

London Cancer

HEPATIC PANCREATIC AND BILIARY (HPB)

FACULTY CLINICAL GUIDELINE

Management of Patients with Pancreatic and Peri-Ampullary Cancer

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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:

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1. MDT coordinator and CNS contact details

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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 staging^{3, 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 180°. SMA encasement, any CA abutment.
 - Pancreatic body/tail—SMA or CA encasement greater than 180°.
 - 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 cholangitis^{1, 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:

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

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 to 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 designation⁶. 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 clearance⁷. Extended lymph node resections are performed in selected cases after discussion at the MDT⁸. 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 2006⁹ and used by the multicenter UK study¹⁰, 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

Dr R Gillmore

Prof T Meyer

Dr G Stewart (clinical oncology)

Royal London Site

Prof T Hagemann

Dr S Slater

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/m², 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/m² infused over 100 min (i.e. 10mg/m²/min), D1, 8 & 15; q28dx6.

3.3. Other options or second line:

Chemoradiotherapy regimens¹⁶⁻¹⁸:

CRT = 45-50.4Gy/28# + concurrent Capecitabine 825-830mg/m²bd Monday-Friday

Or

50.4Gy/28# Gemcitabine 300mg/m² /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/m² po
3. Capecitabine SA (q21, until disease 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/m² IV immediately followed by

D1, 8, 15 Gemcitabine 1000mg/m² IV

4 weekly for 6 cycles

Research Arm Sequential ABX/GEM

D1, 8, 15 Abraxane 125mg/m² IV

D2, 9, 15 IV Gemcitabine 1000mg/m² IV

4 weekly for 6 cycles

CDF options are:

FolFirinOx (q14x12)²¹:

D1 Calcium Folate (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 of 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%)

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