

1 **Intraoperative radiotherapy for pancreatic cancer: **Implementation and initial experience****

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22 Editor,

23 **As the treatment of pancreatic cancer evolves, different multimodal treatment regimens are being**
24 **developed for advanced disease** ¹. In the context of curative surgery, IORT offers delivery of a
25 targeted single fraction of high dose radiation (10-20Gy) to the resection bed, with the aim of
26 reducing local recurrence rates. The main advantages include surgical mobilisation and safe exclusion
27 of vulnerable structures from the radiation field, targeting at-risk margins under vision and short
28 duration of treatment (<10 min). A small randomised controlled trial from Sindelar and colleagues
29 (n=24), demonstrated reduced local recurrence (33 vs. 100%) and improved survival (18 vs. 12
30 months) in the IORT arm ². Supporting this, a recent systematic review including non-randomised
31 studies (seven in total) concluded that IORT in resected pancreatic cancer improves local control
32 without affecting morbidity or mortality ³. Furthermore, the joint analysis of data from the ISIORT-
33 Europe programme (n=270) showed that pre-operative radiotherapy further increased efficacy of
34 IORT in terms of local control and overall survival ⁴.

35 Why has IORT not been commissioned? Although the evidence suggests benefit, there are few
36 prospective randomised trials available. Furthermore, a typical IORT unit costs in the region of 1-1.5
37 million euros and logistically, IORT is a massive multidisciplinary undertaking, requiring trained
38 surgeons, oncologists, physicists, anaesthetists and theatre staff. However, several international HPB
39 units have shown that these hurdles are not insurmountable in their quest to optimise patient
40 outcomes.

41 In 2016, University Hospitals Southampton NHS Trust acquired a Mobetron 2000 linear accelerator
42 (IntraOp, USA) through charitable funding (PLANETS – www.planetscharity.org). Testing was
43 carried out at the National Physical Laboratory (Teddington, UK) between March-May 2016 to
44 acquire beam data and assess consistency of treatment delivery. Staff training, dry runs and visits to
45 the Heidelberg Cancer Centre preceded the first IORT for pancreatic cancer in February 2017.

46 To date, 19 patients with proximal pancreatic adenocarcinomas have had pancreaticoduodenectomy
47 combined with intraoperative electron beam radiotherapy (IOERT) in Southampton (in addition to

48 over 50 colorectal cancer patients). Inclusion criteria were: (i) initially unresectable or borderline
49 resectable tumours based on vascular encroachment (e.g. arterial encasement or superior mesenteric
50 vein/ portal vein contact (180-270°); (ii) WHO Performance Status 0-1 and; (iii) no evidence of
51 distant metastasis on CT (2-4 weeks pre-operation). Decision to explore and resect was based on
52 response to treatment or no progression on treatment.

53 Median age was 66 (42-81) years. Median American Society of Anaesthesia grade was 2 (2-3). 16/19
54 had locally advanced pancreatic cancer and 18/19 had neoadjuvant chemotherapy. Median IOERT
55 dose was 15 (10-15) Gy, energy 7.5 (6-12) MeV, to a mean depth of 1.6 +/- 0.8 cm, with median cone
56 size 5 (4-6) cm and bevel angle 15 (0-30) degrees. Typical theatre set up is shown in (**Figure 1**). All
57 tumours were pT1-T3 and 10/19 had positive regional nodes. 10/19 were R1 resections, with 4/19
58 specimens exhibiting vascular invasion and 6/19 perineural invasion. Mean operating time (including
59 IOERT) was 534 +/- 77 min. Median length of stay was 8.5 (6-41) days. 30-day mortality was zero.
60 6/19 patients had post-operative complications (Clavien-Dindo 1-2), with clinically detectable
61 pancreatic fistula in 1/19.

62 This initial UK series adds to the body of evidence confirming the safety and feasibility of IORT in
63 pancreatic surgery. More importantly, it demonstrates that with a multidisciplinary effort, a functional
64 IORT service can be commenced within 12 months of acquiring the Mobetron system. We believe
65 that our promising preliminary results will prompt more HPB centres in the UK to explore the
66 utilisation of IORT. A prospective multicentre randomised trial including UK and international
67 cohorts would offer invaluable data regarding the potential benefit of IORT in pancreatic cancer.

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86 **Figure Legend**

87 **Figure 1. IOERT in pancreatic resection.** (A) Post-resection, pre-reconstruction view of the
88 operative field in pancreaticoduodenectomy. (B) Positioning of the cone with respect to the operative
89 field. (C) View down the cone of the resection bed. (D) Docking of Mobetron electron beam linear
90 accelerator.

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93 This research was not preregistered in an independent institutional registry. Raw data, analytic
94 methods, and study materials will be made available to other researchers on request from the
95 corresponding author.

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