

London Cancer

Hepatic Pancreatic and Biliary (HPB) Faculty

Management of Patients with Pancreatic and Peri- Ampullary Cancer **CLINICAL GUIDELINES**

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These guidelines are based on latest internationally available guidelines for pancreatic and peri-ampullary cancer¹⁻⁴.

This operational policy is agreed and accepted by:

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2 Diagnosis and staging

2.1 NICE guidelines (February 2018) for diagnosis

2.1.1 People with obstructive jaundice

- For people with obstructive jaundice and suspected pancreatic cancer, offer a pancreatic protocol CT scan before draining the bile duct.
- If the diagnosis is still unclear, offer fluorodeoxyglucose-positron emission tomography/CT (FDG-PET/CT) and/or endoscopic ultrasound (EUS) with EUS-guided tissue sampling.
- Take a biliary brushing for cytology if endoscopic retrograde cholangiopancreatography (ERCP) is being used to relieve the biliary obstruction and there is no tissue diagnosis.

2.1.2 People without jaundice who have pancreatic abnormalities on imaging

- Offer a pancreatic protocol CT scan to people with pancreatic abnormalities but no jaundice.
- If the diagnosis is still unclear, offer FDG-PET/CT and/or EUS with EUS-guided tissue sampling.
- If cytological or histological samples are needed, offer EUS with EUS-guided tissue sampling.

2.1.3 People with pancreatic cysts

- Offer a pancreatic protocol CT scan or magnetic resonance cholangiopancreatography (MRI/MRCP) to people with pancreatic cysts. If more information is needed after one of these tests, offer the other one.
- Offer EUS after CT and MRI/MRCP if more information on the likelihood of malignancy is needed, or if it is not clear whether surgery is needed.
- Consider fine-needle aspiration during EUS if more information on the likelihood of malignancy is needed.
- When using fine-needle aspiration, perform carcinoembryonic antigen (CEA) assay in addition to cytology if there is sufficient sample.
- For people with cysts that are thought to be malignant, follow the recommendations on staging.
- Refer people with high-risk features on imaging for resection. Please also refer to the separate guidance on pancreatic cysts from London Cancer.

2.1.4 People with inherited high risk of pancreatic cancer

- Ask people with pancreatic cancer if any of their first-degree relatives has had it. Address any concerns the person has about inherited risk.
- Offer surveillance for pancreatic cancer to people with:
 - hereditary pancreatitis and a PRSS1 mutation
 - BRCA1, BRCA2, PALB2 or CDKN2A (p16) mutations, and one or more first-degree relatives with pancreatic cancer
 - Peutz–Jeghers syndrome.
- Consider surveillance for pancreatic cancer for people with:
 - or more first-degree relatives with pancreatic cancer, across 2 or more generations
 - Lynch syndrome (mismatch repair gene [MLH1, MSH2, MSH6 or PMS2] mutations) and any first-degree relatives with pancreatic cancer.
- Consider an MRI/MRCP or EUS for pancreatic cancer surveillance in people without hereditary pancreatitis.
- Consider a pancreatic protocol CT scan for pancreatic cancer surveillance in people with hereditary pancreatitis and a PRSS1 mutation.
- Do not offer EUS to detect pancreatic cancer in people with hereditary pancreatitis.

2.2 Staging for Pancreatic and Peri-ampullary cancers

- For people with newly diagnosed pancreatic cancer who have not had a pancreatic protocol CT scan, offer a pancreatic protocol CT scan that includes the chest, abdomen and pelvis.
- Offer fluorodeoxyglucose-positron emission tomography/CT (FDG-PET/CT) to people with localised disease on CT who will be having cancer treatment (surgery, radiotherapy or systemic therapy).
- If more information is needed to decide the person's clinical management, consider one or more of the following:
 - MRI, for suspected liver metastases
 - endoscopic ultrasound, if more information is needed for tumour and node staging
 - laparoscopy with laparoscopic ultrasound, for suspected small-volume peritoneal and/ or liver metastases if resectional surgery is a possibility.

2.2.1 NCCN criteria for pancreatic cancer staging^{3,4}

- **Resectable**
 - Absence of distant metastases
 - Arterial: Clear fat planes around celiac artery (CA), superior mesenteric artery (SMA), and hepatic artery (HA)
 - Venous: No superior mesenteric vein (SMV)/portal vein (PV) 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 (locally advanced)**
 - 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/PV 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 cancer.
- 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 now a standard staging modality of pancreatic cancer based on NIHR HTA PET-PANC study (UK CRM 8166).

- 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.

3 Operative management

3.1 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 (> 200 µmol/L), cholangitic, or in whom surgical resection is expected to be significantly delayed.

3.2 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.

Specifically, for pancreatic cancer

- Offer enteric-coated pancreatin for people with unresectable pancreatic cancer.
- Consider enteric-coated pancreatin before and after pancreatic cancer resection.
- Do not use fish oils as a nutritional intervention to manage weight loss in people with unresectable pancreatic cancer.
- For people who have had pancreatoduodenectomy and who have a functioning gut, offer early enteral nutrition (including oral and tube feeding) rather than parenteral nutrition.
- For more guidance on nutrition support, patient should consult a dietician.

3.3 Surgical resection

There are 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 GK Fusai, Mr C Imber, Mr S Rahman, Mr D Sharma

Royal London Site: Mr AT Abraham, Mr Deepak Hariharan (locum), Mr S Bhattacharya, Mr RR Hutchins, Prof HM Kocher, Mr Vincent Yip

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 on a weekly basis (1:5). The Consultants are supported by 24/7 senior fellow/registrars 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 and SCALLOP-II studies. 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.

3.4 Research

All patients to be considered for inclusion in the PCRFB Tissue Bank (www.thepancreastissuebank.org).

4 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

Dr Nikos Diamantis

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:

4.1.1 Adjuvant

- Give people time to recover from surgery before starting adjuvant therapy.
- Start adjuvant therapy as soon as they are well enough to tolerate all 6 cycles.
- Offer adjuvant Folfirinox or gemcitabine plus capecitabine to people who have had sufficient time to recover after pancreatic cancer resection.
- Consider adjuvant gemcitabine for people who are not well enough to tolerate combination chemotherapy.
- For people who have had resection, offer ongoing specialist assessment and care to identify and manage any problems resulting from surgery.
- For people who have new, unexplained or unresolved symptoms after treatment, provide access to specialist investigation and support services.

4.1.2 Locally advanced/borderline resectable

- Only consider neoadjuvant therapy for people with borderline resectable pancreatic cancer either as part of a clinical trial or after MDT discussion (ideally with patients entered into a database/registry).
- Offer systemic combination chemotherapy - ideally within a clinical trial - to people with locally advanced pancreatic cancer who are well enough to tolerate it. Consider gemcitabine for people with locally advanced pancreatic cancer who are not well enough to tolerate combination chemotherapy.

- When using chemoradiotherapy, consider capecitabine as the radiosensitiser. 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).

4.1.3 Metastatic

First line treatment

- Please consider clinical trials that may be open within the Network.
- Offer FOLFIRINOX to people with metastatic pancreatic cancer and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1.
- Consider gemcitabine combination (e.g. gemcitabine and nab-paclitaxel) therapy for people who are not well enough to tolerate FOLFIRINOX.
- Offer gemcitabine to people who are not well enough to tolerate combination chemotherapy.

Second-line treatment

- Consider oxaliplatin-based chemotherapy as second-line treatment for people who have not had first-line oxaliplatin.
- Consider gemcitabine-based chemotherapy as second-line treatment for people whose cancer has progressed after first-line FOLFIRINOX.

5 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. For people with suspected pancreatic cancer who may need their stent removed later on, consider endoscopically placed self-expanding fully covered metal stents.
- 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.

6 Follow-up arrangements & 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.

7 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.

8 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

9 Quality Performance Indicators

1. Median (+ IQR) time of referral by GP/emergency secondary care to curative resection for pancreatic and peri-ampullary cancer (target 62 days)
2. Percentage of patients with cytological/histological diagnosis (target 50%)
3. Percentage of patients undergoing resection (target 15%)
4. Number of patients undergoing curative resection for pancreatic adenocarcinoma without initial stent placement
5. Proportion of attempted pancreatoduodenectomies for peri-ampullary cancer having resection completed (target 80%)
6. Minimum resections per surgeon (target 15)
7. 90-day mortality post-resection (target <5%)
8. Percentage of patients who receive adjuvant treatment after resection (target 50%)
9. Percentage of patients receiving chemo- or radiotherapy, if not eligible for surgical resection and if fit (PS: 0 or 1) (target 50%). (Tempero et al., 2017)
10. Number of patients participating in clinical trials (target 33%)

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NICE Clinical Guidelines (CG):

- NICE CG12. Suspected cancer: recognition and referral. June 2015 Last updated September 2017.
- NICE CG32. Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition. February 2006. Last updated August 2017.
- NICE CG51. Sepsis: recognition, diagnosis and early management. Last updated September 2017.
- NICE CG74. Surgical site infections: prevention and treatment. October 2008. Last updated February 2017.
- NICE CG85. Pancreatic cancer in adults: diagnosis and management. February 2018.
- NICE CG92. Venous thromboembolism: reducing the risk for patients in hospital. January 2010. Last updated June 2015.
- NICE CG100. Alcohol use disorders: diagnosis and management of physical complications. June 2010. Last updated April 2017.
- NICE CG140. Palliative care for adults: strong opioids for pain relief. May 2012. Last updated August 2016.

NICE Technology Appraisal Guidance (TAG):

- NICE TA440. Pegylated liposomal irinotecan for treating pancreatic cancer after gemcitabine. April 2017.
- NICE TA449. Everolimus and sunitinib for treating unresectable or metastatic neuroendocrine tumours in people with progressive disease. June 2017.
- NICE TA476. Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer. September 2017.

Other:

- Improving outcomes: a strategy for cancer. Department of Health, 2011.
- Improving outcomes: a strategy for cancer: assessment of the impact on equalities. Department of Health, 2011.
- The provision of services for upper gastrointestinal surgery. The Association of Upper Gastrointestinal Surgeons, 2016.
- Delivering World-Class Cancer Outcomes: Guidance for Cancer Alliances and the National Cancer Vanguard. NHS England, 2016.
- Dataset for the histopathological reporting of carcinomas of the pancreas, ampulla of Vater and common bile duct. Royal College of Pathologists, 2017.
- Cancer Outcomes and Services Dataset (COSD) Version 8.0 Specification. Public Health England, 2017.

5.2 Other Applicable National Standards to be met by Commissioned Providers

NICE Interventional Procedures Guidance (IPG):

- NICE IPG204. Laparoscopic distal pancreatectomy. January 2007.
- NICE IPG464. Endoscopic bipolar radiofrequency ablation for treating biliary obstruction caused by cholangiocarcinoma or pancreatic adenocarcinoma. September 2013.
- NICE IPG579. Irreversible electroporation for treating pancreatic cancer. May 2017.

NICE Quality Standards (QS):

- NICE QS124. Suspected cancer. June 2016.

NICE Medtech Innovation Briefing (MIB):

- NICE MIB21. The SpyGlass direct visualisation system for diagnostic and therapeutic procedures during endoscopy of the biliary system. February 2015.
- NICE MIB69. Cellvizio confocal endomicroscopy system for characterising pancreatic cysts. June 2016.

International Guidelines:

- International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. Canto MI et al. *Gut* 2013; 62: 339-347.
- Evidence-based Guidelines for the Management of Exocrine Pancreatic Insufficiency After Pancreatic Surgery. Sabater L et al. *Ann Surg* 2016; 264: 949-958.
- Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. Tanaka M et al. *Pancreatology* 2017; 17: 738-753.