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Pancreatic cancer SBRT

Conformity analysis to demonstrate reproducibility of target volumes for Margin-Intense Stereotactic Radiotherapy for borderline-resectable pancreatic cancer

Daniel L.P. Holyoake [a,e], Maxwell Robinson [a,e], Derek Grose [b], David McIntosh [b], David Sebag-Montefiore [c,d], Ganesh Radhakrishna [d], Neel Patel [e], Mike Partridge [a], Somnath Mukherjee [a,e], Maria A. Hawkins [a,e,*]

[a] CRUK/MRC Oxford Institute for Radiation Oncology, University of Oxford; [b] The Beatson West of Scotland Cancer Centre, Glasgow; [c] University of Leeds, CRUK Leeds Centre; [d] Leeds Cancer Centre, St James's University Hospital, Leeds; and [e] The Churchill Hospital, Oxford, UK

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ABSTRACT

Background and purpose: Margin-directed neoadjuvant radiotherapy for borderline-resectable pancreatic cancer (BRPC) aims to facilitate clear surgical margins. A systematic method was developed for definition of a boost target volume prior to a formal phase-I study.

Material and methods: Reference structures were defined by two oncologists and one radiologist, target structures were submitted by eight oncologist investigators and compared using conformity indices. Resultant risk of duodenal bleed (NTCP) was modelled.

Results: For GTV, reference volume was 2.1 cm^3 and investigator mean was 6.03 cm^3 (95% CI 3.92–8.13 cm^3), for boost volume 1.1 cm^3 and 1.25 cm^3 (1.02–1.48 cm^3). Mean Dice conformity coefficient for GTV was 0.47 (0.38–0.56), and for boost volume was significantly higher at 0.61 (0.52–0.70, $p = 0.01$). Discordance index (DI) for GTV was 0.65 (0.56–0.75) and for boost volume was significantly lower at 0.39 (0.28–0.49, $p = 0.001$). NTCP using reference contours was 2.95%, with mean for investigator contour plans 3.93% (3.63–4.22%). Correlations were seen between NTCP and GTV volume ($p = 0.02$) and NTCP and DI (correlation coefficient 0.83 (0.29–0.97), $p = 0.01$).

Conclusions: Better conformity with reference was shown for boost volume compared with GTV. Investigator GTV volumes were larger than reference, had higher DI scores and modelled toxicity risk. A consistent method of target structure definition for margin-directed pancreatic radiotherapy is demonstrated.

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For patients with a diagnosis of pancreatic cancer surgical resection is the only chance of achieving long-term disease control, yet less than 20% will have resectable disease at diagnosis [1]. Even for resected patients receiving adjuvant chemotherapy, median survival is only around 24 months [2] suggesting there is significant room for improvement by use of optimised multi-modality therapy including neoadjuvant radiotherapy.

In the largest multi-national adjuvant trial in pancreatic cancer (involving over 1000 patients) positive surgical margins were seen in >35% and were associated with poor outcome [2]. Resection margin status is a strong independent prognostic indicator [3] and survival for patients with positive margins may be little better than for those with unresectable disease [4], though reported rates of microscopic margin involvement depend greatly on histopathological techniques [5].

Borderline-resectable pancreatic cancer (BRPC) is a radiological definition to classify tumours that can be surgically excised but with likely requirement for vascular reconstruction and particularly high risk of positive resection margins [6]. In UK high-volume specialist surgical centres the R1 rate for patients undergoing pancreatectomy with vein resection was 62.9% (144/230) and almost half of these were due to disease at the infiltrated mesenteric vessels [7]. The definition of BPRC is controversial with National Comprehensive Cancer Network (NCCN) criteria being the most widely accepted.

The management of BPRC is also controversial as there are few prospective trials and several therapeutic algorithms have been explored: chemotherapy, radiation and chemoradiation. Current radiation technology permits exquisite dose painting and the

* Corresponding author at: CRUK MRC Oxford Institute for Radiation Oncology, Gray Laboratories, University of Oxford, Old Road Campus Research Building, Roosevelt Drive, Oxford OX3 7DQ, UK.
E-mail address: maria.hawkins@oncology.ox.ac.uk (M.A. Hawkins).

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possibility to deliver different radiation doses to adjacent areas in the target. Delivering a higher dose to the vessels could be therefore achieved with the aim to sterilize the margin in the area at highest risk, and Stereotactic Body Radiation Therapy (SBRT) offers the opportunity of delivering an ablative dose of RT with short overall treatment time. Retrospective institutional studies have demonstrated the feasibility of such an approach with standard [8,9] or hypofractionation [10,11] but in the case of SBRT a systematic method of defining the margin at risk has not been defined.

SPARC (UKCRN ID: 18496) is a CRUK-funded phase 1 dose-escalation study of pre-operative Margin-Intense Stereotactic Radiotherapy for patients with BRPC using the NCCN criteria [12], approved by a National Health Service Research Ethics Committee. SPARC incorporates a comprehensive radiotherapy quality assurance programme to ensure consistency in target definition and radiotherapy delivery. This includes a radiotherapy manual with atlas, and pre-trial contouring and planning test-cases followed by a workshop, both of which have been shown to reduce variation in target volume definition [13–15]. The radiotherapy manual specifies that the target structure for the margin-directed boost should be defined following discussion with the radiologist and/or Hepato-Pancreato-Biliary (HPB) surgeon to identify the vascular structures that are responsible for the tumour being classified as borderline resectable according to the NCCN criteria.

We aim to describe a novel method of defining the margin at risk for radiotherapy planning, testing of the applicability of this method, and exploration of the implications for Normal Tissue Complication Probability (NTCP) when SBRT is used.

Materials and methods

On an intravenous contrast-enhanced exhale breath-hold CT (CECT) scan of a suitable test-case of BRPC a set of reference structures were defined by a team of two expert clinical oncologists and one radiologist. A contemporaneous ^{18}FDG-PET scan was used to help interpret CT appearances but the GTV was contoured to define the extent of gross tumour as evident on the CT scan. The target structure for the margin-directed boost was generated in a stepwise manner (see Fig. 1):

(a) The vessel(s) e.g. superior mesenteric artery, superior mesenteric vein or portal vein should be outlined for their length that they are in contact with the tumour. This structure is denoted VesselContact.
(b) This structure is then expanded circumferentially by 3 mm (i.e. anterior/posterior and laterally but not craniocaudally). The resulting structure is denoted Vessel + 3 mmC. The GTV is also expanded circumferentially by 3mm to produce GTV + 3mmC.
(c) A Boolean operator is used to define the region that lies in both Vessel + 3mmC AND GTV + 3mmC, and the resultant structure is denoted the Boost Volume.

Eight clinical oncologist investigators specialising in pancreatic cancer were provided with the CT and PET scans, along with radiologist reports, and asked to follow the written instructions for the delineation of the target structures within the radiotherapy guidance for the SPARC trial protocol. Structure sets were imported into the Eclipse (version 13, Varian, Palo Alto, CA) radiotherapy treatment planning system (TPS) and descriptive parameters (volume, centre of mass) and conformity indexes were calculated:

$$\text{Dice coefficient} = \frac{2 \times (A \cap B)}{A + B}$$

$$\text{Geographical miss index} = \frac{B - (A \cap B)}{B}$$

$$\text{Discordance index} = 1 - \left(\frac{(A \cap B)}{A}\right)$$

where A denotes the investigator structure and B the reference structure, and A∩B denotes intersection of A and B (equivalent to Boolean operator "A AND B").

The trial protocol mandates the use of motion mitigation techniques if motion is greater than 5 mm (for example abdominal

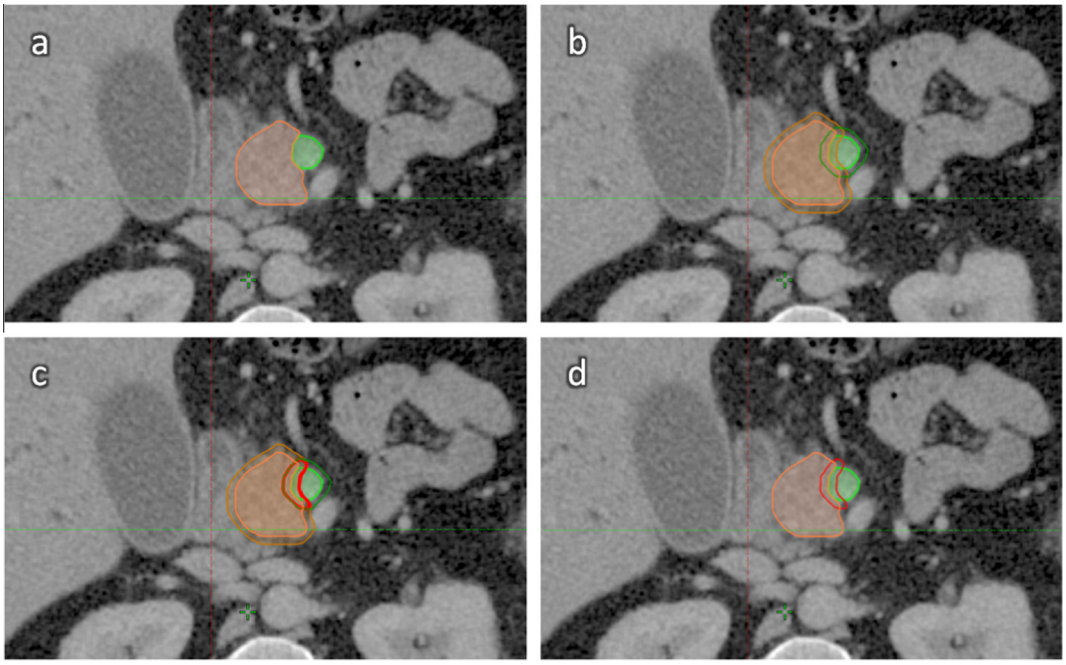

Fig. 1. Definition of target volumes for SPARC trial. Orange = GTV, Green = VesselContact, Red = Boost volume.

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