RADIOTHERAPY PROTOCOL:
Radical Pancreas 15 fraction

(adapted from PRIMUS 002 radiotherapy protocol and RMH research protocol)

Reviewed by:

Derek Grose (Glasgow)
Arabella Hunt (RMH)
Katharine Aitken (RMH)
Somnath Mukherjee (OUH)
Maria Hawkins (UCL)
Ganesh Radhakrishna (Christie)
Rebecca Goody (Leeds)
Daniel Holyoake (Norwich)

This document describes suggested 15# regimes for borderline resectable and locally advanced pancreatic adenocarcinoma (PDAC). Within the UK, 15 fraction regimens (36Gy/15#) will be evaluated in the resectable/borderline resectable setting in the PRIMUS 002 trial (CRT component likely to open end 2020). This dose fractionation was used in the PREOPANC trial (1) with concurrent gemcitabine based chemotherapy. Although this recently reported trial failed to show an overall survival benefit for the addition of gemcitabine based CRT compared to patients going to immediate surgery, a predefined subgroup analysis did show a survival benefit in the borderline resectable setting with an improved R0 resection rate (71% vs. 40%) (2). In this protocol it is given with concurrent capecitabine in accordance with current UK practise.

There is currently no equivalent 15 fraction regimen in regular use in the UK for the LAPC cohort. The potential benefits compared to long course chemoradiation include reducing total treatment time and visits to hospital and reducing the time off full dose systemic treatment. Published retrospective data and protocols using a 15# regimen come predominantly from US experience where 15# protocols have been used in the setting of dose escalated regimens using a SIB technique (up to a boost dose of 67.5Gy/15#) (3-7). In this non-dose escalated protocol 45/15# has been chosen as a single level dose as it has an equivalent BED (α/β 10) to 50.4Gy/28# which is the current UK standard from the SCALOP trial (Table 1). The use of a modified PTV with subtraction of nearby GI organs at risk from the target volume mitigates against the potential for normal tissue toxicity.

Table 1: Table of dose equivalence (not taking into account time factor)

Fractionation	**BED α/β 10**	**BED α/β 3**
50.4Gy/28#	59.47	80.64
54Gy/30#	63.72	86.4
36Gy/15#	44.64	64.8
45Gy/15#	58.5	90

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1. Objective and scope

To summarise the planning and treatment of patients receiving 15# hypofractionated radiotherapy for pancreatic malignancies.

2. Indications

- Patients with locally advanced adenocarcinoma of the pancreas (as defined by local MDT). Dose is 45Gy/15# with concomitant capecitabine.
- Patients with borderline resectable disease (as defined by local MDT). Dose is 36Gy/15# with concomitant capecitabine.

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

- Borderline resectable PDAC
  The dose to PTV_{3600} will be 36Gy in 15 fractions (2.4 Gy per fraction) delivered over 3 weeks (Mon-Fri)
- Locally advanced PDAC
- The dose to PTV_{4500} will be 45Gy in 15 fractions (3 Gy per fraction) delivered over 3 weeks (Mon-Fri)

Chemotherapy

- In both regimes Radiotherapy will be given with concurrent oral capecitabine 830mg/m2 BD on days receiving radiotherapy.

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. Alternatively use assisted breath hold techniques e.g. ABC or gating as per institutional policy
- Whilst motion management, 4DCT and advanced planning techniques (IMRT/VMAT) are strongly recommended, if these are not available it is felt reasonable to consider 45Gy/15# as similar BED to normal tissues compared

to 54Gy/30# (BED3 90 compared with 86.4) where safety without advanced planning techniques has been demonstrated within the LAP-07 trial (8). However normal tissue tolerances must be respected and if on review of the plan there is any concern, it is recommended to drop the prescription dose to 40Gy/15#. 36Gy/15# for BR patients is below GI tolerance, although motion management and advanced planning techniques are again advised where these are available.

- 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).
- 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

CTV

- CTV = ITV plus 5mm (for borderline resectable and locally advanced)

PTV

- PTV_{3600} = CTV. For use in borderline resectable cancers

- PTV_{4500} = CTV – GI PRV*. For use in locally advanced cancers

*GI PRV represents the union structure of duodenum PRV, stomach PRV, small bowel PRV and large bowel PRV (GI OAR + 5mm expansion).

Organs at risk

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.

Duodenum PRV: Duodenum + 5mm

Stomach: The whole stomach should be outlined

Stomach PRV: Stomach + 5mm

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. Consider further additional contouring if non-coplanar beams are used.

Small bowel PRV: Small bowel + 5mm

Large Bowel: Outline all large bowel from 2cm above to 2cm below the PTV

Large Bowel PRV: Large bowel + 5mm

Liver: Outline the whole liver

Kidneys: Both kidneys outlined separately

Spinal cord: The spinal cord from 2cm above to 2cm below PTV. If non-coplanar beams are used, a greater length should be outlined.

Spinal cord PRV: Spinal cord + 5mm

7. Treatment planning

Table 2: PTV constraints

Structure	Constraint	Optimal	Mandatory
PTV_{3600}	D95%		95%
	Dmax 0.1cc		107%

Structure	Constraint	Optimal	Mandatory
PTV_{4500}	D95%	95%	90%*
	Dmax 0.1cc	105%	107%

- where this is not achievable within OAR constraints, coverage of the ITV should be maximised (aiming >90%) as per Koay et al (7)

Table 3: Organ at risk constraints*

Organ		Optimal	Mandatory
Duodenum	Dmax 0.5cc	≤45Gy	≤48Gy
	D5cc	≤36Gy	-
Stomach	Dmax 0.5cc	≤40Gy	≤45Gy
	D5cc	≤36Gy	-
Small bowel	Dmax 0.5cc	≤45Gy	≤48Gy
	D5cc	≤36Gy	-
Large bowel	Dmax 0.5cc	≤48Gy	≤51Gy
Liver			Mean ≤ 24Gy
Kidneys	Mean combined	≤12Gy	≤15Gy
	If one kidney or one kidney mean dose >12Gy		V12Gy ≤10%
Spinal cord	Dmax 0.5cc PRV	≤35Gy	≤37.5Gy

***** *Taken from ABC-07 trial protocol*

8. Treatment delivery

Patients should follow the same fasting and drinking instructions as performed prior to their radiotherapy planning CT. They should remain nil by mouth for 2 hours and to drink 200mls of water prior to treatment.

Daily Online position verification is recommended (CBCT or MR-guided). Imaging and corrections should be carried out as per local policy.

9. Follow up after treatment

CTCAE v5.0 should be used for prospective evaluation of toxicity with recommended time points of data collection at 4 weeks, 3 months and then 3 monthly until 2 years of follow up is reached (intervals for follow up beyond this point at discretion of local investigator).

For borderline resectable - repeat of baseline imaging at 2 weeks post RT. Aim for surgery 4–6 weeks.

For locally advanced patients, CT imaging (+/- other imaging modalities as per local policy) is recommended at 3 months and then as per local policy thereafter.

Table 4: Suggested follow up schedule for locally advanced pancreatic cancer*

	Time point			
	4 weeks	3 months	3 monthly until 2 years	Post 2 years
Toxicity assessment	√	√	√	As per local policy
CT ¥		√	As per local policy	As per local policy
Ca 19-9	As per local policy	As per local policy	As per local policy	As per local policy

¥ +/- additional imaging as per local policy

9. References

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