Haematological and biochemical indices within specified ranges.	1. Definitive metastatic disease or local disease that cannot be encompassed in the SBRT field. 2. History of previous or concurrent malignancy diagnoses for which the expected prognosis is likely to be worse than that of the current diagnosis of pancreatic cancer (excludes for example: eg localised prostate cancer, early colorectal cancer, early breast cancer, curatively-treated basal cell carcinoma of skin, carcinoma in situ of cervix; curatively treated cancer of other sites who are recurrence free for > 3 years). 3. Serious medical or psychological condition precluding trial intervention. 4. Previous upper abdominal or right chest wall radiotherapy where 30% of the liver has received > 15Gy. 5. Pregnancy: Pregnant or breast-feeding women are ineligible. Women of childbearing potential must use effective methods of contraception. 6. Any other psychological, social, or medical condition, physical examination finding or laboratory abnormality that the Investigator considers makes the patient a poor trial candidate or could interfere with protocol compliance or the interpretation of the trial results.

Table 3. SPARC revised eligibility criteria

Description		Optimal	Mandatory
PTV[@]	$D_{95\%}$[†]	≥ 95%	≥ 90%[‡]
PTV_R	$D_{95\%}$	≥ 95%	≥ 90%
	D_{max} (0.1 cc)	≤ 120%	≤ 130%
Combined Kidneys	Mean dose	< 10 Gy	-
If solitary kidney, or if one kidney mean > 10Gy	V_{10Gy}[#]	< 10%	< 45%
Liver	V_{10Gy}	< 70%	-
	Mean dose	< 15 Gy	< 15.5 Gy
Stomach	D_{max} (0.5 cc)	< 33 Gy	< 35 Gy
	D_{5cc}	< 25 Gy	-
	D_{10cc}	-	< 25 Gy
	D_{50cc}	< 12 Gy	-
Small bowel	D_{max} (0.5 cc)	< 30 Gy	< 35 Gy
	D_{5cc}	< 25 Gy	-
	D_{10cc}	-	< 25 Gy
Duodenum	D_{max} (0.5 cc)	-	< 35 Gy
	D_{1cc}	< 33 Gy	-
	D_{5cc}	< 25 Gy	-
	D_{9cc}	< 15 Gy	-
	D_{10cc}	-	< 25 Gy
Spinal Cord PRV	D_{max} (0.5 cc)	-	< 25 Gy
Large Bowel	D_{max} (0.5 cc)	< 32 Gy	-
Common Bile Duct	D_{max} (0.5 cc)	< 50 Gy	-

Table 4. Radiotherapy planning dose-volume constraints

Dose Limiting Toxicity (DLT)	1. Grade ≥ 3 upper GI bleeding 2. Grade ≥ 4 nausea/vomiting uncontrolled after 48 hours of standard treatment 3. Grade ≥ 4 pancreatitis not stent related 4. Interruption of SBRT > 1 week due to SBRT-related AEs 5. Grade ≥ 4 vascular events: SMV thrombosis, bowel ischaemia due to SMA arteritis/stenosis, friable vessels at surgery 6. Other AEs that the TMG agrees to be dose limiting and possibly related to SBRT such as Grade ≥ 3 GI fistula > 30 days after surgery
Adverse Event (AE)	Any unfavourable event or outcome that arises during or after a treatment intervention in a clinical trial.
Suspected Adverse Reaction (SAR)	An adverse event for which there is a reasonable probability that it was caused by the treatment being investigated.
Unexpected Adverse Reaction	An adverse reaction that is not thought to be part of the known toxicity events or risks associated with a treatment intervention.
Serious Adverse Event (SAE) or Reaction (SAR)	Adverse event or adverse reaction that is considered life-threatening, or results in death, admission to hospital or extension of a stay in hospital, or causes lasting or considerable disability or incapacity, or is a congenital anomaly or birth defect.

Table 5. Adverse events constituting a DLT, if observed during the DLT assessment period, graded according to CTCAE v4.03

	CTCAE grade			Any grade	Grade ≥ 2
Adverse event	**1**	**2**	**3**		
Anorexia	1		1	2	1
Nausea	2			2	
Vomiting		1		1	1
Abdominal pain					
Weight loss					
Heartburn/indigestion	1			1	
Any	3	1	1	5	2

Table 6. Worst grade of symptoms or adverse events considered 'upper GI toxicity' experienced by patients in the SPARC trial

Highlights

- We conducted a prospective multicentre phase-1 dose-escalation study of pre-operative margin intensified stereotactic radiotherapy in borderline resectable pancreatic cancer
- Radiotherapy was well tolerated, all treatment completed as scheduled, and dose was escalated one level up from starting dose without encountering DLT
- Few patients had resection after SBRT (2/11) and the suitability of the treatments in combination is difficult to appraise

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