RADIOTHERAPY PROTOCOL:
Hypofractionated Radical Pancreas (5 fraction)

(adapted from Oxford Protocol and SPARC trial)

Author: Adapted from Oxford Pancreas and the SPARC protocols

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**This document describes a hypofractionated precision RT (5 fraction pancreas) regimen developed as emergency response to COVID crisis, and has not been tested in a formal trial. The dose-fractionation (30Gy/5 fractions) was considered to be relatively safe regimen (especially in terms of GI toxicity) and provides meaningful local control/neo-adjuvant dose. The supporting data on efficacy and toxicity of this regimen has been taken from SABR trials however the dose recommended (30Gy/5 fraction) is lower that what would be considered as SABR dose (typically 35-40/5 fractions) and therefore this should not be considered as SABR. This hypo-fractionated treatment can be delivered in centres otherwise capable of delivering non-SABR pancreas RT, without the complex set up and expertise as required for SABR.*

The CRIsP metanalysis reported (TChelebi et al)[1]: 9 studies assessed SBRT and 11 studies for CFRT. For SBRT, the median dose was 30 Gy, and the most common regimen was 30 Gy/5 fractions. For CFRT, doses ranged from 45 to 54 Gy in 1.8- to 2.0-Gy fractions, with the majority of studies delivering 50.4 Gy in 28 fractions with concurrent gemcitabine. The random effects estimate for 2-year OS was 26.9% (95% CI, 20.6%-33.6%) for SBRT versus 13.7% (95% CI, 8.9%-19.3%) for CFRT and was statistically significant in favor of SBRT. The random effects estimate for 1-year OS was 53.7% (95% CI, 39.3%-67.9%) for SBRT versus 49.3% (95% CI, 39.3%-59.4%) for CFRT, and was not statistically significant. The random effects estimate for acute grade 3/4 toxicity was 5.6% (95% CI, 0.0%-20.0%) for SBRT versus 37.7% (95% CI, 24.0%-52.5%) for CFRT and was statistically significant in favor of SBRT. The random effects estimate for late grade 3/4 toxicity was 9.0% for SBRT (95% CI, 3.3%-17.1%) versus 10.1% (95% CI, 1.8%-23.8%) for CFRT, which was not statistically significant.

***CONCLUSION**: These results suggest that a hypofractionated precision radiation option for locally advanced pancreatic cancer (LAPC) may result in a modest improvement in 2-year OS with decreased rates of acute grade 3/4 toxicity and no change in 1-year-OS or late toxicity.*
In our opinion 25-30Gy in 5 fraction is a relatively safe dose that should be deliverable in most UK centres who have experience with pancreas RT, particularly if they have been through in the QA process related to the UK national pancreatic trials (SCALOP, SCALOP2, ESPAC5). Higher dose RT (33-35Gy/5#) can be delivered by clinical oncologists with pancreatic radiation expertise who also deliver CTE SABR, or have participated/participating in national upper abdominal SABR trials (eg SPARC, ABC07,CORE).

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1. Objective and scope

To summarise the planning and treatment of patients receiving hypo-fractionated radiotherapy for pancreatic malignancies.

2. Indications

- Locally advanced unresectable, or borderline resectable, or recurrent pancreatic cancer, or where patient is unsuitable for surgery.
- Tumour size < 7cm

3. Pre-radiotherapy investigations

- Patients may require an MRI to aid tumour definition, if not well defined on CECT (discretion of clinician)
- PET to rule out metastatic disease (if part of departmental policy)
- DMSA scan may be required if renal dose likely to be significant

4. Therapeutic Schemata

Dose prescription

- 30Gy in 5 fractions daily or on alternate days
- Accepted variations: 25Gy-35Gy in 5 fractions (for dose >30Gy, 4D CT and motion management is mandatory, and should be delivered in centres with experience of delivering SABR).
- If no 4D CT, it is recommended a dose prescription of 25 Gy

Chemotherapy

- NO concurrent chemotherapy will be given alongside RT. Last dose of chemotherapy should be at least 2 weeks before, and post RT chemotherapy should not be recommenced for at least 4 weeks.

5. Pre-treatment

Patient simulation and immobilisation:

- Motion management varies in each institution
- Preferred: Patient supine with arms above the head either using the abdominal compression board with vac bag or the wing board together with knee immobilization. Or active breathing control
- If no motion management available use 4DCT and consider reducing prescription dose
- Two hours nil by mouth prior to scan and treatment
- ~150mL of dilute oral contrast or water 10-15 minutes prior to scanning to aid visualisation of upper GI tract. Record volume given in setup note.
- Intravenous contrast with scan delay for pancreatic phase
- Exhale breath hold contrast enhanced CT followed by 4DCT

Where necessary, the planning MRI should be ideally performed on the same day of planning CT, with the patient immobilized in the treatment position. An exhale breath-hold series and a dynamic series should be performed as per MRI protocol.

6. Volume definitions

On the 3D CECT, outline GTV_T and GTV_N :-

- GTV_T = includes the macroscopic pancreatic tumour visible on imaging
- GTV_N = peritumoural lymph nodes (> 1cm in short axis diameter and considered suggestive of involvement on diagnostic imaging). If a peri-tumoural node is < 1cm, confirm with radiologist that lymph node is non-malignant and do not include in GTV. If nodes >1cm away from GTV discuss with CI. No prophylactic lymph node target volumes should be produced
- On the maximum inhale and maximum exhale bins of the 4D-CT outline each GTV again to create GTV_T_inhale, GTV_N_inhale, GTV_T_exhale and GTV_N_exhale.
- On the 3D CECT create the ITV using a Boolean operator. Produce a union of GTV_T, GTV_N, GTV_T_inhale, GTV_N_inhale, GTV_T_exhale and GTV_N_exhale
- Once ITV is created, verify that the involved tumour/nodes are adequately covered on all phases of 4DCT
- ITV may be manually adjusted to cover additional areas of risk at discretion of treating physician
- PTV = ITV + 3-5mm symmetrically,. If no motion management consider 5mm 3D for PTV and reducing prescription dose.

  PTV MUST be edited off GI tract with 2mm margin.

Organs at risk

- Spinal cord: Outline the spinal cord (not the bony spinal canal) from 2cm above to 2cm below the PTV. If non-coplanar beams are used, a greater length should be outlined.
- Spinal Cord Planning Risk Volume (PRV): Spinal cord + 0.5cm isotropic margin.
- Liver: The whole liver should be outlined
- Kidneys: Both kidneys should be outlined separately
- Stomach: The whole stomach should be outlined
- Duodenum: The whole of the duodenum from below the pylorus to the fourth part of duodenum (up to the ligament of Treitz) should be outlined.
- Small Bowel: Individual loops of small bowel should be outlined on all slices from 2cm above to 2cm below the PTV not including colon and duodenum. If non-coplanar beams are used, consider outlining further loop
- Large Bowel: All parts of the colon should be outlined on all slices from 2cm above to 2cm below the PTV. If non-coplanar beams are used, consider outlining further loop

7. Treatment planning

Planning parameters

- IMRT/VMAT is mandated
- 27Gy and 30Gy isodose structures to be generated and exported to aid in image matching and avoidance of GI tract

Dose constraints*

Organ		Constraint	
		Optimal	Mandatory
Duodenum	Dmax (0.5cc)	<33Gy	<35Gy
	D5cc	<25Gy	
	D9cc	<15Gy	
	D10cc		<25Gy
Kidneys (individual and combined)	Mean dose	<10Gy	
Solitary Kidney or if one kidney mean dose >10Gy	V10Gy	<10%	<45%
Large bowel	Dmax (0.5cc)		<32Gy
Liver	Mean dose	<13Gy	<15Gy
Small bowel	Dmax (0.5cc)	<30Gy	<35Gy
	D5cc	<25Gy	
	D10cc		<25Gy
Spinal cord+5mm	Dmax (0.5cc)		<25Gy
Stomach	Dmax (0.5cc)	<33Gy	<35Gy
	D5cc	<25Gy	
	D10cc		<25Gy

**these constraints are taken from Hanna et al (see ref). These constraints are for SABR, and assumes 4DCT and appropriate motion management. When editing PTV off the GI Tract with 2mm margin, and using 30Gy/5 fraction, it is expected that Dmax to GI tract would be much lower. For Non SABR sites (and clinicians with less experience of pancreas/upper abdomen RT), delivering 25-30Gy/5fractions, particularly without motion management, a more conservative GI Tract tolerance for Dmax could be considered (eg Dmax (0.5cc) optimal <30Gy, mandatory <33Gy)*

Other organs are relevant per national UK consensus on normal tissue dose constraint in SABR (Hanna et al).

8. Treatment delivery

Treatment delivery

- Nil by mouth 2 hours prior to treatment delivery
- Oral contrast should be ideally used on all treatment days to aid image matching. If no oral contrast given (eg. contrast allergy), equivalent amount of water as that from planning to be given prior to treatment delivery to maintain consistent GI filling.
- Radiotherapy will be undertaken in accordance with department policy
- Patients shall be positioned as per their set up instructions
- For RapidArc plans, the couch longitudinal value when at the isocentre must not be equal to or greater than 158cm as gantry movement for treatment is prevented.
- For all fractions and particularly on fraction 1 of RapidArc or Volumetric Modulated Arc therapy treatments, the radiographers treating MUST ensure the gantry will not collide with the patient or couch during the treatment.

Verification imaging

- Daily volumetric imaging (eg. CBCT) with oral contrast to be used for image matching with tolerances of 0.1cm and 3°
- 27Gy and 30Gy isodose structures should be used to aid image matching. Ideally the 27Gy isodose structure should not overlap GI Tract; 30Gy isodose structure should never overlap GI tract. If 30Gy isodose structure overlaps with GI tract, clinician should be consulted immediately with potential deferral of treatment

9. Follow-up after treatment

- Following completion of treatment, patients should be followed up as per clinician preference. A restaging CT scan should be performed at 8-10 weeks to assess response. CT scans should then be performed 3-4 monthly intervals (year 1), then 6 monthly (year 2-3) then yearly (year 4-5). The scanning protocol will be abandoned if patient develops progressive disease at any stage, and patient should be managed as per clinician choice.

10. References

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