Management of Locally Advanced Pancreatic Cancer Meeting
10th July 2012

This was an excellent meeting with a comprehensive programme covering many aspects of locally advanced pancreatic cancer (LAPC) treatment. The aim was to bring together experts in the field to look at current treatment, in particular the role of radiotherapy, for pancreatic cancer and the way forward so that the newly funded SCALOP II and the proposed ESPAC 5 are able to maximise improvement in pancreatic cancer treatment in the next few years. It was held in the Gray Institute for Radiation Oncology, Old Road Campus Research Building, Oxford. There were 48 attendees, including 35 clinical oncologists involved in treating LAPC, as well as surgeons, radiologists, medical physicists and radiographers.

Prof Tim Maughan and Prof Gillies McKenna chaired the morning session. Dr Somnath Mukherjee opened the talks, giving an overview of progress in treatment of LAPC. Prior to the start of the SCALOP trial, only about 16% of patients were treated with Chemoradiotherapy (CRT) and there was a wide variation in how tumours were outlined and what margins were used. There was agreement between clinical oncologists that there was a need for a CRT trial in pancreatic cancer.

SCALOP has now completed recruitment with 114 patients registered, and 75 randomised to the CRT at the 3 month point. A total of 28 centres were opened, and 20 recruited at least one patient showing good support from across the UK. This proved that a CRT trial in pancreatic cancer could be successfully run and the results will be analysed later this year. Most centres now offer CRT as standard treatment using a SCALOP type protocol and this has improved CRT treatment for pancreatic cancer in UK.

SCALOP II has been reviewed favourably by Cancer Research UK (CTAAC) and although the main design of the trial has been formulated, there is still the opportunity for input into the finer detail. This is the chance to shape treatment of pancreatic cancer in the next 5 years.

Dr Stephen Falk, recently appointed chair of the NCRI Upper GI pancreatic subgroup, then gave an excellent review of the literature relating to radiotherapy (RT) in LAPC. However, the trials that have been done have generally been small Phase IIs which looked at different endpoints (e.g. resectability, local progression, overall survival). Generally, there is more toxicity with CRT over chemotherapy offset by a small improvement in outcome. A variety of different chemotherapy regimens and doses, and also different RT doses and fraction numbers made it hard to compare effectiveness of treatment. Selecting patients for CRT who responded to induction chemotherapy (CT) did give better results and it was agreed that clinicians should select patients for the best treatment.

Dr Raj Roy talked on dose escalation of RT. Increasing the dose does appear to improve local control, but this needs to be done with careful consideration to Organs at Risk. Implementation of new RT techniques such as IMRT is a way forward. He reported on the progress of his own RT dose escalation trial with IMRT being done locally with a particular interest in the bowel toxicity associated with the treatment.

Dr Esme Hill gave a really good overview on how cancer associated fibroblasts mediates hypoxia in pancreatic cancer. Hypoxia is known to limit the affectivity of chemo-radiotherapy treatment and

contributes to genomic and molecular changes. Blocking the ras pathway is known to reduce hypoxia and Nelfinivir inhibits a target downstream of ras making it a useful drug. Dr Hill summarised the ARC I trial which showed a complete FDG-PET response in 5 out of 10 patients when nelfinivir was used in combination with CRT. ARC II builds on this, and is now recruiting patients. Here a moderate dose of 50.4Gy (28 fractions) is given to the PTV1 (GTV and nodes at risk) then a subsequent boost of 9Gy (5 fractions) to a smaller PTV2 (GTV2 plus 1.5-2cm margin). The radiotherapy is given concomitant with gemcitabine, cisplatin chemotherapy and nelfinavir. Additional imaging studies (FDG PET, Miso-PET and perfusion CT) are being conducted looking at areas of hypoxia and vascularity to determine how these areas are influenced by treatment.

Zahir Soonawalla gave a surgeon's perspective on pancreatic cancer treatment. The best chance of survival for these patients is a R0 resection. However, results are poor and in many cases could be considered palliative. As it can take 4 to 6 months to regain quality of life, if patients progress at 6 months they have not really benefited. There is some evidence that CRT or neoadjuvant therapies improve outcome, but the evidence needs to be better and clearer on the best treatment. The optimal timing post treatment of surgery is also not known. Overall survival is about 14% so there is plenty of scope for improvement.

There was some debate on how patients were classified as resectable, borderline resectable and inoperable. Although there was guidance, MDT interpretation did appear to vary. There were also a number of patients who were operated on, but tumour was not removed as on opening they were found to be inoperable. It is apparent that current diagnostic scanning is not providing clear enough assessment of these patients.

Chris Hurt presented the adaptive design of SCALOP II which allows for modification of arms depending on the results of ongoing clinical trials. Currently, SCALOP 2 involves 5 arms; Arm A: GEMCAP chemotherapy alone, Arm B: induction GEMCAP chemotherapy followed by GEM plus 50.4Gy in 28 fractions, Arm C: induction GEMCAP chemotherapy followed by GEM plus 50.4Gy in 28 fractions plus nelfinavir, Arm D: induction GEMCAP chemotherapy followed by GEM plus 59.4Gy in 33 fractions, Arm E: induction GEMCAP chemotherapy followed by GEM plus 59.4Gy in 33 fractions plus nelfinavir.

Prof. John Neoptolemos gave an overview of a proposed neo-adjuvant study, ESPAC 5. The aim of ESPAC 5 is to assess feasibility of randomising to a neo-adjuvant trial as previous trials have failed to recruit. It will compare standard of care (surgery followed by adjuvant chemotherapy) with neoadjuvant GEMCAP chemotherapy vs neo-adjuvant FOLFIRINOX chemotherapy vs neo-adjuvant CRT prior to surgery. Biopsies will be an important part of assessment and therefore all sites will need access to EUS. There will also be a central review of CT scans to confirm resectability. ESPAC 5 will use FOLFIRINOX, and includes investigators from France who have experience with this regimen. There was discussion on the possible use of a central radiology review in SCALOP II, but although this had some support, it was suggested that mentoring radiologists would be a better way forward for both SCALOP II and ESPAC 5.

During the afternoon there were a series of talks looking at the more practical and technical aspects of radiotherapy. Dr Helen Bungay gave a radiologists perspective on tumour CT imaging. She included several examples of PET-CT and CT images, indicating where tumour growth allowed or

prevented surgical removal of the tumour and why. This helped answer earlier questions relating to how tumours were viewed resectable, borderline resectable, and non resectable.

Charlotte Halle talked about the variation in GTV delineation seen in the SCALOP test cases, Dr Jenny Branagan talked about use of PET in delineation of the GTV, and Dr Sebastian Cummins talked on defining CTV and PTV. GTV is defined using CT, PET CT and EUS, and therefore there is variation even using these modalities. However, there is no evidence based consensus for CTV. Should the tumour alone be included, or should elective nodes also be considered? If so, which nodes, and are some nodes more likely to lead to progression or clinical spread than others? Whilst larger volumes are more likely to be sure to encompass all disease, they also are more likely to give greater toxicity. Movement, particularly from breathing is also significant, it can be up to 4cm which is larger than the margins currently being added. The use of 4D CT was discussed and it was agreed that it would be beneficial to implement, although there was little experience in using this technique in pancreatic cancer RT currently in the UK. Cynthia Eccles described the Oxford experience from the ARC II study and how to match images and the patient prior to treatment to reduce set up errors. Helen Summers talked about technical developments in pancreatic radiotherapy and the differences between 2D and 3D imaging for on-treatment verification. Most centres should now be doing 3D imaging (cone beam CT), and in some centres 4D cone beam CT was now being used. Especially for radiotherapy dose escalation, 4D CT planning scan and the use of IMRT may reduce bowel toxicity.

David Sebag-Montefiore then requested people's views on the way forward with SCALOP II. Whilst the main design was fixed, there were a lot of details to be finalised and he gave the audience a chance to input into these decisions.

A handful of people said they were using 4DCT for planning, but most said they would like to do so in SCALOP II. There was also the option of incorporating IMRT and other aspects of IGRT, in SCALOP II. The extent and margins for the CTV and PTV needed to be agreed on. The safety aspect with the dose escalation meant that increasing volumes from the SCALOP protocol needed to be done cautiously. There was also the view that, whilst the trial would be a good way to implement new technology, this should not be too specific, as it would then exclude sites currently unable to deliver these techniques. Good support would be needed across the UK to reach the target recruitment. As the trial has just been funded the pressure was on to develop a detailed and acceptable protocol quickly. Those who would like an input into either the main protocol or the radiotherapy guidelines were invited to contact the trial team on SCALOP2@cardiff.ac.uk. The RTTQA aspect of SCALOP II builds on SCALOP experience and RT workshops, as was done for ARISTOTLE trial, are planned. Those interested in attending future workshops should register their interest with the SCALOP II trial team.

The good turnout and enthusiasm of those present showed that this kind of meeting has good support from the clinical community. Those who attended said that it had been an excellent meeting which they had thoroughly enjoyed, and these comments were reflected in the feedback sheets. Thank you to all the presenters and attendees for making this an excellent day.

Appendix I: Final Programme

Final programme
Management of Locally Advanced Pancreatic Cancer Meeting
10th July 2012

Venue: ***Gray Institute for Radiation Oncology & Biology Seminar Rooms, Old Road Campus Research Building, Roosevelt Drive, Oxford, OX3 7DQ***

9.30 am - 9.55 am Registration, tea and coffee

10.00 am - 12.50 pm Session 1: Management strategies in LAPC
Chairs: Gillies McKenna/Tim Maughan

09:55 - 10:00	Welcome	5 mins	Somnath Mukherjee
10:00 - 10:20	Is there a role for RT in LAPC?	20 mins	Stephen Falk
10:20 - 10:40	Radiotherapy dose escalation in pancreatic cancer	20 mins	Raj Roy
10:40 - 11:00	Modulating hypoxia and vascularity in pancreatic cancer	20 mins	Esme Hill
11:00 - 11:30	SCALOP II + discussions	30 mins	Somnath Mukherjee and Chris Hurt
11:30 - 11:50	TEA/COFFEE BREAK	20 mins	
11:50 - 12:20	Surgery following CRT	30 mins	Zahir Soonawalla
12:20 - 12:30	Neo-adjuvant therapy; which patients, what treatment strategies, which end points	10 mins	Somnath Mukherjee
12:30 - 12:40	Introduction to ESPAC5	10 mins	John Neoptolemos
12:40 - 13:05	Neo-adjuvant trial in pancreatic cancer; Open discussion	30 mins	To facilitate - Stephen Falk
13:05 - 13:45	LUNCH	40 mins	

13:45pm - 16:15pm Session 2: Technical RT
Chairs: David Sebag-Montefiore/Tom Crosby

13:45 - 14:00	Variation in GTV delineation in pancreas: the SCALOP Test case experience	15 mins	Charlotte Halle
14:00 - 14:15	PET assisted GTV delineation	15 mins	Jenny Branagan
14:15 - 14:35	Radiology: how to delineate a pancreatic tumour	20 mins	Helen Bungay
14:35 - 15:05	INTERACTIVE SESSION "Defining GTV on a test case, group participation"	30 mins	Sarah Gwynne
15:05 - 15:20	TEA/COFFEE BREAK	15 mins	
15:20 - 15:35	How do we define CTV and PTV in pancreatic cancer?	15 mins	Sebastian Cummins
15:35 - 15:50	Technical developments in pancreatic radiotherapy	15 mins	Helen Summers
15:50 - 16:05	Radiotherapy for Pancreatic cancer – The Oxford experience	15 mins	Cynthia Eccles
16:05 - 16:15	Closing remarks	10 mins	Somnath Mukherjee

Close of main meeting

CPD credits awarded: 5

Appendix II: Attendees

Name	Occupation	Site
Dr Gerard Andrade	Consultant Clinical Oncologist	Northampton General Hospital
Dr Seema Arif	Consultant Clinical oncologist	Velindre Hospital
Dr Andrew Bateman	Consultant Clinical oncologist	Southampton General Hospital
Dr Claire Blesing	Consultant Clinical oncologist	Churchill Hospital
Dr Jenny Branagan	Clinical Oncologist	Northampton General Hospital
Dr Helen Bungay	Consultant Radiologist	Oxford Radcliffe Hopsitals NHS Trust
Dr Tom Crosby	Clinical Director	Velindre Hospital
Dr Sebastian Cummins	Consultant Clinical oncologist	Royal Surrey County Hospital
Dr Nicole Dorey	Consultant Clinical oncologist	Torbay District General Hospital
Cynthia Eccles	Radiographer	Churchill Hospital
Dr Stephen Falk	Consultant Clinical Oncologist	Bristol Haematology and Oncology Centre
Dr Sarah Gwynne	Radiotherapy Research Fellow	Singleton Hospital
Charlotte Halle	Trainee Clinical Scientist	Northampton General Hospital
Dr Noor Haris	Clinical oncologist	NICR Newcastle
Dr Andrew Hartley	Consultant Clinical oncologist	Queen Elizabeth Hospital
Dr Maria Hawkins	Consultant Clinical oncologist	The Royal Marsden
Dr Brian Haylock	Clinical Director for Radiotherapy	Clatterbridge Hospital
Dr Esme Hill	Clinical Research Fellow	Oxford University
Dr Richard Hubner	Consultant Clinical oncologist	Christie Hospital
Chris Hurt	Scientific Lead	WCTU
Dr Eleanor James	Consultant Clinical oncologist	City Hospital, Nottingham
Dr Catherine Jephcott	Consultant Clinical oncologist	Peterborough City Hospital
Dr Bramis Konstantinos	Senior Clinical Fellow	
Dr Spyros Manolopoulos	Consultant Clinical Scientist	University Hospitals Coventry and Warwickshire
Prof. Tim Maughan	Professor of Clinical Oncology	University of Oxford
Dr Philip Mayles	Head of Physics	Clatterbridge Hospital
Prof. David McIntosh	Consultant Clinical oncologist	Beatson West of Scotland Oncology Centre
Prof. Gillies McKenna	Director of the Gray Institute	University of Oxford
Dr Somnath Mukherjee	Consultant Clinical oncologist	Northampton General Hospital
Prof. John Neoptolemos	Professor of Surgery	University of Liverpool
Dr Rekha Neupane	Consultant Clinical oncologist	Ysbyty Gwynedd
Dr Lisette Nixon	Senior Trials Manager	WCTU
Dr Kinnari Patel	Medical Oncologist	Oxford Radcliffe Hopsitals NHS Trust
Dr Ruby Ray	Trials Manager	WCTU
Dr Rajarshi Roy	Consultant Clinical oncologist	Castle Hill Hospital
Dr Martin Scott-Brown	ConsulantClinical Oncologist	University Hospitals Coventry
Prof. David Sebag-montefiore	Consultant Clinical oncologist	St James's University Hospital
Mr Mike Silva	Consultant HPB Surgeon	University of Oxford
Dr Rajaram Sripadam	Consultant Clinical oncologist	Clatterbridge Hospital
Dr Rubin Soomal	Consultant Clinical oncologist	The Ipswich Hospital NHS Trust
Mr Zahir Soonawala	Consultant hepatobiliary and pancreatic surgeon	Oxford Radcliffe Hopsitals NHS Trust
Dr Sharmila Sothi	Consultant Clinical oncologist	University Hospitals Coventry and Warwickshire
Helen Summers	Advanced Practitioner in Radiotherapy	St James's University Hospital
Dr Liz Toy	Consultant Clinical oncologist	Royal Devon and Exeter Hospital
Dr Jonathan Wadsley	Consultant Clinical oncologist	Weston Park Hospital
Dr James Wilson	Clinical Research Fellow	University of Oxford
Dr Kein Yim	Consultant Clinical oncologist	Velindre Hospital