Barts Health NHS
NHS Trust

LONDON CANCER
NORTH AND EAST

NHS
Royal Free London
NHS Foundation Trust

London Cancer

HEPATIC PANCREATIC AND BILIARY (HPB)

FACULTY CLINICAL GUIDELINE

Management of Patients with Pancreatic and Peri-Ampullary Cancer

SEPTEMBER 2014

VERSION 1: 1st April 2014

Document history

First pre-draft v0.1,	16th March 2014
Tumour group meeting,	20th March 2014
Second pre-draft v0.2,	27th March 2014
Finalised	31st March 2014

Date for revision: 1st April 2015

These guidelines are based on latest internationally available guidelines for pancreatic and peri-ampullary cancer [1-4].

This operational policy is agreed and accepted by:

Designated individuals	**Signed**	**Date**
HPB Pathway Director		
Dr Andrew Millar		15/09/2014
Pancreatic Tumour Specific Group		
Mr Hemant Kocher (chair, surgeon)	Finalised and incorporated 31st March 2014	
Mr Kito Guiseppe Fusai (surgeon)	Authorised by email communication 27th March 2014	
Dr Stephen Pereira (gastroenterologist)	Authorised by email communication 29th March 2014	
Dr Roopinder Gillmore (medical oncologist)	Authorised by email communication 27th March 2014	
Prof Thorsten Hagemann (medical oncologist)	Authorised by email communication 30th March 2014	
RN Karen Mawire (CNS)	Authorised by email communication 27th March 2014	
Dr Grant Stewart (clinical oncologist)	Authorised by email communication 24th March 2014	
Dr Amen Sibtain (clinical oncologist)	Authorised by email communication 18th March 2014	

Contents

1. MDT coordinator and CNS contact details

1.1. CNS Royal Free Hospital (RFH)

Claire Frier (020 7794 0500 Extension: 31405, Bleep: 1066, claire.frier@nhs.net)

Paula Noone (020 7794 0500 Extension: 33762, Bleep: 2648, paula.noone@nhs.net)

Gemma Keating (020 7794 0500 Extension: 33838, Bleep: 2721, gemmakeating@nhs.net)

1.2. CNS Royal London Hospital (RLH)

Karen Mawire (020 35945696, Karen.mawire@bartshealth.nhs.uk)

Katie Ryan (020 35940759, Kathleen.ryan@bartshealth.nhs.uk)

Rosie Hesling (020 35945740, rosie.hesling@bartshealth.nhs.uk)

1.3. MDT -coordinator RFH

Scott Green (020 7794 0500 Ext: 35812, ScottGreen@nhs.net)

1.4. MDT -coordinator RLH

Sally Howe (020 35940762, sally.howe@bartshealth.nhs.uk, emma.grimshaw@bartshealth.nhs.uk).

2. Diagnosis and staging

- All patients for whom there is clinical suspicion of pancreatic cancer or evidence of a dilated duct (stricture) should undergo initial evaluation by CT according to a defined pancreas protocol4 .
- Subsequent decision making regarding diagnostic management and resectability should involve multidisciplinary discussion3-5.
- Pancreas specific MRI is rapidly becoming comparable to CT scan and can be considered for patients allergic to contrast4.
- PET/CT is not a standard staging modality of pancreatic cancer. The results of NIHR HTA PET-PANC study (UK CRM 8166) are still awaited.

2.1. NCCN criteria for pancreatic cancer staging3, 4

- Resectable
    - Absence of distant metastases
    - Arterial : Clear fat planes around CA, SMA, and HA
    - Venous: No SMV/portal vein distortion
- Borderline resectable
    - Absence of distant metastases
    - Arterial: Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery without

extension to the CA. Tumour abutment of the SMA not to exceed greater than 180_ of the circumference of the vessel wall

- Venous: Involvement of the SMV or portal vein with distortion or narrowing of the vein or occlusion of the vein with suitable vessel proximal and distal, allowing for safe resection and replacement

- Unresectable
  - Absence of distant metastases
  - Arterial: Aortic invasion or encasement. And based on tumour location:
    - Pancreatic head—More than 180º. SMA encasement, any CA abutment.
    - Pancreatic body/tail—SMA or CA encasement greater than 180º.
  - Venous: IVC encasement. Unreconstructable SMV/portal vein occlusion

- Metastatic
  - Evidence of distant metastases (loco-regional lymphadenopathy is excluded).

- Positive histology and cytology are essential for confirmation of a diagnosis of PC and are particularly important in patients who are undergoing neo-adjuvant protocols, for those entering clinical trials and for patients with locally advanced or metastatic disease being considered for palliative chemo-(radio-) therapy5.
- Tissue diagnosis should, however, not delay surgery for a suspected resectable cancer, provided the MDT considers the presentation to have sufficient suspicion of cancer5.
- Options to obtain a tissue diagnosis are biliary brushings at ERCP, EUS-FNA or cholangioscopic, percutaneous (CT- or ultrasound-guided) or laparoscopic biopsy of primary or metastatic lesions.
- There is a risk of tumour seeding with some techniques, so surgical assessment of resectability should be established prior to a biopsy or FNA being performed.
- PET/CT is not a standard staging modality of pancreatic cancer. The results of NIHR HTA PET-PANC study (UK CRM 8166) are still awaited.
- All patients should be seen by a dedicated key worker (CNS: Clinical Nurse Specialist) at the first clinical encounter with clinicians when the diagnosis of pancreatic cancer is mentioned. This ensures a contact with a dedicated clinical team member who can follow the patient throughout their entire journey of care and expedite across any bottle-necks should they occur.

2.2. Preoperative biliary drainage

- The main goals of preoperative biliary drainage are to alleviate the symptoms of pruritus and cholangitis1, 3.
- The ERCP route is usually favoured above percutaneous drainage for low bile duct strictures.
- In patients being considered for resection without neo-adjuvant treatment, biliary decompression is only indicated in patients who are deeply jaundiced (> 250 µmol/L), cholangitic, or in whom surgical resection is expected to be significantly delayed.

2.3. B1. Research:

All patients to be considered for inclusion in PCRF National Pancreas Registry and Tissue Bank (in set-up, nptb.org.uk).

2.4. Nutritional assessment

Once the diagnosis has been confirmed all patients should be screened for unintentional weight loss to identify those at nutritional risk and in need of nutrition support pre- treatment. Weight loss is calculated as a percentage of pre-illness weight:

$$\% \text{ Weight loss} = \frac{\text{Usual weight (kg)} - \text{Current weight (kg)} \times 100}{\text{Usual weight (kg)}}$$

10% weight loss within the last 6 months is classified as clinically significant and a referral to the dietician is recommended. Such weight loss has been associated with negative outcomes post operatively. All patients should also have their BMI calculated and those with a BMI of <20 should be referred the dietician.

2.5. Surgical resection

There are seven and four designated pancreatobiliary surgeons based at the Royal Free Hospital (Royal Free London NHS Foundation Trust) and the Royal London Hospital (Barts Health NHS trust) respectively. These are:

Royal Free Site Prof BR Davidson, Mr KG Fusai, Mr C Imber, Prof M Malago, Mr S Rahman, Mr A Shankar, Mr D Sharma

Royal London Site Mr AT Abraham, Mr S Bhattacharya, Mr RR Hutchins, Mr HM Kocher

All HPB surgery is performed by the designated surgeons, who must meet the AUGIS guidelines for HPB surgery volumes in order to retain designation[6]. All adult HPB surgery takes place at The Royal Free (RFH) or The Royal London (RLH) Hospitals. Any adult surgery taking place outside RFH/RLH, unless specifically agreed by special arrangement with the MDT, is considered to be a serious untoward incident reportable at sector level as the infrastructure to support complex HPB surgery has now been centralised at these two institutions.

Selected patients considered high-risk for surgery either in terms of co-morbidity or in terms of complexity of surgery should be considered for Cardio-pulmonary exercise testing (CPET) for high-risk anaesthetic assessment.

Surgical patients are managed on HDU/ITU in immediate post-operative period and then on ward 9 West at RFH and ward 13D at RLH sites. There is in place a 1:8 HPB Consultant of the week on call rota providing 24/7 Consultant cover at RFH site and 1:9 General Surgery Consultant at RLH site with availability of designated HPB Consultant. The Consultants are supported by 24/7 senior fellow/registrar cover.

A standard or a pylorus preserving pancreaticoduodenectomy will be performed with regional lymph node clearance[7]. Extended lymph node resections are performed in selected cases after discussion at the MDT[8]. Tumours in the body or tail are offered a distal pancreatectomy and splenectomy following appropriate immunization. In selected instances, spleen preserving surgery may be carried out. Portal vein resection and reconstruction is performed routinely with the exception of those cases where the vein is occluded (see below criteria for resectability). In cases where the tumour is found to be unresectable a biliary and gastric bypass is usually performed.

The older criteria for resectability proposed by the MD Anderson group in 2006[9] and used by the multicenter UK study[10], has been superseded by NCCN as well as APA/ SAI guidelines[3, 4]. Further definitions are included in the ESPAC-5 (in set-up) and SCALLOP-II (in set-up) studies proposed (see below). In parallel, a prospective international study (in set-up) to assess safety and survival in patients undergoing arterial resection for pancreatic cancer is in set-up. Therefore, these patients should be discussed in HPB MDT for fuller discussion and inclusion in various studies.

3. Oncology

Chemotherapy when indicated is delivered at the most convenient designated unit at any of the hospitals of *London Cancer* Consortium. At the two designated HPB surgical units the names of oncologists are;

Royal Free Site	**Royal London Site**
Dr R Gillmore	Prof T Hagemann
Prof T Meyer	Dr S Slater
Dr G Stewart (clinical oncology)	Dr DJ Propper
	Dr A Sibtain (clinical oncology)

Common protocols are available for the treatment of upper GI cancers which have been approved by the upper GI tumour board. In addition, all patients with a new diagnosis of pancreatic cancer should be considered for entry into clinical trials within the network. The treatment specific to pancreatic cancer is as follows:

3.1. Adjuvant:

Standard 1st Line[11, 12]: Gemcitabine: 1g/m^2 , D1, 8 & 15; q28dx6.

Clinical Trial: ESPAC4 (UKCRN ID 4307) –Gemcitabine vs Gemcitabine plus Capecitabine (enrolling)

3.2. Locally advanced/borderline resectable:

Standard 1st line [13-15]:

Gemcitabine: 1g/m^2 infused over 100 min (i.e. 10mg/m^2/min), D1, 8 & 15; q28dx6.

3.3. Other options or second line:

Chemoradiotherapy regimens[16-18]:

CRT = 45-50.4Gy/28# + concurrent Capecitabine 825-830mg/m^2bd Monday-Friday

Or

50.4Gy/28# Gemcitabine 300mg/m^2 /week IV infusion over 30 mins for 6 weeks

Following completion of chemo-radiotherapy the patient should have repeat imaging which again should be discussed at the HPB MDT to determine any evidence of resectability. If no evidence of resectability the patient should remain on surveillance and treated upon evidence of disease progression.

For those patients with locally advanced disease considered inoperable then referral for Stereotactic Body radiotherapy should be discussed. This can be facilitated via the weekly Cyberknife MDT at either Mount Vernon (Mark Harrison) or Barts Hospital (Amen Sibtain).

3.4. Clinical Trials (NCRN):

SCALLOP2, ESPAC5: both in set-up phase.

SCALLOP 2: SCALOP 2 currently 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.

ESPAC5: ESPAC 5 is to assess feasibility of randomising to a neo-adjuvant trial.

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.

3.5. Metastatic:

First line[13-15, 19, 20]:

1. Standards available are (patient and clinician choice):Gemcitabine SA (q28): D1, 8, 15 gemcitabine 1,000mg/m2 IV
2. Gemcitabine + Capecitabine (q28x6): D1, 8, 15 gemcitabine 1,000mg/m2 IV, D1-21 Capecitabine 825-830mg/m^2 po
3. Capecitabine SA (q21, until dise[a]se progression), D1-14 Capecitabine 1000mg/m2 po

3.6. Clinical trials: SIEGE (first line metastatic PDAC, UKCRN 15344):

Control Arm Concomitant ABX/GEM

D1, 8, 15 Abraxane 125mg/m^2 IV immediately followed by

D1, 8, 15 Gemcitabine 1000mg/m^2 IV

4 weekly for 6 cycles

Research Arm Sequential ABX/GEM

D1, 8, 15 Abraxane 125mg/m^2 IV

D2, 9, 15 IV Gemcitabine 1000mg/m^2 IV

4 weekly for 6 cycles

CDF options are:

FolFirinOx (q14x12)[21]:

D1 C[a]lcium Folinate (Folinic Acid) 350mg IV

D1 Oxaliplatin 85mg/m2 IV

D1 Irinotecan 180mg/m2 IV

(D1 5-Fluorouracil 400mg/m2 IV) – modified regime drops the bolus

D1 5-Fluorouracil 2400mg/m2 IV over 46 h

Assessment after 4 cycles, as per Conroy (2011) treatment indefinite.

Gemcitabine / Nab-Paclitaxel (q28x6)[22]

D1, 8, 15 gemcitabine 1,000mg/m2 IV

D1, 8, 15 nab-Paclitaxel 125 mg/m2 IV

Second line treatment

a) FOLFOX after GEM

b) GEM after FOLFIRINOX

4. Management of biliary / gastric outlet obstruction in locally advanced and metastatic disease

Symptoms related to biliary obstruction in unresectable disease may be palliated by insertion of a biliary endoprosthesis. Stenting procedures resulting in adequate biliary drainage improve survival.

- In patients with unresectable disease, metal stents have greater patency rates and are associated with fewer ERCPs, shorter hospital stay and fewer complications, compared with plastic stents. In those patients where ERCP is not feasible, percutaneous drainage should be considered.
- Metal stents are also more cost effective than plastic stents in patients with an expected survival of more than three months.
- Uncovered metal stents should not be deployed for biliary strictures prior to an MDT decision being made on resectability and histological/cytological confirmation of malignancy obtained.

- In the case of cholangitis or decrease in total bilirubin level of <20% from baseline at 7 days post stent insertion, repeat imaging and urgent endoscopic revision should be considered.
- For patients with jaundice and potentially resectable disease who are found to have unresectable tumours at laparotomy, an open biliary-enteric bypass +/- gastrojejunostomy provides durable palliation.
- Patients with locally advanced or metastatic disease and a short life expectancy or poor performance status who develop gastric outflow obstruction may be palliated with an endoscopically placed enteral stent.
- For a fit patient with locally advanced disease, an open or laparoscopic gastrojejunostomy may provide more durable and effective palliation than an enteral stent23.

5. FOLLOWUP ARRANGMENTS & COMMUNITY SERVICES

Specific follow-up arrangements for local patients will be agreed at MDT meetings. These guidelines include arrangements for patients who are referred to the MDT but are found to be unsuitable for specialist care.

a) Resected patients:

- Surgical review 2 weeks following discharge, provided on day of discharge to facilitate patient choice
- Oncology review regarding adjuvant chemotherapy.
- CT scan 6 monthly for first two years and then yearly until 5 years3.
- CA19-9 levels at each clinic visit3.
- Monitor of exocrine and endocrine pancreatic insufficiency and treat where required3.

b) Unresected patients

- Review by Oncology team at cancer centre during in-patient stay or appointment with cancer unit oncologist week following discharge from hospital.
- During oncology clinic visit arrangements made with community palliative care team.

Hospital or community follow-up dependent on plans for therapy, patient needs and availability of community support.

6. Community Services

Before discharge support in the community is always considered. This could be referral to local district nurses; various professionals allied to medicine, or in the majority of cases specialist palliative care teams. The nurses in the hospital, clinic and the consultant nurse in palliative care have responsibility to ensure that appropriate referrals are made and that patients and their carers have information on who, when and how contact will be made prior to their discharge home.

7. PALLIATIVE SUPPORT AND BEREAVEMENT

A dedicated palliative care service is available through all the hospitals within *London Cancer*.

Contact list

Camden and UCLH (University College London Hospital) Palliative Care Team
Consultant Lead: Dr Caroline Stirling
Macmillan CNS: Shirley Lendor N'Guessan.

Royal Free London NHS Trust Palliative Care Team
Consultant Lead: Dr Philip Lodge
Pancreas / Biliary Cancer CNS

Barts Health Palliative Care Team:
Consultant Lead: Dr Claire Phillips
Macmillan CNS: Adrian Mabbott

8. Quality Performance Indicators

1. Percentage of patients with cytological/histological diagnosis (target 50%)
2. Percentage or patients undergoing resection (target 15%)
3. Minimum resections per surgeon (target 15)
4. 30-day mortality post-resection (target <5%)
5. 90-day mortality post-resection (target <5%)
6. Percentage of patients who receive adjuvant treatment after resection (target 50%)
7. Percentage of patients receiving chemo- or radiotherapy, if not eligible for surgical resection and if fit (PS: 0 or 1) (target 50%).
8. Number of patients participating in clinical trials (target 33%)

9. References

1. Guidelines for the management of patients with pancreatic cancer periampullary and ampullary carcinomas. Gut 2005;54 Suppl 5:v1-16.
2. Seufferlein T, Bachet JB, Van Cutsem E, et al. Pancreatic adenocarcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23 Suppl 7:vii33-40.
3. Tempero MA, Arnoletti JP, Behrman SW, et al. Pancreatic Adenocarcinoma, version 2.2012: featured updates to the NCCN Guidelines. J Natl Compr Canc Netw 2012;10:703-13.
4. Al-Hawary MM, Francis IR, Chari ST, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the society of abdominal radiology and the american pancreatic association. Gastroenterology 2014;146:291-304 e1.

5. Asbun HJ, Conlon K, Fernandez-Cruz L, et al. When to perform a pancreatoduodenectomy in the absence of positive histology? A consensus statement by the International Study Group of Pancreatic Surgery. Surgery 2014.
6. Charnley RM, Paterson-Brown S. Surgeon volumes in oesophagogastric and hepatopancreatobiliary resectional surgery. Br J Surg 2011;98:891-3.
7. Iqbal N, Lovegrove RE, Tilney HS, et al. A comparison of pancreaticoduodenectomy with pylorus preserving pancreaticoduodenectomy: a meta-analysis of 2822 patients. Eur J Surg Oncol 2008;34:1237-45.
8. Iqbal N, Lovegrove RE, Tilney HS, et al. A comparison of pancreaticoduodenectomy with extended pancreaticoduodenectomy: a meta-analysis of 1909 patients. Eur J Surg Oncol 2009;35:79-86.
9. Varadhachary GR, Tamm EP, Abbruzzese JL, et al. Borderline resectable pancreatic cancer: definitions, management, and role of preoperative therapy. Ann Surg Oncol 2006;13:1035-46.
10. Ravikumar R, Sabin C, Abu Hilal M, et al. Portal vein resection in borderline resectable pancreatic cancer: a United kingdom multicenter study. J Am Coll Surg 2014;218:401-11.
11. Neoptolemos JP, Stocken DD, Bassi C, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA 2010;304:1073-81.
12. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA 2007;297:267-77.
13. Cunningham D, Chau I, Stocken DD, et al. Phase III Randomized Comparison of Gemcitabine Versus Gemcitabine Plus Capecitabine in Patients With Advanced Pancreatic Cancer. J Clin Oncol 2009;27:5513-5518.
14. Sultana A, Smith CT, Cunningham D, et al. Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer. J Clin Oncol 2007;25:2607-15.
15. Sultana A, Tudur Smith C, Cunningham D, et al. Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer: results of secondary end points analyses. Br J Cancer 2008;99:6-13.
16. Sultana A, Tudur Smith C, Cunningham D, et al. Systematic review, including meta-analyses, on the management of locally advanced pancreatic cancer using radiation/combined modality therapy. Br J Cancer 2007;96:1183-90.
17. Mukherjee S, Hurt CN, Bridgewater J, et al. Gemcitabine-based or capecitabine-based chemoradiotherapy for locally advanced pancreatic cancer (SCALOP): a multicentre, randomised, phase 2 trial. Lancet Oncol 2013;14:317-26.
18. Huguet F, Girard N, Guerche CS, et al. Chemoradiotherapy in the management of locally advanced pancreatic carcinoma: a qualitative systematic review. J Clin Oncol 2009;27:2269-77.
19. Sultana A, Ghaneh P, Cunningham D, et al. Gemcitabine based combination chemotherapy in advanced pancreatic cancer-indirect comparison. BMC Cancer 2008;8:192.
20. Burris HA, 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997;15:2403-13.

21. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817-25.
22. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369:1691-703.
23. Mukherjee S, Kocher HM, Hutchins RR, et al. Palliative surgical bypass for pancreatic and peri-ampullary cancers. J Gastrointest Cancer 2007;38:102-7.