**Diagnosis and management of pancreatic cancer in adults: a summary of guidelines from the UK National Institute for Health and Care Excellence**

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**Abstract**

To enable standardisation of care of pancreatic cancer patients and facilitate improvement in other outcomes, the United Kingdom’s National Institute for Health and Care Excellence (NICE) developed a clinical guideline for the diagnosis and management of pancreatic cancer in adults. Systematic literature searches, a systematic review and meta-analysis process were undertaken. Recommendations were drafted on the basis of the group’s interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. There was patient involvement and public consultation. Recommendations were made on the diagnosis; monitoring of inherited high risk; staging; psychological support; pain and nutrition management; and specific management of people with resectable-, borderline-resectable- and unresectable- pancreatic cancer. The guideline committee also made recommendations for future research into neoadjuvant therapy, cachexia interventions, minimally invasive pancreatectomy, pain management and psychological support needs. With these guidelines, NICE wants not just to promote best current practice but equally to support and stimulate research and innovation in pancreatic cancer.

**Introduction**

Pancreatic cancer is the fifth commonest cause of cancer death in the UK, with an annual incidence of nearly 9,600. The UK has one of the worst survival rates in Europe, with average life expectancy on diagnosis of 4 to 6 months and a relative survival to 1 year of approximately 20%. Only 3% of people survive for 5 years or longer. This figure has barely improved in over 50 years; it is not yet clear whether recent trends towards increased surgery and adjuvant chemotherapy will affect survival [1-3].

At diagnosis, only around 8% of people with pancreatic cancer are eligible for potentially curative surgery. However, 5 year survival rates of up to a 30% can be achieved if surgical removal and adjuvant chemotherapy are feasible [4].

Pancreatic cancer symptoms are non-specific. There are often delays in access to diagnosis and treatment (as highlighted in the NHS England Five Year Forward View) [8]. One survey found that 40% of people with pancreatic cancer in England had visited their GP 3 or more times before diagnosis [5]. Fifty per cent of people are diagnosed as an emergency in A&E [6]. Following diagnosis, evidence from the National Cancer Intelligence Network suggests wide variation in practice throughout England [7].

The aim of this guideline is to help reduce the variation in the standard of care received by people with pancreatic cancer and contribute towards other improvement in other outcomes. The authors believe that these observations may have application in other healthcare systems.

**Guideline development methodology**

This guidance was developed using the methodology outlined in the United Kingdom’s National Institute for Health and Care Excellence (NICE) guidelines manual 2014 (PMG 20) [8]. The review questions were drafted by the National Guidelines Alliance, and refined and validated by the committee. A total of 17 questions were identified based on the key areas identified in the guideline scoping exercise.

For intervention reviews; population, intervention, comparator and outcome (PICO) frameworks guided the literature searching process, critical appraisal and synthesis of evidence and facilitated the development of recommendations by the committee. Reviews of diagnostic test accuracy were done using the population, diagnostic test (index tests), reference standard and target condition framework, while qualitative reviews used a population, area of interest and themes of interest framework.

Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions. Databases were searched using relevant medical subject headings, free-text terms and study type filters where appropriate. Only English language studies were reviewed. All searches were conducted in MEDLINE, Embase and The Cochrane Library, with some additional database searching in AMED, PsycINFO and Web of Science Core Collection for certain topic areas. Searches were updated in April 2017. Search strategies were quality assured by cross-checking reference lists of highly relevant papers, analysing search strategies in other systematic reviews and asking the group members to highlight any additional studies. The titles and abstracts of records retrieved by the searches were inspected for relevance, with potentially significant publications obtained in full text and assessed against the inclusion criteria.

A systematic review process was then undertaken. Summaries of evidence were generated by outcome or study where appropriate. For randomised studies; meta-analysis was carried out where appropriate using Cochrane Review Manager (RevMan5) software [9]. When conventional pairwise meta-analyses of direct evidence did not help assess the most effective intervention, a network meta-analysis (NMA) was undertaken. For intervention reviews, the quality of the evidence for outcomes from the included RCTs and observational studies were evaluated and graded using software developed by the GRADE working group (GRADEpro) [10]. For diagnostic studies, data were presented individually by study as measures of diagnostic test accuracy (sensitivity and specificity, positive and negative likelihood ratios) and the QUADAS-2 checklist of bias and applicability was used [11]. For qualitative studies, each study was summarised by theme and meta-synthesis was carried out where appropriate to identify an overarching framework of themes and subthemes and quality was assessed using a checklist for qualitative studies based on the Critical Appraisal Skills Programme (CASP) checklist [8, 12]. Risk of bias for intervention studies was assessed using the Cochrane Risk of Bias tool for randomised control trials [8, 13]. For observational studies, quality was assessed using the Newcastle-Ottawa Scale [8, 14]. Evidence statements were presented by outcome or theme and encompassed the following key features of the evidence: the quality of the evidence (GRADE rating); the number of studies and the number of participants for a particular outcome; a brief description of the participants; the clinical significance of the effect and an indication of its direction (beneficial or harmful); evidence of cost effectiveness in terms of quality-adjusted life-years (QALYs).

Over the course of the guideline development process, the committee was presented with evidence tables of the clinical and economic evidence reviewed from the literature; summaries of clinical and economic evidence and quality assessment; forest plots; and a description of the methods and results of cost-effectiveness analysis. Recommendations were drafted on the basis of the group’s interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. The wording and strength of recommendations was agreed by the group and focused on the actions healthcare professionals need to take (for example the word ‘offer’ was used for strong recommendations and ‘consider’ for weak recommendations). When areas were identified for which good evidence was lacking, the committee made recommendations for future research. This guidance was then subject to a 6-week public consultation.

**Recommendations**

**Diagnosis**

*People with obstructive jaundice*

Review question: What is the most effective diagnostic pathway for adults with suspected pancreatic cancer in secondary care who have jaundice?

**Recommendations:**

**1. For people with obstructive jaundice and suspected pancreatic cancer, offer a pancreatic protocol CT scan before draining the bile duct.**

**2. 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.**

**3. 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.**

Comments: Diagnostic accuracy and adverse events were considered the critical outcomes for all the diagnostic and staging questions. Six observational studies, 1 multicentre prospective cohort study and 5 single-centre retrospective cohort studies were included [15]. The committee noted that all studies, except for FDG-PET/CT [16], had either a serious or a very serious risk of bias due to: different reference standards being used across the study sample; a lack of blinding; the test being evaluated being included in the reference standard (potentially leading to an overestimation of test accuracy); and people inappropriately excluded from the analysis. It had more confidence in the quality of evidence from the report related to FDG-PET/CT [16], because it was the largest multicentre study and the study design was judged to be more robust than that of the other included studies [16]. Given that CT is less invasive than EUS and would capture most positive cases (according to the higher quality evidence) the committee recommended a pancreatic protocol CT scan as the first investigation to diagnose pancreatic cancer as a rule-out test in obstructive jaundice. If biliary drainage is required to relieve jaundice, CT should be done first, as interpretation of the CT scan may be less accurate after stent-placement. For people with uncertain findings after CT scanning, FDG-PET/CT adds significant information, particularly in the detection of metastatic disease. If EUS is used, taking a tissue sample at the same time as EUS is recommended. If an ERCP is performed, biliary brushing for cytology should be done if no tissue diagnosis is established.

*People without jaundice who have pancreatic abnormalities on imaging*

Review question: What is the most effective diagnostic pathway for adults with suspected pancreatic cancer in secondary care who do not have jaundice but have a pancreatic abnormality on imaging?

**Recommendations:**

**4. Offer a pancreatic protocol CT scan to people with pancreatic abnormalities but no jaundice.**

**5. If the diagnosis is still unclear, offer FDG-PET/CT and/or EUS with EUS-guided tissue sampling.**

**6. If cytological or histological samples are needed, offer EUS with EUS-guided tissue sampling.**

Comments: Twenty-one articles reporting a total of 32 datasets were identified: 3 were RCTs, 13 were prospective cohort studies and 5 were retrospective cohort studies [15]. The committee noted that of the investigations with moderate or high quality evidence, EUS had shown the highest sensitivity but the lowest specificity for diagnosing malignancy in a solid lesion suspected to be pancreatic cancer. As other investigations had similar sensitivities but better specificities, they agreed not to make a recommendation about EUS without tissue sampling. While the positive likelihood ratio for CT was not as good as that for EUS-FNA/FNB, CT had a better negative likelihood ratio. As CT is more widely available than EUS-FNA and is non-invasive, the risk of adverse events is lower. Therefore, they recommended a pancreatic protocol CT scan as the first option in people with a solid lesion suspected to be pancreatic cancer as a ruling out test. Although there was no direct evidence on FDG-PET/CT as a diagnostic test for pancreatic solid lesions, the committee believed that the evidence regarding its use in the diagnosis of pancreatic cancer in people with jaundice and without jaundice but with pancreatic abnormalities, such as cysts merited its wider use in the diagnosis of people with solid lesions [16]. The committee noted that EUS with tissue sampling had both high sensitivity and specificity whereas FDG-PET/CT had high sensitivity but lower specificity. They decided that the non-invasive nature of FDG-PET/CT, the low false negative rate and the additional information related to metastatic disease that it can provide, puts FDG-PET/CT alongside EUS with tissue sampling as the next step if further diagnostic information is required after the CT scan.

*People with pancreatic cysts*

Review question: In adults with a pancreatic cyst, what is the diagnostic pathway to identify the cyst(s) at high risk of pancreatic malignancy?

**Recommendations:**

**7. 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.**

**8. Refer people with any of these high-risk features for resection:**

* **obstructive jaundice with cystic lesions in the head of the pancreas**
* **enhancing solid component in the cyst**
* **a main pancreatic duct that is 10 mm diameter or larger.**

**9. 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.**

**10. Consider fine-needle aspiration during EUS if more information on the likelihood of malignancy is needed.**

**11. When using fine-needle aspiration, perform carcinoembryonic antigen (CEA) assay in addition to cytology if there is sufficient sample.**

**12. For people with cysts that are thought to be malignant, follow the recommendations on staging.**

Comments: Thirty-five publications were included in this review: 2 systematic reviews; 6 prospective cohort studies and 27 retrospective cohort studies [15]. There are several limitations with the evidence base: a good proportion of the studies were old and imaging quality has subsequently improved; many did not differentiate between IPMN and mucinous cystic neoplasms; no validated assay for CEA was consistently used across all laboratories; the evidence was very fragmented, due to different descriptions for malignancy, diagnostic gold standard, study design and cyst-type. The committee noted, whilst there was good information on the diagnostic accuracy of investigations to differentiate mucinous cysts from non-mucinous cysts, there was very little about which investigations can accurately identify those mucinous cysts at high risk of becoming pancreatic cancer. MRI had moderate sensitivity and specificity for detecting pancreatic cancer in people with pancreatic cysts. CT had low sensitivity, but high specificity for detecting pancreatic cancer in this population. Both of these investigations are widely available, non-invasive and can provide information on high-risk features of cysts. Despite the evidence that the sensitivity of CT was not equivalent to that of MRI, the committee recommended a pancreatic protocol CT or MRI-MRCP as the initial diagnostic investigation for people with pancreatic cysts as MRI is more expensive than CT, waiting lists are longer and MRI can be contraindicated for some people. If the initial CT or MRI identified any high-risk features, the cyst was likely to become malignant and surgical resection was indicated. In equivocal cases EUS/ FNA could provide additional information to determine whether to operate or not. Although the evidence suggested that FDG-PET/CT may be helpful in both ruling-in and ruling-out malignancy of pancreatic cysts, they did not recommend its use as it would lead to very significant cost-increases given the wide variety of cystic lesions and that they are relatively commonplace. While cyst fluid CEA was not helpful in distinguishing benign from malignant pancreatic cysts it can provide additional useful diagnostic information, therefore, if FNA was undertaken, CEA should also be requested.

*People with inherited high risk of pancreatic cancer*

Review question: What is the most effective monitoring protocol for adults with an inherited high risk of pancreatic cancer in secondary care to ensure early diagnosis?

**13. Ask people with pancreatic cancer if any of their first-degree relatives has had it. Address any concerns the person has about inherited risk.**

**14. 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.**

**15. Consider surveillance for pancreatic cancer for people with:**

* **2 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.**

**16. Consider an MRI/MRCP or EUS for pancreatic cancer surveillance in people without hereditary pancreatitis.**

**17. Consider a pancreatic protocol CT scan for pancreatic cancer surveillance in people with hereditary pancreatitis and a PRSS1 mutation.**

**18. Do not offer EUS to detect pancreatic cancer in people with hereditary pancreatitis.**

Comments: Eighteen articles were identified: 17 concerned screening/surveillance programs, while 1 was a secondary study reporting on the psychological burden/quality of life of participating in a screening program [15]. All 17 primary studies reported diagnostic yield (early diagnosis). For screening or surveillance, there were high quality studies for diagnostic yield and overall survival. The studies reporting adverse events were mostly high quality. The committee acknowledged that the data on survival were too limited to prove a survival benefit of surveillance for people carrying a higher risk of developing pancreatic cancer. However, the data from Vasen et al. were suggestive that surveillance could confer benefits to survival outcomes [17]. A weaker recommendation was made for surveillance in people from a familial pancreatic cancer kindred with at least 2 first degree relations (FDRs) with pancreatic cancer in 2 or more generations and those with mismatch repair gene mutations (Lynch syndrome) and one affected FDR with pancreatic cancer. This is consistent with the current EUROPAC registry entry requirements [18] and the International Cancer of the Pancreas Screening (CAPS) Consortium consensus statement on inherited risk [19]. The committee made a **research recommendation** that work should be undertaken to evaluate the most clinically effective and cost effective initial surveillance tests, additional tests and the frequency of surveillance that produces the greatest diagnostic yield and overall surveillance efficiency.

**Specialist pancreatic multidisciplinary teams (MDT)**

Review question: Does referral of all adults with suspected pancreatic cancer to a specialist MDT for review improve patient management and outcomes?

**Recommendations:**

**19. A specialist pancreatic cancer multidisciplinary team should decide what care is needed, and involve the person with suspected or confirmed pancreatic cancer in the decision. Care should be delivered in partnership with local cancer units.**

Comments: Survival outcomes, proportion of people receiving chemotherapy, entry into clinical trials, resection rates, post-operative mortality, patient satisfaction and quality of life were the critical outcomes for this question. No evidence was identified that met the inclusion criteria for this question. Therefore the committee made recommendations based on their knowledge and experience. They agreed that people with pancreatic cancer have multiple, complex needs which would be optimally managed by early referral to a specialist MDT that ensures a range of opinions by specialists are considered, that there is more access to novel treatments and a greater knowledge of relevant ongoing clinical trials. As there are likely to be some people for whom it would be advantageous for their management to be undertaken by a local MDT, specialist MDT should develop management protocols that can be delivered locally.

**Staging**

Review question: What is the most effective investigative pathway for staging adults with newly diagnosed pancreatic cancer or a non-definitive diagnostic result as resectable, borderline resectable, locally advanced or metastatic disease?

**Recommendations:**

**20. 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.**

**21. 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).**

**22. 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.**

Comments: Thirty-two datasets in 30 observational studies (23 prospective cohort studies and 7 retrospective reviews of prospective databases) were identified [15]. The evidence quality varied: for resectability from very low for CT and EUS, to low for abdominal US and moderate for laparoscopy with LUS and combination CT and EUS; for overall TNM staging, it was low (EUS-FNA and MRI), moderate (CT and FDG-10 PET/CT) or high (CT, EUS and MRI). The committee placed relatively more weight on the findings of one study (of FDG-PET/CT) because it was the largest, multicentre and the study design was judged to be more robust than for other included studies. This study showed that FDG-PET/CT corrected staging in a significant proportion of people; influenced management in 45 percent, and prevented resection in 20 percent of patients scheduled for surgery [16]. The committee agreed that CT, in terms of accessibility, non-invasiveness and ability to image local and distant sites, was the best initial staging investigation. FDG-PET/CT added significant information, particularly in detecting metastatic disease, and would reduce the number of patients having unnecessary surgery or radical local treatment. Therefore, FDG-PET/CT should be offered where disease is localised on CT and cancer treatment is planned. Although this represents a significant change in practice, the evidence showed that FDG-PET/CT is clinically important and cost effective, mostly through reducing unnecessary resections. MRI should be limited to those who have indeterminate liver lesions on CT and FDG-PET/CT and where confirmation of liver metastases will change the treatment plan. The committee agreed that the potential benefits of the recommendations made would be a more effective and streamlined sequence of staging investigations for pancreatic cancer, leading to improved staging and people getting the correct treatment.

**Psychological support**

Review question: What are the specific psychological support needs (including information) of adults who are diagnosed with pancreatic cancer and their families or carers throughout the care pathway?

**Recommendations:**

**23. Throughout the person's pancreatic cancer care pathway, specifically assess the psychological impact of: fatigue; pain; gastrointestinal symptoms (including changes to appetite); nutrition; anxiety; and depression.**

**24. Provide people and their family members or carers (as appropriate) with information and support to help them manage the psychological impact of pancreatic cancer on their lives and daily activities. This should be available on an ongoing basis; relevant to the stage of the person's condition; and tailored to the person's needs.**

Comments: The evidence for this topic was drawn from fourteen studies employing primarily qualitative methodologies to investigate the information and support needs of patients or the family and/or care-givers of people with pancreatic cancer [15]. The committee noted that the majority of studies included in the evidence employed some form of questionnaire or interview to assess patient opinion and experience. In most cases, these were pre-existing, validated tools designed for the purpose of the study. Most studies had small sample sizes. As there is very little evidence about the effective information and support interventions to address the psychological needs of people with pancreatic cancer, they agreed to make a r**esearch recommendation** that a qualitative study should be undertaken to evaluate information and support interventions to address psychological needs at different points in the care pathway for people with pancreatic cancer.

**Pain management**

Review question: What is the role of interventional techniques in the management of pain from pancreatic cancer?

**Recommendations:**

**25. Consider EUS-guided or image-guided percutaneous neurolytic coeliac plexus block to manage pain for people with pancreatic cancer who:**

* **have uncontrolled pancreatic pain or**
* **are experiencing unacceptable opioid adverse effects or**
* **are receiving escalating doses of analgesics.**

**26. Do not offer thoracic splanchnicectomy to people with pancreatic cancer.**

Six RCTs and 1 systematic review involving 6 RCTs were included in the review [15]. The committee made no clinical practice recommendations for several of the comparisons of interest as they considered the quality of the evidence to be insufficient to allow assessment of their benefits and harms for people. They noted that current pain management practice in people with pancreatic cancer is medical management with analgesics. If analgesic control is inadequate or the person has problematic side effects from the analgesia neurolytic coeliac plexus block (NCPB) may be considered, as pain relief, constipation and quality of life appeared to improve. Given the lack of evidence showing effectiveness of thoracic splanchnicectomy, particularly for pain relief, the committee recommended that this procedure should not be performed. As it is not clear if early NCPB is superior to on-demand NCPB, in terms of important outcomes for the patient and duration of effect, the committee made a **research recommendation** that a randomised trial should be undertaken comparing early endoscopic ultrasound-guided NCPB with on-demand EUS-guided NCPB in people with unresectable pancreatic cancer.

**Nutritional management**

Review question: What nutritional interventions are effective for patients with newly diagnosed or recurrent pancreatic cancer?

**Recommendations:**

**27. Offer enteric-coated pancreatin for people with unresectable pancreatic cancer.**

**28. Consider enteric-coated pancreatin before and after pancreatic cancer resection.**

**29. Do not use fish oils as a nutritional intervention to manage weight loss in people with unresectable pancreatic cancer.**

**30. 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.**

Comments: Eleven randomised trials involving nine comparisons were included in the review [15]. Overall, the evidence for the efficacy of particular nutritional interventions is poor as the evidence for the majority of outcomes was ‘Very Low’ or ‘Low’ quality, and the identified comparisons made it difficult to evaluate whether a particular intervention is better or worse than standard care. The evidence for PERT was on people with unresectable PC and showed improvement in nutritional status. Hence, the use of PERT in this group can be recommended. Enteric-coated pancreatin treatment should be used as this was the type used in the identified studies. People with resectable PC would probably benefit from taking PERT (before and after resection) - as they are also likely to have pancreatic enzyme deficiency. Following pancreatoduodenectomy, there were less post-operative complications with enteral nutrition compared with parenteral nutrition but no clinically-important difference in overall survival. Therefore EN rather than PN should be the method of post-operative nutrition; whether oral or tube feeding is superior remains to be determined. Moderate quality evidence showed that fish oils do not reduce weight loss in people with unresectable PC, and therefore should not be used for managing weight loss in this group of patients. The committee agreed to make a **research recommendation** that a cohort study followed by phase II and III studies should be undertaken in people with pancreatic cancer and cachexia or pre-cachexia, to compare cachexia assessment methods and anti-cachexia interventions with standard care.

**Relieving biliary and duodenal obstruction**

*Biliary obstruction*

Review question: What is the optimal treatment of biliary obstruction in adults with newly diagnosed or recurrent pancreatic cancer?

**Recommendations:**

**31. Offer resectional surgery rather than preoperative biliary drainage to people who:**

* **have resectable pancreatic cancer and obstructive jaundice and**
* **are well enough for the procedure and**
* **are not enrolled in a clinical trial that requires preoperative biliary drainage.**

**32. During attempted resection for pancreatic cancer, consider surgical biliary bypass if the cancer is found to be unresectable.**

**33. If biliary drainage is needed in a person who has resectable pancreatic cancer and obstructive jaundice and is not yet fit enough for resectional surgery, offer endoscopically placed self-expanding metal stents.**

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

**35. Offer endoscopically placed self-expanding metal stents rather than surgical biliary bypass to people with unresectable pancreatic cancer.**

Comments: Twenty-two RCTs were included in the review [15]. Several of the studies included non- pancreatic cancer patients. Generally, only studies having at least 66% pancreatic cancer patients were included. The quality of the outcomes for the comparisons identified ranged from very low to moderate. The committee noted, that preoperative biliary drainage was associated with an increased delay to surgery, more complications, more serious complications within 120 days, more hospitalisations and more pre-surgery pancreatitis compared to surgery alone. This evidence together with the economic analysis showing that going straight to surgery was both cost saving and health improving, led to a strong recommendation to offer surgery to people with resectable pancreatic cancer. The committee made a strong recommendation for the use of SEMS, rather than plastic stents because: the time to dysfunction was shorter with plastic stents than SEMS; there was a decrease in stent occlusion and stent migration with SEMS; there was no difference in the prevalence of pancreatitis or cholecystitis with the different types of stent, but the prevalence of cholangitis was lower for SEMS. Overall SEMS was the most cost effective intervention. They agreed that stent-placement should be endoscopic as this is safer than percutaneous insertion and that fully covered metal stents should be considered where stent removal may be required, because removal of uncovered or partially covered metal stents can be very difficult. As endoscopic stenting was associated with improved quality of life compared to surgical bypass, they strongly recommended endoscopic stenting for unresectable pancreatic cancer. Surgical biliary bypass should be considered where pancreatic cancer was deemed unresectable at attempted resection as this would avoid a potential additional stent-insertion procedure.

*Duodenal obstruction*

Review question: What is the optimal treatment of duodenal obstruction?

**Recommendations:**

**36. During attempted resection for head of pancreas cancer, consider prophylactic gastrojejunostomy if the cancer is found to be unresectable.**

**37. If possible, relieve symptomatic duodenal obstruction caused by unresectable pancreatic cancer.**

**38. When deciding between gastrojejunostomy and duodenal stent placement, consider gastrojejunostomy for people with a more favourable prognosis.**

Comments: Six studies –2 RCTs from a recent Cochrane review, and 4 additional RCTs were included in the review [15, 20]. The evidence was either very low or low quality for all outcomes across all comparisons of interest. The committee agreed that it is very important to relieve duodenal obstruction in people with unresectable pancreatic cancer. The evidence indicated a trend that stenting was more effective in the short term whilst gastrojejunostomy was more effective in the longer term, so they recommended both as options with gastrojejunostomy being considered for people with a more favourable prognosis. As duodenal obstruction is known to impair quality of life, they agreed that for people with large tumours, judged especially at risk of duodenal obstruction but otherwise fit, with a relatively good prognosis, prophylactic gastrojejunostomy could be considered, as the benefits outweighed the potential harm of surgical complications.

**Managing resectable and borderline resectable pancreatic cancer**

*Neoadjuvant therapy*

Review question: Is neoadjuvant therapy for people with resectable and borderline resectable pancreatic adenocarcinoma an effective treatment?

**Recommendations:**

**39. Only consider neoadjuvant therapy for people with borderline resectable pancreatic cancer as part of a clinical trial.**

**40. Only consider neoadjuvant therapy for people with resectable pancreatic cancer as part of a clinical trial.**

Comments: Six studies were included in the evidence review: 2 systematic reviews, 1 retrospective review of a prospective database and 3 prospective single-arm phase II clinical trials [15]. The quality of the evidence for the comparison of chemoradiotherapy followed by surgery against surgery alone ranged from very low to moderate across all outcomes. Most of the data came from single-arm studies with no comparator. The committee agreed that the ideal use of neoadjuvant therapy is in clinical trials in order to collect the required comparative data for both resectable and borderline-resectable disease. They made a **research recommendation** that prospective randomised trials should be undertaken to compare preoperative (neoadjuvant) therapy with standard postoperative therapy in resectable pancreatic cancer.

*Surgery*

Review question: What is the most effective surgery (type and extent) for adults with newly diagnosed resectable and borderline resectable pancreatic cancer?

**Recommendations:**

**41. For people having surgery for head of pancreas cancer, consider pylorus-preserving resection if the tumour can be adequately resected.**

**42. Consider standard lymphadenectomy [21] rather than extended lymphadenectomy for people having head of pancreas resection.**

Comments: Sixteen studies were included in this review: 15 systematic reviews/meta-analyses and 1 RCT [15]. The quality of the evidence for comparisons of minimally invasive surgery versus open surgery was very low for all outcomes. The populations included in the studies were not exclusively people with pancreatic cancer. This entailed a high risk of overestimating the benefit of minimally invasive and/or robotic surgery as people with periampullary cancer, benign disease or other malignancies are likely to have better outcomes. Additionally, there was a risk of selection bias as studies included in the review were not randomised trials. The Committee considered it is possible that those selected for surgery represented the proportion of patients considered most likely to benefit from minimal access surgery and therefore have more favourable outcomes. Due to the limitations of evidence, they were unable to determine whether minimally invasive laparoscopic, robotic or open pancreatoduodenectomy or distal pancreatectomy was the most effective. They agreed not to make any recommendations for clinical practice but instead to make a **research recommendation** that prospective randomised trials should be undertaken to compare the effectiveness of minimally invasive pancreatectomy or pancreatoduodenectomy (laparoscopic or robotic) with open pancreatectomy or pancreatoduodenectomy in people with pancreatic cancer. The quality of the evidence comparing pylorus preserving Whipple (PPW) with classic Whipple (CW) was very low to low quality but they recommended PPW based on the evidence that, compared with CW, blood loss and operative time appeared to be reduced, but with no difference in survival. They noted that no survival difference had been shown between standard and extended lymphadenectomy. Based on their clinical experience that extended lymphadenectomy increased morbidity, they recommended standard lymphadenectomy as defined by Tol et al. [21]. The committee acknowledged evidence that portal venous resection to obtain a clear surgical margin (R0) appears safe and is increasingly practiced in high-volume centres. However, given the low quality of this evidence, they agreed not to make recommendations for clinical practice. The quality of the evidence for the comparisons of arterial resection versus no arterial resection and venous resection versus no venous resection was very low for all outcomes. Arterial resection is a high-risk procedure with uncertain benefits, based on the available evidence so they agreed not to make recommendations for clinical practice about this type of surgery.

*Adjuvant treatment*

Review question: What is the most effective adjuvant therapy (chemotherapy, chemoradiotherapy, biological therapy, immunotherapy, combinations of therapies) for adults who have undergone surgical resection of pancreatic adenocarcinoma?

**Recommendations:**

**43. 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.**

**44. Offer adjuvant gemcitabine plus capecitabine to people who have had sufficient time to recover after pancreatic cancer resection.**

**45. Consider adjuvant gemcitabine for people who are not well enough to tolerate combination chemotherapy.**

Comments: Data from seventeen RCTs (n=4617) were included in the review. The committee noted that, on directly relevant evidence, adjuvant gemcitabine plus capecitabine showed the most benefit to overall survival following pancreatic resection [4] and considered the overall survival benefits outweighed the potential for increased toxicity. They made a strong recommendation for this intervention. Where the toxicity of combination therapy may not be tolerated, they agreed to recommend adjuvant gemcitabine monotherapy as this has also shown overall survival benefit. Valle et al’s analysis of ESPAC3 data showed that overall survival favoured people receiving all 6 cycles of adjuvant therapy (compared with only 1-5 cycles) [22] and that delaying adjuvant therapy did not negatively affect outcomes. The committee noted that the clinical evidence from Japan indicates adjuvant S1 is also effective as adjuvant chemotherapy [23]. However as there are differences between the Japanese and European populations, these results may not be directly applicable to a western population. The committee also noted that the data for the use of adjuvant chemoradiotherapy were limited, of very low to low quality and reported a restricted set of outcomes. Consequently they were unable to make recommendations about chemoradiotherapy.

*Follow-up for resected pancreatic cancer*

Review question: What is the optimal follow-up protocol for people with resected pancreatic adenocarcinoma?

**46. For people who have had resection, offer ongoing specialist assessment and care to identify and manage any problems resulting from surgery.**

**47. For people who have new, unexplained or unresolved symptoms after treatment, provide access to specialist investigation and support services.**

Comments: Two studies were included in this review [15]. Evidence was available for the comparisons of follow-up imaging with CT/MRI versus PET, no imaging versus PET and imaging with CT versus symptoms and CA19-9. The evidence for all comparisons was very low quality. The main reasons for follow-up after pancreatic cancer resection are to manage post-operative sequelae, to detect recurrence and to provide psychological support. The committee unanimously agreed, based on their experience and knowledge rather than high quality evidence, that specialist post-operative assessment was essential to achieving this. As new or persistent symptoms following surgery are often a source of concern, additional open access to specialist services should be available to provide information and support. There was no evidence to show whether detecting recurrence improves overall survival. The committee was, therefore, unable to make any recommendations about what tests should be done to detect recurrence, the frequency of testing or the duration of follow-up.

**Managing unresectable pancreatic cancer**

*Locally advanced pancreatic cancer*

Review question: What is the most effective treatment (chemotherapy, chemoradiotherapy, radiotherapy, combination of chemotherapy and chemoradiotherapy, biological therapies or other local therapies) for adults with newly diagnosed or recurrent unresectable locally advanced non-metastatic pancreatic cancer?

**48. Offer systemic combination chemotherapy to people with locally advanced pancreatic cancer who are well enough to tolerate it.**

**49. Consider gemcitabine for people with locally advanced pancreatic cancer who are not well enough to tolerate combination chemotherapy.**

**50. When using chemoradiotherapy, consider capecitabine as the radiosensitiser.**

Comments: Eighteen studies were included in the review: ten phase III RCTs, seven phase II RCTs and 1 prospective cohort study [15]. Based on the results of a NMA and economic analysis the committee agreed that combination chemotherapy was more clinically effective than monotherapy in terms of overall survival and the most cost effective option. The health economic analysis showed FOLFIRINOX was cost effective but there was uncertainty about the clinical data used to inform the model. Therefore they agreed not to make a specific recommendation but noted that the offer of combination chemotherapy allowed FOLFIRINOX to be considered. They also recommended gemcitabine as an option for those unlikely to tolerate combination therapy. Consolidation chemoradiotherapy was found to be relatively safe, improved local control and may be cost effective but survival was not superior to chemotherapy alone. Therefore they agreed that they were unable to make a specific recommendation on the use of consolidation chemoradiotherapy but as there was improved overall survival and less haematological toxicity with capecitabine-based chemoradiotherapy compared with gemcitabine-based chemoradiotherapy, they agreed to recommend capecitabine as the radiosensitiser where chemoradiotherapy is offered. Existing NICE Interventional Procedure guidance on irreversible electroporation for treating pancreatic cancer (IPG579) concluded that current evidence on its safety and efficacy is inadequate and therefore recommended that it should only be used in a research context [24].

*Metastatic pancreatic cancer-*

Review question: What are the most effective interventions for adults with newly diagnosed or recurrent metastatic pancreatic cancer (Chemotherapy, surgery, radiotherapy)?

**51. Offer FOLFIRINOX to people with metastatic pancreatic cancer and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1.**

**52. Consider gemcitabine combination therapy for people who are not well enough to tolerate FOLFIRINOX. For guidance on combination therapy with gemcitabine and nab–paclitaxel, see the NICE technology appraisal guidance on paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer [26].**

**52. Offer gemcitabine to people who are not well enough to tolerate combination chemotherapy.**

**53. Consider oxaliplatin-based chemotherapy as second-line treatment for people who have not had first-line oxaliplatin.**

**54. Consider gemcitabine-based chemotherapy as second-line treatment for people whose cancer has progressed after first-line FOLFIRINOX.**

Comments:

Thirty-nine phase II/III RCTs and 1 network-meta analysis of 23 RCTs were included in this review [15]. A substantial number of studies in the evidence base included mixed locally advanced and metastatic cancer populations, but did not report the subgroups separately. As there is a continuum between locally advanced and metastatic disease, the committee agreed it was appropriate to use evidence with mixed populations but applied more weight to studies having exclusively metastatic populations or reporting that population separately. They noted that high quality evidence showed improvements in overall survival for FOLFIRINOX in metastatic disease with ECOG performance status 0-1, outweighing potential side effects experienced by those fitter people receiving it [26] and made a strong recommendation for its use. For those unlikely to tolerate FOLFIRINOX, evidence for both gemcitabine combination therapy and gemcitabine monotherapy showed improved overall survival and progression free survival in metastatic disease. It was not possible, based on the evidence, to determine the optimal gemcitabine combination therapy. Second-line oxaliplatin-based chemotherapy showed improved progression-free survival but overall survival results were inconsistent. They also agreed to recommend gemcitabine or gemcitabine-based chemotherapy as second line treatment for people progressing on first line FOLFIRINOX, noting that 80% of patients treated in the PRODIG4/ACCORD11 trial of first line FOLFIRINOX received this as second line chemotherapy [26]. Existing NICE guidance states that paclitaxel (as albumin-bound nanoparticles) in combination with gemcitabine is an option for previously untreated metastatic pancreatic cancer if other combination chemotherapies are unsuitable and gemcitabine monotherapy would otherwise be offered [25]. Pegylated liposomal irinotecan (combined with 5‑fluorouracil and leucovorin), is not recommended for treating pancreatic cancer after gemcitabine [27]. Other NICE guidance recommends considering venous thromboembolism prophylaxis with low-molecular-weight heparin during chemotherapy for pancreatic cancer [28]. The committee also made a **research recommendation** that a randomised phase II feasibility study be undertaken comparing surgery/ablative treatment (combined with chemotherapy) against chemotherapy in hepatic oligometastatic potentially resectable pancreatic cancer.

**Conclusion**

These NICE guidelines encompass evidence-based recommendations on diagnosis; monitoring inherited high-risk; staging; psychological support; pain and nutrition management; and management of resectable, borderline resectable and unresectable pancreatic cancer.

The guideline committee often drew upon their knowledge of existing guidelines on pancreatic cancer. Examples include the International Study Group on Pancreatic Surgery and the National Comprehensive Cancer Network (NCCN), whose definitions of standard versus extended lymphadenectomy [21] and resectable versus borderline resectable tumours [29] respectively, were adopted. There is much concordance with other recent practice guidelines, such as those of the NCCN [29] and the European Society for Medical Oncology (ESMO) [30] but inevitably some divergence will exist, depending on the weight that guideline committee members place on the strength and quality of evidence. One example is neoadjuvant therapy. The ESMO recommendation for borderline resectable pancreatic cancer is “a period of chemotherapy (gemcitabine or FOLFIRINOX) followed by chemoradiation and then surgery” while NCCN assumes planned neoadjuvant therapy for this group, albeit with the rider that “there is limited evidence to recommend specific neoadjuvant regimens off study” [29, 30]. Although theoretically attractive, there is not yet a single phase 3 RCT of neoadjuvant therapy in full publication, so the NICE committee took the view that until then, they would recommend this approach only in the context of existing clinical trials, boosted by a research recommendation for further studies. If a neoadjuvant approach ultimately proves superior, our guideline will be adjusted.

Putting recommendations into practice can take time but implementing change is most effective when aligned with local priorities. Some, such as changes in prescribing practice should be shared quickly because healthcare professionals should use guidelines to guide their work - as is required by professional regulating bodies. Different organisations may need different approaches to implementation and NICE has produced tools and resources to help put this guideline into practice [31]. Pointers to help put NICE guidelines on pancreatic cancer into practice include: raising awareness through routine communication channels; identify a lead with an interest in the topic to champion the guideline; carry out a baseline assessment against the recommendations; think about what data you need to measure improvement; develop an action plan; include milestones and a business case, for big changes (such as incorporating FDG-PET CT into staging) which will set out additional costs, savings and possible areas for disinvestment; implement the action plan with oversight from the lead and the project group; review and monitor how well the guideline is being implemented and share progress with those involved in making improvements, as well as relevant boards and local partners.

The guideline committee wanted not just to promote best current practice but equally to support and stimulate research and innovation in pancreatic cancer. The guideline committee has made recommendations for research on neoadjuvant therapy, cachexia, minimal-access surgery, pain management and psychological support, and on other topics, where evidence to underpin key practice questions is lacking but essential to improve outcomes for people with pancreatic cancer.

The full guidance, supporting evidence, and tools and resources are available at: <https://www.nice.org.uk/guidance/ng85>

This guideline is due for review in February 2021.

**Conflict of interests:**

The details of declared interests and the actions taken are shown in the Committee Member List in accordance with the NICE conflict of interest policy. (provide www.link)

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