

SPARC: A Phase-I trial of pre-operative, margin intensive, stereotactic body radiation therapy for pancreatic cancer

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1. Background

- Standard therapy for resectable and borderline-resectable pancreatic cancer in the UK is surgery with adjuvant chemotherapy, rates of resection with clear margins (R0) are unsatisfactory and overall survival is poor. Research shows the potential of neo-adjuvant chemo-radiotherapy but the efficacy of conventional dose schedules is limited [1]. SBRT achieves accuracy and precision enabling pre-operative margin-intensive dose escalation (Figure 1) aiming to increase rates of R0 resection and local disease control.

2. Aims

- Primary endpoint:** the **maximum tolerated dose (MTD)** of margin-intensive SBRT delivered pre-operatively in the management of pancreatic cancer.
- Secondary endpoints:** resection rate, resection margin status, response rate, late toxicity, overall survival and progression free survival at 12 and 24 months.
- Exploratory endpoints:** relationship between treatment response and resection margin, and immune-related responses to SBRT.

3. Trial Design

- Eligible patients:** histologically/cytologically proven pancreatic cancer, defined as borderline-resectable per NCCN criteria, or operable tumour in contact with vein (SMV or PV) increasing the risk of positive margin, untreated or after neo-adjuvant chemotherapy.
- Up to 24 patients are assigned to a SBRT dose level using **rolling six design**.
- SBRT will be delivered in five daily fractions, six weeks before intended surgical resection (Figure 2).

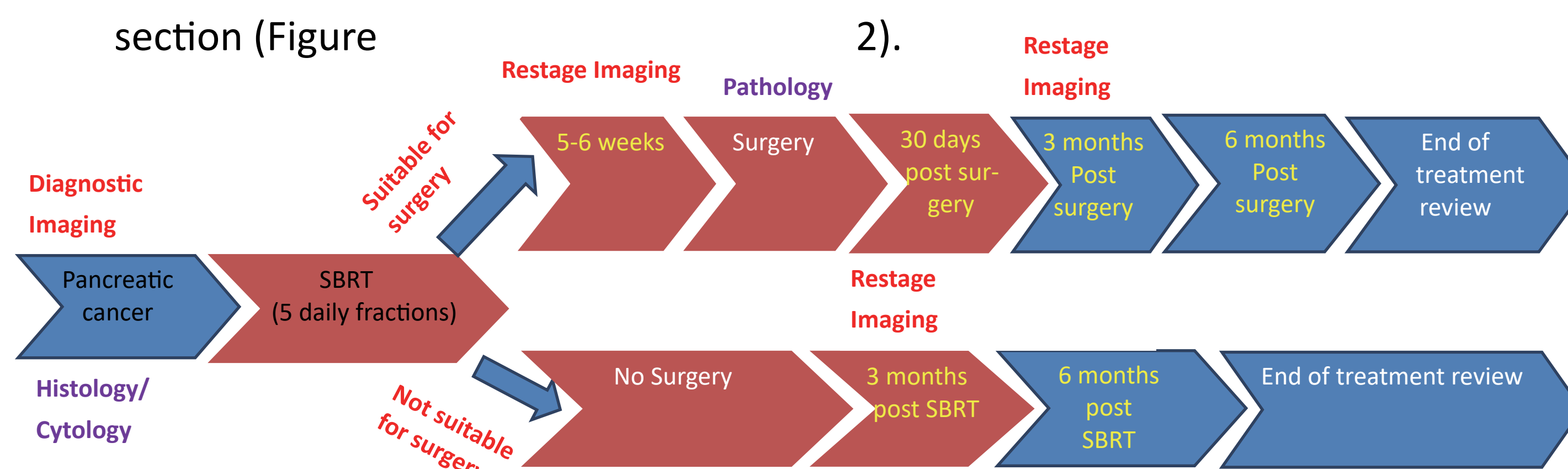


Figure 2: Trial Schema

- A maximum of 4 dose levels (including one de-escalated dose level, Table 1) are expected to be needed to establish the MTD.
- MTD is the highest dose at which no more than 1 of 6 patients or 0 of 3 patients experience a Dose Limiting Toxicity (DLT).

4. Dose Limiting Toxicities (DLTs)

DLTs are the following list of SBRT treatment related adverse events (AEs) (defined according to CTCAE v4.03) seen at the DLT assessment period (red boxes in Figure 2).

- ≥ grade 3 upper gastro-intestinal bleeding.
- ≥ grade 4 uncontrolled nausea/vomiting after 48 hours of standard treatment.
- ≥ grade 4 pancreatitis not stent related.
- Interruption of SBRT for > 1 week due to SBRT related AEs.
- Grade 4 vascular events.
- Other AEs that the Trial Management Group (TMG) agrees to be dose limiting and possibly related to SBRT such as ≥ grade 3 GI fistula ≥ 30 days after surgery.

Table 1. Radiotherapy dose levels

Radiotherapy dose level	Tumour (PTV)		Area at risk of R1 (PTV_R)	
	Dose/#[Gy]	Total dose[Gy]	Dose/#[Gy]	Total dose[Gy]
Level -1	6	30	8Gy	40Gy
Level 1	6	30	9Gy	45Gy
Level 2	6.5	32.5	9.5Gy	47.5Gy
Level 3	7	35	10Gy	50Gy

5. Statistical Considerations

- Dose level assignment and MTD** will be based on an **evaluable population**- includes patients with a DLT or those who have received at least 4 fractions of SBRT and are fully assessed during the DLT assessment period.
- Other analyses will be based on an **intention-to-treat population**.

6. Study Status

- Recruitment began in April 2015 and eleven patients have been treated. Cohort 1 was completed without DLT and recruitment to cohort 2 began in September 2016.
- Recruitment will stop as soon as MTD is established, or a maximum of 24 patients.
- Sites open to recruitment: Churchill Hospital, Oxford; The Beatson West of Scotland Cancer Centre, Glasgow; Leeds Cancer Centre, Leeds; Nottingham University Hospital, Nottingham; Northern Cancer Centre, Newcastle.

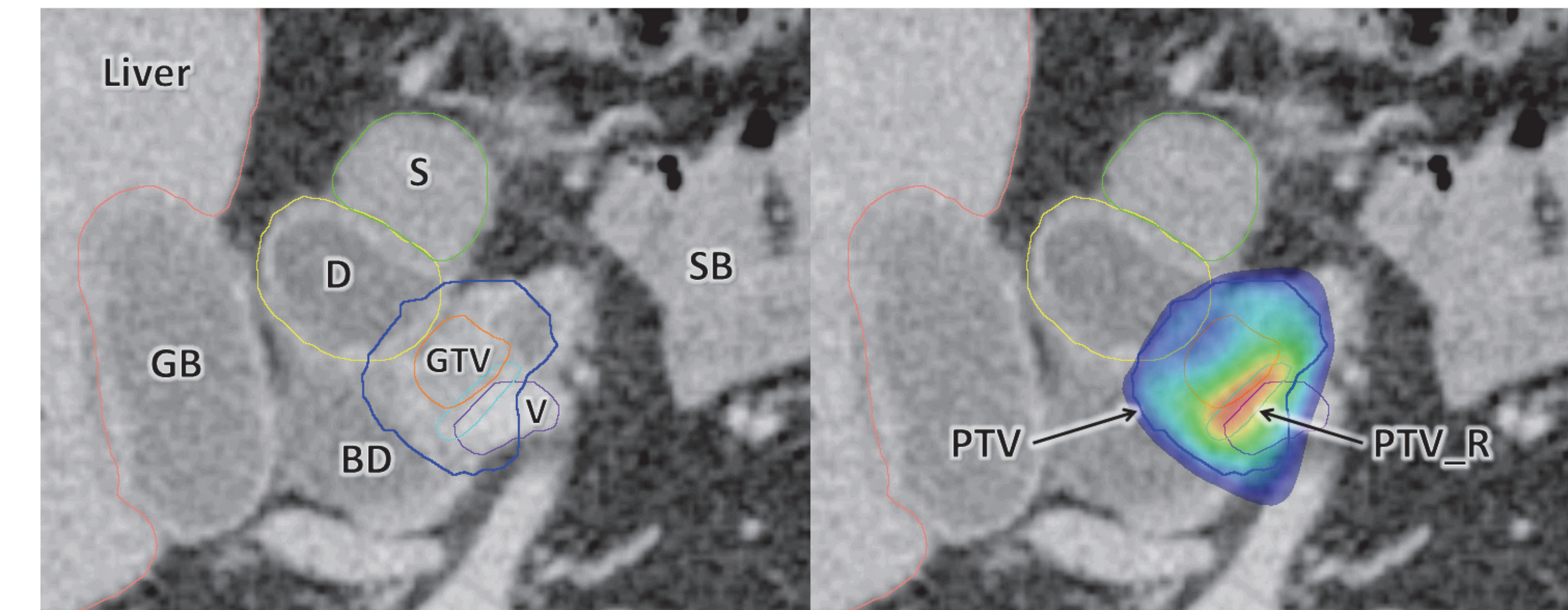


Figure 1. Planning CT of patient with borderline-resectable pancreatic cancer (BRPC). Left -: (clockwise) GB = gall-bladder, D = duodenum, S = stomach, SB = small-bowel, V = vessel in contact with tumour, GTV = Gross Tumour Volume, BD = bile duct. Right - radiotherapy plan dose colourwash PTV_R (boost volume, light blue contour), and PTV (dark blue)

7. Samples and Radiotherapy Quality Assurance (RTQA)

- Translational biology:** peripheral blood samples taken pre-SBRT, at day 3 & 5 of SBRT and 1 month post-SBRT will be used to study possible immune-related responses to SBRT (exploratory endpoint).
- Pre-trial RTQA:** all centres must be approved on delineation planning test cases.
- On-trial RTQA:** web-enabled pre-treatment rapid review of contours and plans is conducted for the first 3 patients treated at each centre.

8. References

[1] Holyoake D., et al., A phase-I trial of pre-operative, margin intensive, stereotactic body radiation therapy for pancreatic cancer: the 'SPARC' trial protocol. BMC Cancer (2016) 16: 728. doi:10.1186/s12885-016-2765

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- Trial Management:** OCTO and **Statistical Input:** CSM; both part of OCTRU, a UKCRC and NCRI registered Clinical Trials Unit. **Radiotherapy Quality Assurance:** Mr Maxwell Robinson, Prof. Maria A. Hawkins, Dr. Daniel Holyoake, Dr. Somnath Mukherjee.



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