COLLEGE OF ONCOLOGY

National Clinical Practice Guidelines

Pancreatic Cancer

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Continue

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PANCREATIC CANCER

PANCREATIC CANCER

General algorithm

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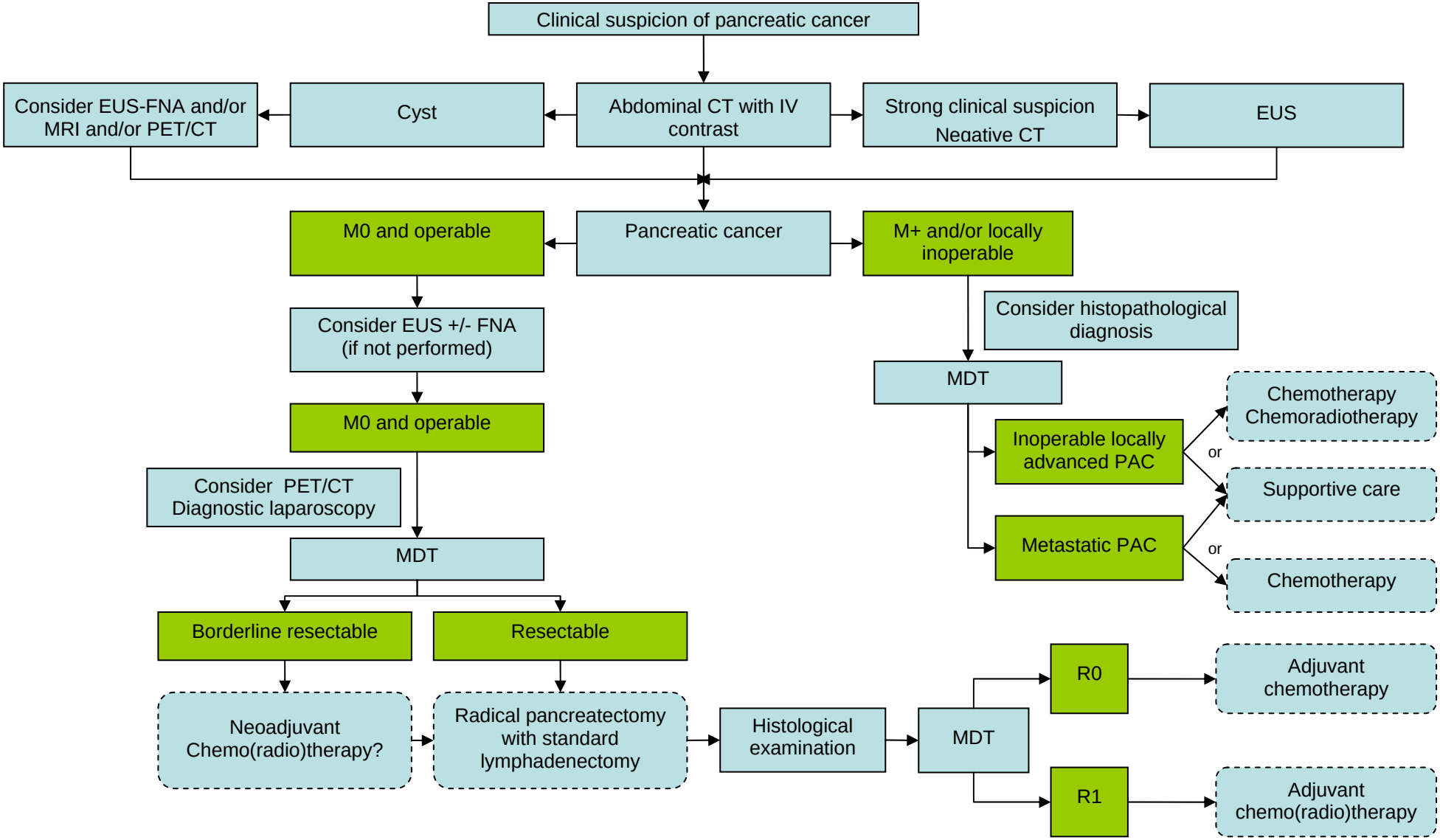

National Guidelines Pancreatic Cancer

INTRODUCTION

This document provides an overview of the clinical practice guidelines for pancreatic cancer and covers a broad range of topics: screening, diagnosis, staging, treatment, supportive therapy, and follow-up. The guideline primarily concerns individuals with primary exocrine and ductal pancreatic cancer, including cystic tumours and intraductal papillary mucinous tumours (IPMT). For more in-depth information and the scientific background, we would like to ask the readers to consult the full scientific report at www.kce.fgov.be.

The guidelines are developed by a panel of experts (see 'expert panel') comprising clinicians of different specialties and were reviewed by relevant professional associations (see 'external reviewers')

The guidelines are based on the best evidence available at the time they are derived (date restriction 2001-2008). The aim of these guidelines is to assist all care providers involved in the care of patients with pancreatic cancer.

SEARCH FOR EVIDENCE

Clinical practice guidelines

Sources

A broad search of electronic databases (Medline, EMBASE), specific guideline websites and websites of oncologic organisations (Table 1) was conducted in February 2008.

In- and exclusion criteria

Both national and international clinical practice guidelines (CPGs) on pancreatic cancer were searched. A language (English, Dutch, French) and date restriction (2001 – 2008) were used. CPGs without references were excluded, as were CPGs without clear recommendations.

Additional evidence

For each clinical question, the evidence – identified through the included CPGs – was updated by searching Medline and the Cochrane Database of Systematic Reviews, DARE, and the proceedings of the annual meetings of the American Society of Clinical Oncology (ASCO) from the search date of the CPG on (search date May-August 2008).

Grade of recommendation

A grade of recommendation was assigned to each recommendation using the GRADE system (Table 2).

EPIDEMIOLOGY

Pancreatic cancer is the fifth leading cause of cancer-related death in Western countries [1]. In 2004, pancreatic cancer was the fourth and fifth most frequent cause of cancer-related death in males (n = 674; 4.6%) and females (n = 627; 5.5%) respectively in Belgium [2].

Pancreatic cancer is the most fatal of all major cancers, with a median survival time of around 6 months and a 5-year relative survival of 5.1% [3]. Although survival rates are highest (21%) when the tumour is localised at diagnosis, less than 10% of tumours are detected at an early stage [3].

Pancreatic cancer is very rare in the first 5 decades of life. After the age of 60, however, incidence rates increase exponentially, peaking in the seventh to eighth decades (56.1 per 100 000 person-years in persons older than 60 years vs. 2.7 per 100 000 person-years in younger age categories) [4].

Men have higher incidence and mortality rates than women. Incidence and mortality rates of pancreatic cancer show also important regional disparities. Pancreatic cancer rates are higher in more developed regions, such as Northern America, Europe and Australia, and lower in less developed countries. In Europe, the highest incidence is found in Latvia, Estonia, Austria, Italy and Denmark, whereas the lowest incidence is found in Sweden, The Netherlands and Belgium.

In Belgium, the crude incidence rate of pancreatic cancer rose from 7.4 per 100 000 males in 1999 to 10.2 per 100 000 males in 2005, and from 7.6 per 100 000 females in 1999 to 9.6 per 100 000 females in 2005. Age standardised incidence increased by 5.4% and 7.3% per year (1999-2005) for males and females respectively. Compared with incidence rates from The Netherlands between 1999 and 2005, Belgian rates remained lower (probably due to underreporting), but followed the same upwards trend.

SCREENING

Mass screening [5-6]

- Mass screening for pancreatic cancer is not recommended ***(2C recommendation)***.

Surveillance for patients at high-risk [7-14]

Candidates for pancreatic cancer surveillance are:

- 3 first-degree, second-degree, or third-degree relatives with pancreatic cancer in the same lineage;
- Known mutation carrier for BRCA1, BRCA2 or p16, with at least one first-degree or second-degree relative with pancreatic cancer;
- A member, ideally a verified germ line carrier, of a Peutz-Jeghers Syndrome kindred;
- Two relatives in the same lineage (directly connected) affected with pancreatic cancer, at least one a first-degree relative of the candidate;
- An affected individual with hereditary pancreatitis.

- Surveillance of persons at high risk of developing pancreatic cancer should only be performed within the context of peer-reviewed protocols ***(expert opinion)***.

DIAGNOSIS

History and physical exam [15-16]

- Diagnosis of pancreatic cancer should be considered with the presence of the following risk factors: adult-onset diabetes without predisposing features or family history of diabetes, jaundice, unexplained pancreatitis, rapid weight loss and unexplained back pain ***(expert opinion)***.

Conventional imaging, serum tumour markers, cyst fluid analysis, ERCP, PET-scan [17-66]

- In addition to a history taking and clinical examination, all patients with clinically suspected pancreatic cancer should undergo diagnostic imaging with abdominal CT ***(1B recommendation)***.
- In patients with a high suspicion of pancreatic cancer and a negative CT scan, an EUS is recommended ***(1B recommendation)***.
- When tissue diagnosis of pancreatic cancer is needed to guide treatment, imaging-guided FNA is recommended ***(1B recommendation)***.
- Diagnostic imaging with US, MRI, ERCP or PET scan should be considered in specific cases (see text) of clinically suspected pancreatic cancer ***(1C recommendation)***.
- Serum tumour markers are not part of the routine diagnostic work-up of patients with clinically suspected pancreatic cancer ***(1C recommendation)***.
- EUS-guided cyst fluid analysis, including cytology, amylase and CEA, can be useful in the differential diagnosis between benign and (pre)malignant pancreatic cysts ***(2C recommendation)***.

STAGING [17,18,20,21,25,59,61,66-73]

- In patients with pancreatic cancer, abdominal CT with intravenous contrast should be performed routinely. The liver should at least be imaged in the arterial and portal venous phase ***(1B recommendation)***.
- In selected patients with pancreatic cancer, EUS and diagnostic laparoscopy can be considered ***(2C recommendation)***.
- In patients with pancreatic cancer with an option for curative treatment after conventional staging, PET(/CT) scan may be considered for the staging of lymph nodes (loco-regional, distal or all lymph nodes) and distant sites other than lymph nodes ***(2C recommendation)***.
- Ultrasonography and MRI are not routinely recommended as staging procedures in patients with pancreatic cancer, but can be considered in specific cases ***(2C recommendation)***.
- In patients with pancreatic cancer, the results of the diagnostic and staging workup should be discussed during a multidisciplinary team meeting to guide further treatment ***(expert opinion)***.

NEOADJUVANT TREATMENT [74-81]

- Neoadjuvant treatment is not recommended in patients with resectable pancreatic cancer outside clinical trials ***(2C recommendation)***.
- In patients with borderline resectable locally advanced pancreatic cancer, treatment with chemotherapy or chemoradiotherapy can be considered. Evaluation of resectability is recommended after 2 – 3 months ***(2C recommendation)***.

SURGICAL TREATMENT WITH CURATIVE INTENT

Preoperative biliary drainage [82-88]

- Preoperative biliary drainage is not routinely recommended in patients with resectable pancreatic cancer and obstructive jaundice ***(1B recommendation)***.

Radical pancreatic resection and lymphadenectomy

Resectability criteria [89-98]

Resectable tumours
No distant metastases Clear fat plane around celiac and superior mesenteric arteries (SMA) Patent * superior mesenteric vein (SMV)/ portal vein
Borderline resectable tumours
Head/body Severe unilateral SMV/portal impingement * Tumour abutment * on SMA Gastroduodenal artery encasement * up to origin at hepatic artery Tumours with limited involvement of the inferior vena cava (IVC) SMV occlusion, if of a short segment, with open vein both proximally and distally Colon or mesocolon invasion *Tail* Adrenal, colon or mesocolon, or kidney invasion
Unresectable tumours
Distant metastases Metastases to lymph nodes beyond the field of resection *Head* SMA, celiac encasement SMV/portal occlusion Aortic, IVC invasion or encasement Invasion of SMV below transverse mesocolon [$] *Body* SMA, celiac, hepatic encasement SMV/portal occlusion Aortic invasion *Tail:* SMA, celiac encasement Rib, vertebral invasion

* No uniform and generally accepted definition exists for patency, impingement, abutment or encasement.

[$] I.e. bifurcation of the splanchnic branches.

Resectable and borderline resectable tumors [29,99-102]

The different lymph node stations and the definitions of standard, radical and extended radical lymphadenectomy are listed in Table 3.

- Patients with resectable pancreatic cancer who are fit for surgery should undergo radical pancreatic resection (pancreaticoduodenectomy for pancreatic head tumours, distal pancreatectomy for pancreatic body and tail tumours) and standard lymphadenectomy with the intent of a R0 resection ***(1C recommendation)***.

- Radical and extended radical lymphadenectomy are not recommended during pancreatic resection ***(1B recommendation)***.
- Pancreatic resection with arterial reconstruction is not recommended in patients with pancreatic cancer in whom major arteries (arteria hepatica, arteria mesenterica superior, truncus coeliacus) are involved ***(2C recommendation)***.
- Venous invasion is not a contra-indication for surgery ***(2C recommendation).***
- In left-sided tumours, local invasion of the splenic artery and/or vein is not a contraindication for resection ***(expert opinion)***.

Reconstruction after pancreaticoduodenectomy

Pylorus preservation versus antrectomy [104-106]

- The choice between standard and pylorus-preserving pancreaticoduodenectomy (PD), both equivalent techniques, should be based on individual surgeon preference ***(1B recommendation)***.

Pancreaticoenteric anastomosis [107-116]

- The choice between pancreaticojejunostomy and pancreaticogastrostomy, both equivalent techniques of pancreatic anastomosis after pancreaticoduodenectomy, should be based on individual surgeon preference ***(1B recommendation)***

Role of laparoscopy [72]

- Laparoscopic pancreatic resection with curative intent is strictly investigational ***(2C recommendation)***.

Relation volume-outcome [117-119]

- Pancreatic oncologic surgery should be restricted to high-volume centres in which a multidisciplinary expertise and adequate facilities are available ***(1C recommendation)***.

HISTOPATHOLOGIC EXAMINATION

Specimen handling/gross and microscopic examination/frozen section diagnosis [21,120-145]

- A standardized protocol for the examination of a pancreatic carcinoma resection specimen is recommended ***(1C recommendation)***.
- The retroperitoneal margin of the pancreas should be inked before fixation of the resection specimen ***(expert opinion)***.
- In the literature, no consensus exists on the definition of a R0 resection. In the present guideline, margins histologically positive for disease or with cancer at less than 1 mm from a margin are considered not to be a R0 resection ***(expert opinion)***.
- Gross examination of the resection specimen includes ***(1C recommendation)*** :
  - the measurement of all components;
  - the description of the presence of a tumour;
  - the tumour site and probable site of origin;
  - tumour size (at least maximum diameter);
  - number of lymph nodes;
  - distance to the nearest margin.

- Microscopic examination includes ***(1C recommendation)*** :
  - histological type;
  - tumour differentiation;
  - tumour size;
  - status of the margins;
  - lymph node status;
  - presence of local invasion;
  - presence of vascular or perineural invasion;
  - presence of distal spread.

Staging systems [146,147]

Currently, two different staging systems are available for the classification of pancreatic tumours: the International Union Against Cancer (UICC) or TNM classification (Table 4 and 5) and the Japanese Pancreas Society (JCS) classification (Table 6).

- In view of the widespread use in Europe, the use of the UICC classification is recommended for the staging of pancreatic cancers in Belgium.

ADJUVANT TREATMENT [74,135,148-155]

- Postoperative chemotherapy with single-agent gemcitabine is recommended for patients with R0 and R1 resected pancreatic cancer ***(1B recommendation)***.
- Postoperative radiotherapy alone cannot be recommended in patients with R0 and R1 resected pancreatic cancer ***(expert opinion)***.

FOLLOW-UP AFTER CURATIVE TREATMENT [156-161]

- In patients with curatively treated pancreatic cancer, surveillance visits are recommended every 3 – 6 months. Technical examinations should be limited to a minimum in asymptomatic patients ***(expert opinion)***.

PALLIATIVE TREATMENT [154,162-222]

- In patients with metastatic pancreatic cancer and a good performance status, chemotherapy (gemcitabine alone or gemcitabine combined with erlotinib) is recommended ***(1B recommendation)***.
- In patients with inoperable locally advanced pancreatic cancer, chemotherapy is recommended. Based on an evaluation after 2 – 3 months, addition of radiotherapy can be considered ***(expert opinion)***.
- In patients with inoperable pancreatic cancer (based on imaging) and obstructive jaundice, treatment with metal stents is recommended ***(1A recommendation)***.

SUPPORTIVE TREATMENT

Patients undergoing surgical resection

Nutrition [223-234]

- In patients undergoing pancreaticoduodenectomy, a preoperative enriched nutritional oral diet should be considered ***(1B recommendation)***.
- Patients undergoing surgery for pancreatic cancer should be considered for early postoperative nutritional support preferably by the enteral route ***(1B recommendation)***.
- In patients undergoing surgery for pancreatic cancer, immunomodulatory diets are not routinely recommended ***(1A recommendation)***.

Prevention of postoperative pancreas-related complications [107,235-246]

- Prophylactic treatment with somatostatin or somatostatin analogues should not be administered routinely, but may be considered in high-risk patients undergoing pancreatic resection ***(2B recommendation)***.
- Patients with symptomatic exocrine pancreatic insufficiency after radical pancreatic resection should be supplemented with pancreatic enzymes ***(expert opinion)***.

Patients with inoperable disease

- Optimal palliative and symptomatic treatment is recommended in all patients with inoperable pancreatic cancer ***(expert opinion)***.

Nutrition [247-252]

- In patients with advanced pancreatic cancer who have lost weight or who are anorexic, nutritional advice should be considered ***(1C recommendation)***.
- Control of symptoms such as pain, nausea, vomiting and diarrhoea should be considered, to enable patients to maintain an oral intake in a form appropriate to their condition ***(expert opinion)***.

Enzyme replacement therapy [244]

- Pancreatic enzyme replacement therapy can be considered for patients with inoperable advanced pancreatic cancer and proved steatorrhoea ***(2C recommendation)***.

Pain [253-257]

- A three-step approach of pain drug administration (WHO analgesic ladder) should be followed in patients with pain associated with pancreatic cancer ***(expert opinion)***.
- Neurolytic celiac plexus block (NCPB) is a treatment option in patients with pancreatic cancer and severe upper abdominal pain that is unresponsive to other analgesic measures ***(1A recommendation)***.

Psychological support [258]

- Patients with pancreatic cancer should be offered specific psychological support from professionals belonging to the multidisciplinary team ***(1C recommendation)***.

RECURRENT DISEASE [259-264]

In patients with recurrent disease presenting with metastases, the same principles are applicable as discussed in the section on palliative treatment. In these patients, chemotherapy has a central role.

ADDENDUM: INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS (IPMN) [24,100,145]

IPMNs represent a well-defined clinical and pathologic entity, separated into different categories according to the degree of cytoarchitectural atypia (Table 7). On the basis of the anatomic involvement of the pancreatic duct, IPMNs can be subclassified into 'main duct types' (predominant involvement of the main pancreatic duct, 'branch duct types' (predominant involvement of the secondary pancreatic ducts) or 'mixed types'. Branch duct types are known to be less aggressive than main duct IPMNs, with malignancy associated with up to 70% of main duct IPMNs compared to 25% of branch duct types.

Both diagnosis and staging of IPMNs are challenging. For the visualisation of the ductal system, MRCP followed by dynamic MRI is the radiologic test of choice in patients with IPMN. To evaluate extrapancreatic invasion and resectability of invasive IPMNs, abdominal CT is recommended. In case of diagnostic uncertainty, EUS can be considered.

Treatment of IPMNs is difficult, and should be restricted to specialised teams, involving oncologists, gastroenterologists, pathologists and surgeons. In the absence of RCTs, it is difficult to provide clear-cut recommendations. In selected cases (asymptomatic non-invasive branch duct IPMNs sized < 3cm, no mural nodules, normal pancreatic duct; poor surgical candidates; older patients) 'watchful waiting' can be considered. However, for patients with IPMN who are fit for surgery, surgical resection should be considered and discussed at the multidisciplinary team meeting.

Since recurrence occurs in 50 – 65% of patients after resection of invasive IPMN, long-term follow-up is recommended.

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References

[1] Ghadirian P, Lynch H, Krewski D. Epidemiology of pancreatic cancer: an overview. Cancer Detection & Prevention. 2003;27:87-93.

[2] Belgian Cancer Registry. Cancer Incidence in Belgium, 2004-2005. Brussels: Fondation Registre du Cancer; 2008.

[3] Ries LAG, Melbert D, Krapcho M, Stinchcomb DG, Howlader N, Horner MJ, et al. SEER Cancer Statistics Review, 1975-2005. 2008 2007 [cited 2008 12-10-2008]; Available from: http://seer.cancer.gov/csr/1975_2005/

[4] Zhang J, Dhakal I, Yan H, Phillips M, Kesteloot H. Trends in pancreatic cancer incidence in nine SEER Cancer Registries, 1973–2002. Ann Oncol. 2007;18:1268-79.

[5] U.S. Preventive Services Task Force. Screening for Pancreatic Cancer. *Recommendation Statement*. Rockville: AHRQ 2004.

[6] Kim J-E, Lee KT, Lee JK, Paik SW, Rhee JC, Choi KW. Clinical usefulness of carbohydrate antigen 19-9 as a screening test for pancreatic cancer in an asymptomatic population.[see comment]. J Gastroenterol Hepatol. 2004;19(2):182-6.

[7] Brand RE, Lerch MM, Rubinstein WS, Neoptolemos JP, Whitcomb DC, Hruban RH, et al. Advances in counselling and surveillance of patients at risk for pancreatic cancer. Gut. 2007;56(10):1460-9.

[8] Canto MI, Goggins M, Hruban RH, Petersen GM, Giardiello FM, Yeo C, et al. Screening for early pancreatic neoplasia in high-risk individuals: a prospective controlled study. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2006 Jun;4(6):766-81.

[9] Canto MI, Goggins M, Yeo CJ, Griffin C, Axilbund JE, Brune K, et al. Screening for pancreatic neoplasia in high-risk individuals: an EUS-based approach. Clinical Gastroenterology & Hepatology. 2004;2(7):606-21.

[10] Tamm EP, Loyer EM, Faria SC, Evans DB, Wolff RA, Charnsangavej C. Retrospective analysis of dual-phase MDCT and follow-up EUS/EUS-FNA in the diagnosis of pancreatic cancer. Abdom Imaging. 2007;32(5):660-7.

[11] Mortensen MB, Fristrup C, Holm FS, Pless T, Durup J, Ainsworth AP, et al. Prospective evaluation of patient tolerability, satisfaction with patient information, and complications in endoscopic ultrasonography. Endoscopy. 2005 Feb;37(2):146-53.

[12] Topazian M, Enders F, Kimmey M, Brand R, Chak A, Clain J, et al. Interobserver agreement for EUS findings in familial pancreatic-cancer kindreds. Gastrointest Endosc. 2007 Jul;66(1):62-7.

[13] Grocock CJ, Vitone LJ, Harcus MJ, Neoptolemos JP, Raraty MGT, Greenhalf W. Familial pancreatic cancer: a review and latest advances. Advances in medical sciences. 2007;52:37-49.

[14] Rulyak SJ, Kimmey MB, Veenstra DL, Brentnall TA. Cost-effectiveness of pancreatic cancer screening in familial pancreatic cancer kindreds. Gastrointest Endosc. 2003;57(1):23-9.

[15] Palsson B, Masson P, Andren-Sandberg A. Tumour marker CA 50 levels compared to signs and symptoms in the diagnosis of pancreatic cancer. Eur J Surg Oncol. 1997 Apr;23(2):151-6.

[16] Li Q, Gao C, Li H, Juzi JT, Chen H, Hao X. Factors associated with survival after surgical resection in Chinese patients with ductal adenocarcinoma of the pancreatic head. Dig Surg. 2008;25(2):87-92.

[17] Bipat S, Phoa SSKS, van Delden OM, Bossuyt PMM, Gouma DJ, Lameris JS, et al. Ultrasonography, computed tomography and magnetic resonance imaging for diagnosis and determining resectability of pancreatic adenocarcinoma: a meta-analysis. 2005 Jul-Aug;29(4):438-45.

[18] Dewitt J, Devereaux BM, Lehman GA, Sherman S, Imperiale TF. Comparison of endoscopic ultrasound and computed tomography for the preoperative evaluation of pancreatic cancer: a systematic review. 2006 Jun;4(6):717-25; quiz 664.

[19] Bang S, Chung HW, Park SW, Chung JB, Yun M, Lee JD, et al. The clinical usefulness of 18-fluorodeoxyglucose positron emission tomography in the differential diagnosis, staging, and response evaluation after concurrent chemoradiotherapy for pancreatic cancer. J Clin Gastroenterol. 2006 Nov-Dec;40(10):923-9.

[20] Heinrich S, Goerres GW, Schafer M, Sagmeister M, Bauerfeind P, Pestalozzi BC, et al. Positron emission tomography/computed tomography influences on the management of resectable pancreatic cancer and its cost-effectiveness. Ann Surg. 2005 Aug;242(2):235-43.

[21] Imbriaco M, Smeraldo D, Liuzzi R, Carrillo F, Cacace G, Vecchione D, et al. Multislice CT with single-phase technique in patients with suspected pancreatic cancer. La Radiologia medica. 2006 Mar;111(2):159-66.

[22] Okamoto Y, Kawamoto H, Takaki A, Ishida E, Ogawa T, Kuwaki K, et al. Contrast-enhanced ultrasonography depicts small tumor vessels for the evaluation of pancreatic tumors. Eur J Radiol. 2007 Jan;61(1):163-9.
[23] Rickes S, Wermke W. Differentiation of cystic pancreatic neoplasms and pseudocysts by conventional and echo-enhanced ultrasound. J Gastroenterol Hepatol. 2004 Jul;19(7):761-6.
[24] Belyaev O, Seelig MH, Muller CA, Tannapfel A, Schmidt WE, Uhl W. Intraductal papillary mucinous neoplasms of the pancreas. 2008 Mar;42(3):284-94.
[25] Ruf J, Lopez Hanninen E, Bohmig M, Koch I, Denecke T, Plotkin M, et al. Impact of FDG-PET/MRI image fusion on the detection of pancreatic cancer. Pancreatology. 2006;6(6):512-9.
[26] Zhong L, Yao Q-Y, Li L, Xu J-R. Imaging diagnosis of pancreato-biliary diseases: a control study. World J Gastroenterol. 2003 Dec;9(12):2824-7.
[27] Calvo MM, Bujanda L, Calderon A, Heras I, Cabriada JL, Bernal A, et al. Comparison between magnetic resonance cholangiopancreatography and ERCP for evaluation of the pancreatic duct. Am J Gastroenterol. 2002 Feb;97(2):347-53.
[28] Glasbrenner B, Schwarz M, Pauls S, Preclik G, Beger HG, Adler G. Prospective comparison of endoscopic ultrasound and endoscopic retrograde cholangiopancreatography in the preoperative assessment of masses in the pancreatic head. Dig Surg. 2000;17(5):468-74.
[29] Hocke M, Schulze E, Gottschalk P, Topalidis T, Dietrich CF. Contrast-enhanced endoscopic ultrasound in discrimination between focal pancreatitis and pancreatic cancer. World J Gastroenterol. 2006 Jan 14;12(2):246-50.
[30] Legmann P, Vignaux O, Dousset B, Baraza AJ, Palazzo L, Dumontier I, et al. Pancreatic tumors: comparison of dual-phase helical CT and endoscopic sonography. AJR American journal of roentgenology. 1998 May;170(5):1315-22.
[31] Nakaizumi A, Uehara H, Iishi H, Tatsuta M, Kitamura T, Kuroda C, et al. Endoscopic ultrasonography in diagnosis and staging of pancreatic cancer. Dig Dis Sci. 1995 Mar;40(3):696-700.
[32] Rocca R, Daperno M, Crocella L, Lavagna A, Salvetto M. Endoscopic ultrasound-fine needle aspiration (EUS-FNA) for pancreatic lesions: effectiveness in clinical practice. 2007 Aug;98(4):339-42.
[33] Rosch T, Lorenz R, Braig C, Feuerbach S, Siewert JR, Schusdziarra V, et al. Endoscopic ultrasound in pancreatic tumor diagnosis. Gastrointest Endosc. 1991 May-Jun;37(3):347-52.
[34] Becker D, Strobel D, Bernatik T, Hahn EG. Echo-enhanced color- and power-Doppler EUS for the discrimination between focal pancreatitis and pancreatic carcinoma. 2001 Jun;53(7):784-9.
[35] Saftoiu A, Popescu C, Cazacu S, Dumitrescu D, Georgescu CV, Popescu M, et al. Power Doppler endoscopic ultrasonography for the differential diagnosis between pancreatic cancer and pseudotumoral chronic pancreatitis. 2006 Mar;25(3):363-72.
[36] Micames C, Jowell PS, White R, Paulson E, Nelson R, Morse M, et al. Lower frequency of peritoneal carcinomatosis in patients with pancreatic cancer diagnosed by EUS-guided FNA vs. percutaneous FNA. Gastrointest Endosc. 2003 Nov;58(5):690-5.
[37] Eloubeidi MA, Varadarajulu S, Desai S, Shirley R, Heslin MJ, Mehra M, et al. A prospective evaluation of an algorithm incorporating routine preoperative endoscopic ultrasound-guided fine needle aspiration in suspected pancreatic cancer. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2007 Jul;11(7):813-9.
[38] Fritscher-Ravens A, Topalidis T, Bobrowski C, Krause C, Thonke E, Jackle S, et al. Endoscopic ultrasound-guided fine-needle aspiration in focal pancreatic lesions: a prospective intraindividual comparison of two needle assemblies. 2001 Jun;33(6):484-90.
[39] Gress F, Gottlieb K, Sherman S, Lehman G. Endoscopic ultrasonography-guided fine-needle aspiration biopsy of suspected pancreatic cancer. Annals of internal medicine. 2001;134(6):459-64.
[40] Harewood GC, Wiersema MJ. Endosonography-guided fine needle aspiration biopsy in the evaluation of pancreatic masses. Am J Gastroenterol. 2002 Jun;97(6):1386-91.
[41] Horwhat JD, Paulson EK, McGrath K, Branch MS, Baillie J, Tyler D, et al. A randomized comparison of EUS-guided FNA versus CT or US-guided FNA for the evaluation of pancreatic mass lesions.[see comment]. 2006 Jun;63(7):966-75.
[42] Iglesias-Garcia J, Dominguez-Munoz E, Lozano-Leon A, Abdulkader I, Larino-Noia J, Antunez J, et al. Impact of endoscopic ultrasound-guided fine needle biopsy for diagnosis of pancreatic masses. World J Gastroenterol. 2007 Jan 14;13(2):289-93.
[43] Mishra G. DNA analysis of cells obtained from endoscopic ultrasound-fine needle aspiration in pancreatic adenocarcinoma: Fool's Gold, Pandora's Box, or Holy Grail? Am J Gastroenterol. 2006 Nov;101(11):2501-3.
[44] Goonetilleke KS, Siriwardena AK. Systematic review of carbohydrate antigen (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer. 2007 Apr;33(3):266-70.
[45] Hathurusinghe HR, Goonetilleke KS, Siriwardena AK. Current status of tumor M2 pyruvate kinase (tumor M2-PK) as a biomarker of gastrointestinal malignancy. 2007 Oct;14(10):2714-20.

[46] Kumar Y, Gurusamy K, Pamecha V, Davidson BR. Tumor M2-pyruvate kinase as tumor marker in exocrine pancreatic cancer a meta-analysis. Pancreas. 2007 Aug;35(2):114-9.

[47] 2006 Update of ASCO Recommendations for the Use of Tumor Markers in Gastrointestinal Cancer. J Oncol Pract. 2006 November 1, 2006;2(6):314-6.

[48] Kuno N, Kurimoto K, Fukushima M, Hayakawa T, Shibata T, Suzuki T, et al. Effectiveness of multivariate analysis of tumor markers in diagnosis of pancreatic carcinoma: a prospective study in multiinstitutions. Pancreas. 1994 Nov;9(6):725-30.

[49] Malesci A, Montorsi M, Mariani A, Santambrogio R, Bonato C, Bissi O, et al. Clinical utility of the serum CA 19-9 test for diagnosing pancreatic carcinoma in symptomatic patients: a prospective study. Pancreas. 1992;7(4):497-502.

[50] Sperti C, Pasquali C, Chierichetti F, Liessi G, Ferlin G, Pedrazzoli S. Value of 18-fluorodeoxyglucose positron emission tomography in the management of patients with cystic tumors of the pancreas. Ann Surg. 2001 Nov;234(5):675-80.

[51] Urgell E, Puig P, Boadas J, Capella G, Queralto JM, Boluda R, et al. Prospective evaluation of the contribution of K-ras mutational analysis and CA 19.9 measurement to cytological diagnosis in patients with clinical suspicion of pancreatic cancer. 2000 Oct;36(16):2069-75.

[52] Wang TH, Lin JT, Chen DS, Sheu JC, Sung JL. Noninvasive diagnosis of advanced pancreatic cancer by real-time ultrasonography, carcinoembryonic antigen, and carbohydrate antigen 19-9. Pancreas. 1986;1(3):219-23.

[53] Carr-Locke DL. Serum and pancreatic juice carcinoembryonic antigen in pancreatic and biliary disease. Gut. 1980 Aug;21(8):656-61.

[54] van der Waaij LA, van Dullemen HM, Porte RJ. Cyst fluid analysis in the differential diagnosis of pancreatic cystic lesions: a pooled analysis. Gastrointest Endosc. 2005 Sep;62(3):383-9.

[55] Khalid A, McGrath KM, Zahid M, Wilson M, Brody D, Swalsky P, et al. The role of pancreatic cyst fluid molecular analysis in predicting cyst pathology. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2005 Oct;3(10):967-73.

[56] Shami VM, Sundaram V, Stelow EB, Conaway M, Moskaluk CA, White GE, et al. The level of carcinoembryonic antigen and the presence of mucin as predictors of cystic pancreatic mucinous neoplasia. Pancreas. 2007 May;34(4):466-9.

[57] Agency for Healthcare Research and Quality. Endoscopic Retrograde Cholangiopancreatography. Summary, Evidence Report/Technology Assessment: Number 50. Rockville, MD: AHRQ 2002.

[58] Stavropoulos S, Larghi A, Verna E, Battezzati P, Stevens P. Intraductal ultrasound for the evaluation of patients with biliary strictures and no abdominal mass on computed tomography. 2005 Aug;37(8):715-21.

[59] Cleemput I, Dargent G, Poelmans J, Camberlin C, Van den Bruel A, Ramaekers D. HTA Positronen Emissie Tomografie in België. Report. Brussel: Federaal Kenniscentrum voor de Gezondheidszorg (KCE); 2005. Report No.: D2005/10.273/29.

[60] Orlando LA, Kulasingam SL, Matchar DB. Meta-analysis: the detection of pancreatic malignancy with positron emission tomography. 2004 Nov 15;20(10):1063-70.

[61] Agency for Healthcare Research and Quality. Positron Emission Testing For Six Cancers (Brain, Cervical, Small Cell Lung, Ovarian, Pancreatic and Testicular). Rockville, MD: AHRQ 2004.

[62] Nishiyama Y, Yamamoto Y, Monden T, Sasakawa Y, Tsutsui K, Wakabayashi H, et al. Evaluation of delayed additional FDG PET imaging in patients with pancreatic tumour. Nucl Med Commun. 2005 Oct;26(10):895-901.

[63] Rasmussen I, Sorensen J, Langstrom B, Haglund U. Is positron emission tomography using 18F-fluorodeoxyglucose and 11C-acetate valuable in diagnosing indeterminate pancreatic masses? Scandinavian journal of surgery : SJS : official organ for the Finnish Surgical Society and the Scandinavian Surgical Society. 2004;93(3):191-7.

[64] Singer E, Gschwantler M, Plattner D, Kriwanek S, Armbruster C, Schueller J, et al. Differential diagnosis of benign and malign pancreatic masses with 18F-fluordeoxyglucose-positron emission tomography recorded with a dual-head coincidence gamma camera. Eur J Gastroenterol Hepatol. 2007 Jun;19(6):471-8.

[65] Sperti C, Pasquali C, Chierichetti F, Ferronato A, Decet G, Pedrazzoli S. 18-Fluorodeoxyglucose positron emission tomography in predicting survival of patients with pancreatic carcinoma. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2003 Dec;7(8):953-9; discussion 9-60.

[66] Fédération Nationale des Centres de Lutte Contre le Cancer. Recommandations pour la pratique clinique: Standards, Options et Recommandations 2003 pour l'utilisation de la tomographie par émission de positons au [18F]-FDG (TEP-FDG) en cancérologie. Paris: FNCLCC 2003.

[67] Li H, Zeng MS, Zhou KR, Jin DY, Lou WH. Pancreatic adenocarcinoma: the different CT criteria for peripancreatic major arterial and venous invasion. J Comput Assist Tomogr. 2005 Mar-Apr;29(2):170-5.

[68] Satoi S, Yamamoto H, Takai S, Tanigawa N, Komemushi A, Yanagimoto H, et al. Clinical impact of multidetector row computed tomography on patients with pancreatic cancer. 2007 Mar;34(2):175-9.
[69] van Vliet EPM, Eijkemans MJC, Kuipers EJ, Poley JW, Steyerberg EW, Siersema PD. Publication bias does not play a role in the reporting of the results of endoscopic ultrasound staging of upper gastrointestinal cancers. Endoscopy. 2007 Apr;39(4):325-32.
[70] Puli SR, Singh S, Hagedorn CH, Reddy J, Olyaee M. Diagnostic accuracy of EUS for vascular invasion in pancreatic and periampullary cancers: a meta-analysis and systematic review. Gastrointest Endosc. 2007 May;65(6):788-97.
[71] Nishiyama Y, Yamamoto Y, Yokoe K, Monden T, Sasakawa Y, Tsutsui K, et al. Contribution of whole body FDG-PET to the detection of distant metastasis in pancreatic cancer. 2005 Sep;19(6):491-7.
[72] Croce E, Olmi S, Bertolini A, Magnone S. Laparoscopic surgery of pancreatic cancer: state of the art. 2005 Nov-Dec;52(66):1889-94.
[73] Ong SL, Garcea G, Thomasset SC, Mann CD, Neal CP, Abu Amara M, et al. Surrogate markers of resectability in patients undergoing exploration of potentially resectable pancreatic adenocarcinoma. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2008 Jun;12(6):1068-73.
[74] Jonker D, Bouttell E, Kamra J, Spithoff K, and the Gastrointestinal Cancer Disease Site Group. Chemotherapy or Radiotherapy for Resectable Pancreatic Adenocarcinoma: Clinical Practice Guidelines. Evidence-based Series #2-23. Ottawa, Ontario: CCO 2007.
[75] Nakamori S, Nakahira S, Miyamoto A, Marubashi S, Nagano H, Dono K, et al. Long-term outocomes of preoperative chemoradiation therapy with gemcitabine and accelerated hyperfractionated radiation for respectable pancreatic cancer. J Clin Oncol (Meeting Abstracts). 2006 June 20, 2006;24(18_suppl):14004-.
[76] Brunner TB, Grabenbauer GG, Meyer T, Golcher H, Sauer R, Hohenberger W. Primary resection versus neoadjuvant chemoradiation followed by resection for locally resectable or potentially resectable pancreatic carcinoma without distant metastasis. A multi-centre prospectively randomised phase II-study of the Interdisciplinary Working Group Gastrointestinal Tumours (AIO, ARO, and CAO). BMC Cancer. 2007;7(41).
[77] Palmer DH, Stocken DD, Hewitt H, Markham CE, Hassan AB, Johnson PJ, et al. A randomized phase 2 trial of neoadjuvant chemotherapy in resectable pancreatic cancer: gemcitabine alone versus gemcitabine combined with cisplatin. 2007 Jul;14(7):2088-96.
[78] Lind PA, Isaksson B, Almstrom M, Johnsson A, Albiin N, Bystrom P, et al. Efficacy of preoperative radiochemotherapy in patients with locally advanced pancreatic carcinoma. Acta Oncol. 2008;47(3):413-20.
[79] Sa Cunha A, Rault A, Laurent C, Adhoute X, Vendrely V, Bellannee G, et al. Surgical resection after radiochemotherapy in patients with unresectable adenocarcinoma of the pancreas. J Am Coll Surg. 2005 Sep;201(3):359-65.
[80] Katz MHG, Pisters PWT, Evans DB, Sun CC, Lee JE, Fleming JB, et al. Borderline resectable pancreatic cancer: the importance of this emerging stage of disease. J Am Coll Surg. 2008 May;206(5):833-46; discussion 46-8.
[81] Massucco P, Capussotti L, Magnino A, Sperti E, Gatti M, Muratore A, et al. Pancreatic resections after chemoradiotherapy for locally advanced ductal adenocarcinoma: analysis of perioperative outcome and survival. Ann Surg Oncol. 2006 Sep;13(9):1201-8.
[82] Mumtaz K, Hamid S, Jafri W. Endoscopic retrograde cholangiopancreaticography with or without stenting in patients with pancreaticobiliary malignancy, prior to surgery. Cochrane Database Syst Rev. 2007;3.
[83] Saleh MMA, Norregaard P, Jorgensen HL, Andersen PK, Matzen P. Preoperative endoscopic stent placement before pancreaticoduodenectomy: a meta-analysis of the effect on morbidity and mortality. Gastrointest Endosc. 2002 Oct;56(4):529-34.
[84] Sewnath ME, Karsten TM, Prins MH, Rauws EJA, Obertop H, Gouma DJ. A meta-analysis on the efficacy of preoperative biliary drainage for tumors causing obstructive jaundice. Ann Surg. 2002 Jul;236(1):17-27.
[85] Aly EA, Johnson CD. Preoperative biliary drainage before resection in obstructive jaundice. Dig Surg. 2001;18(2):84-9.
[86] van der Gaag NA, de Castro SMM, Rauws EAJ, Bruno MJ, van Eijck CHJ, Kuipers EJ, et al. Preoperative biliary drainage for periampullary tumors causing obstructive jaundice; DRainage vs. (direct) OPeration (DROP-trial). BMC Surgery. 2007;7(3).
[87] Lygidakis NJ, van der Heyde MN, Lubbers MJ. Evaluation of preoperative biliary drainage in the surgical management of pancreatic head carcinoma. Acta chirurgica Scandinavica. 1987 Nov-Dec;153(11-12):665-8.
[88] Lai EC, Mok FP, Fan ST, Lo CM, Chu KM, Liu CL, et al. Preoperative endoscopic drainage for malignant obstructive jaundice.[see comment]. British Journal of Surgery. 1994 Aug;81(8):1195-8.
[89] National Comprehensive Cancer Network. Pancreatic Adenocarcinoma. V.I. 2008.: NCCN 2008.
[90] Kondo S, Katoh H, Hirano S, Ambo Y, Tanaka E, Okushiba S, et al. Results of radical distal pancreatectomy with en bloc resection of the celiac artery for locally

advanced cancer of the pancreatic body. Langenbecks Arch Surg. 2003 Apr;388(2):101-6.
[91] Konishi M, Kinoshita T, Nakagori T, Inoue K, Oda T, Kimata T, et al. Distal pancreatectomy with resection of the celiac axis and reconstruction of the hepatic artery for carcinoma of the body and tail of the pancreas. J Hepatobiliary Pancreat Surg. 2000;7(2):183-7.
[92] Stitzenberg KB, Watson JC, Roberts A, Kagan SA, Cohen SJ, Konski AA, et al. Survival after pancreatectomy with major arterial resection and reconstruction. Ann Surg Oncol. 2008 May;15(5):1399-406.
[93] Nakano H, Bachellier P, Weber J-C, Oussoultzoglou E, Dieng M, Shimura H, et al. Arterial and vena caval resections combined with pancreaticoduodenectomy in highly selected patients with periampullary malignancies. Hepatogastroenterology. 2002 Jan-Feb;49(43):258-62.
[94] Nakao A, Takeda S, Inoue S, Nomoto S, Kanazumi N, Sugimoto H, et al. Indications and techniques of extended resection for pancreatic cancer. World Journal of Surgery. 2006 Jun;30(6):976-82; discussion 83-4.
[95] Tseng JF, Raut CP, Lee JE, Pisters PWT, Vauthey J-N, Abdalla EK, et al. Pancreaticoduodenectomy with vascular resection: margin status and survival duration. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2004 Dec;8(8):935-49; discussion 49-50.
[96] Li B, Chen F-Z, Ge X-H, Cai M-Z, Jiang J-S, Li J-P, et al. Pancreatoduodenectomy with vascular reconstruction in treating carcinoma of the pancreatic head. Hepatobiliary & pancreatic diseases international : HBPD INT. 2004 Nov;3(4):612-5.
[97] Siriwardana HPP, Siriwardena AK. Systematic review of outcome of synchronous portal-superior mesenteric vein resection during pancreatectomy for cancer. British Journal of Surgery. 2006 Jun;93(6):662-73.
[98] Lygidakis NJ, Singh G, Bardaxoglou E, Dedemadi G, Sgourakis G, Nestoridis J, et al. Mono-bloc total spleno-pancreaticoduodenectomy for pancreatic head carcinoma with portal-mesenteric venous invasion. A prospective randomized study. Hepatogastroenterology. 2004 Mar-Apr;51(56):427-33.
[99] Schmidt CM, White PB, Waters JA, Yiannoutsos CT, Cummings OW, Baker M, et al. Intraductal papillary mucinous neoplasms: predictors of malignant and invasive pathology. Ann Surg. 2007 Oct;246(4):644-51; discussion 51-4.
[100] Bassi C, Sarr MG, Lillemoe KD, Reber HA. Natural history of intraductal papillary mucinous neoplasms (IPMN): current evidence and implications for management. 2008 Apr;12(4):645-50.
[101] Michalski CW, Kleeff J, Wente MN, Diener MK, Buchler MW, Friess H. Systematic review and meta-analysis of standard and extended lymphadenectomy in pancreaticoduodenectomy for pancreatic cancer. 2007 Mar;94(3):265-73.
[102] Pedrazzoli S, DiCarlo V, Dionigi R, Mosca F, Pederzoli P, Pasquali C, et al. Standard versus extended lymphadenectomy associated with pancreatoduodenectomy in the surgical treatment of adenocarcinoma of the head of the pancreas: a multicenter, prospective, randomized study. Lymphadenectomy Study Group. Ann Surg. 1998 Oct;228(4):508-17.
[103] Imamura M, Doi R. Treatment of locally advanced pancreatic cancer: should we resect when resectable? 2004 Apr;28(3):293-5.
[104] Karanicolas PJ, Davies E, Kunz R, Briel M, Koka HP, Payne DM, et al. The pylorus: take it or leave it? Systematic review and meta-analysis of pylorus-preserving versus standard whipple pancreaticoduodenectomy for pancreatic or periampullary cancer. 2007 Jun;14(6):1825-34.
[105] Diener MK, Knaebel H-P, Heukaufer C, Antes G, Buchler MW, Seiler CM. A systematic review and meta-analysis of pylorus-preserving versus classical pancreaticoduodenectomy for surgical treatment of periampullary and pancreatic carcinoma. 2007 Feb;245(2):187-200.
[106] Paraskevas KI, Avgerinos C, Manes C, Lytras D, Dervenis C. Delayed gastric emptying is associated with pylorus-preserving but not classical Whipple pancreaticoduodenectomy: a review of the literature and critical reappraisal of the implicated pathomechanism. 2006 Oct 7;12(37):5951-8.
[107] Alexakis N, Halloran C, Raraty M, Ghaneh P, Sutton R, Neoptolemos JP. Current standards of surgery for pancreatic cancer. British Journal of Surgery. 2004 Nov;91(11):1410-27.
[108] McKay A, Mackenzie S, Sutherland FR, Bathe OF, Doig C, Dort J, et al. Meta-analysis of pancreaticojejunostomy versus pancreaticogastrostomy reconstruction after pancreaticoduodenectomy. British Journal of Surgery. 2006 Aug;93(8):929-36.
[109] Bassi C, Falconi M, Molinari E, Salvia R, Butturini G, Sartori N, et al. Reconstruction by pancreaticojejunostomy versus pancreaticogastrostomy following pancreatectomy: results of a comparative study. Ann Surg. 2005 771-3, 2005 Dec;242(6):767-71.
[110] Duffas J-P, Suc B, Msika S, Fourtanier G, Muscari F, Hay JM, et al. A controlled randomized multicenter trial of pancreatogastrostomy or pancreatojejunostomy after pancreatoduodenectomy. Am J Surg. 2005 Jun;189(6):720-9.

[111] Chou FF, Sheen-Chen SM, Chen YS, Chen MC, Chen CL. Postoperative morbidity and mortality of pancreaticoduodenectomy for periampullary cancer. Eur J Surg. 1996 Jun;162(6):477-81.
[112] Peng SY, Wang JW, Lau WY, Cai XJ, Mou YP, Liu YB, et al. Conventional versus binding pancreaticojejunostomy after pancreaticoduodenectomy: a prospective randomized trial. 2007 May;245(5):692-8.
[113] Reissman P, Perry Y, Cuenca A, Bloom A, Eid A, Shiloni E, et al. Pancreaticojejunostomy versus controlled pancreaticocutaneous fistula in pancreaticoduodenectomy for periampullary carcinoma. 1995 Jun;169(6):585-8.
[114] Tran K, Van Eijck C, Di Carlo V, Hop WCJ, Zerbi A, Balzano G, et al. Occlusion of the pancreatic duct versus pancreaticojejunostomy: a prospective randomized trial. 2002 Oct;236(4):422-8; discussion 8.
[115] Bassi C, Falconi M, Molinari E, Mantovani W, Butturini G, Gumbs AA, et al. Duct-to-mucosa versus end-to-side pancreaticojejunostomy reconstruction after pancreaticoduodenectomy: results of a prospective randomized trial. Surgery. 2003 Nov;134(5):766-71.
[116] Yeo CJ, Cameron JL, Maher MM, Sauter PK, Zahurak ML, Talamini MA, et al. A prospective randomized trial of pancreaticogastrostomy versus pancreaticojejunostomy after pancreaticoduodenectomy. Ann Surg. 1995 Oct;222(4):580-8; discussion 8-92.
[117] Halm EA, Lee C, Chassin MR. Is volume related to outcome in health care? A systematic review and methodologic critique of the literature. Annals of internal medicine. 2002 Sep 17;137(6):511-20.
[118] Killeen SD, O'Sullivan MJ, Coffey JC, Kirwan WO, Redmond HP. Provider volume and outcomes for oncological procedures. British Journal of Surgery. 2005 Apr;92(4):389-402.
[119] Topal B, Van de Sande S, Fieuws S, Penninckx F. Effect of centralization of pancreaticoduodenectomy on nationwide hospital mortality and length of stay. British Journal of Surgery. 2007 Nov;94(11):1377-81.
[120] Esposito I, Kleeff J, Bergmann F, Reiser C, Herpel E, Friess H, et al. Most pancreatic cancer resections are R1 resections. Ann Surg Oncol. 2008 Jun;15(6):1651-60.
[121] Verbeke CS, Leitch D, Menon KV, McMahon MJ, Guillou PJ, Anthoney A. Redefining the R1 resection in pancreatic cancer. British Journal of Surgery. 2006 Oct;93(10):1232-7.
[122] Staley CA, Cleary KR, Abbruzzese JL, Lee JE, Ames FC, Fenoglio CJ, et al. The need for standardized pathologic staging of pancreaticoduodenectomy specimens. Pancreas. 1996 May;12(4):373-80.
[123] Demetter P, Cuvelier CA, Working Party for GIc. Guidelines for adequate histopathological reporting of pancreatic ductal adenocarcinoma resection specimens. Acta Gastroenterol Belg. 2004 Jan-Mar;67(1):46-9.
[124] Royal College of Pathologists. Standards and Minimum Datasets for Reporting Cancers. *Minimum dataset for the histopathological reporting of pancreatic, ampulla of Vater and bile duct carcinoma*. London: Royal College of Pathologists 2002.
[125] Luttges J, Zamboni G, Kloppel G. Recommendation for the examination of pancreaticoduodenectomy specimens removed from patients with carcinoma of the exocrine pancreas. A proposal for a standardized pathological staging of pancreaticoduodenectomy specimens including a checklist. Dig Surg. 1999;16(4):291-6.
[126] Howard TJ, Krug JE, Yu J, Zyromski NJ, Schmidt CM, Jacobson LE, et al. A margin-negative R0 resection accomplished with minimal postoperative complications is the surgeon's contribution to long-term survival in pancreatic cancer. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2006 Dec;10(10):1338-45; discussion 45-6.
[127] Raut CP, Tseng JF, Sun CC, Wang H, Wolff RA, Crane CH, et al. Impact of resection status on pattern of failure and survival after pancreaticoduodenectomy for pancreatic adenocarcinoma. Ann Surg. 2007 Jul;246(1):52-60.
[128] Verbeke CS. Resection margins and R1 rates in pancreatic cancer--are we there yet? Histopathology. 2008 Jun;52(7):787-96.
[129] Garcea G, Dennison AR, Pattenden CJ, Neal CP, Sutton CD, Berry DP. Survival following curative resection for pancreatic ductal adenocarcinoma. A systematic review of the literature. Jop. 2008;9(2):99-132.
[130] Mitsunaga S, Hasebe T, Kinoshita T, Konishi M, Takahashi S, Gotohda N, et al. Detail histologic analysis of nerve plexus invasion in invasive ductal carcinoma of the pancreas and its prognostic impact. The American journal of surgical pathology. 2007 Nov;31(11):1636-44.
[131] Westgaard A, Tafjord S, Farstad IN, Cvancarova M, Eide TJ, Mathisen O, et al. Pancreatobiliary versus intestinal histologic type of differentiation is an independent prognostic factor in resected periampullary adenocarcinoma. BMC Cancer. 2008;8:170.
[132] Doi R, Kami K, Ito D, Fujimoto K, Kawaguchi Y, Wada M, et al. Prognostic implication of para-aortic lymph node metastasis in resectable pancreatic cancer. World Journal of Surgery. 2007 Jan;31(1):147-54.
[133] Yekebas E-F, Bogoevski D, Bubenheim M, Link B-C, Kaifi J-T, Wachowiak R, et al. Strong prognostic value of nodal and bone marrow micro-involvement in patients

with pancreatic ductal carcinoma receiving no adjuvant chemotherapy. World J Gastroenterol. 2006 Oct 28;12(40):6515-21.
[134] Tani M, Kawai M, Terasawa H, Ina S, Hirono S, Shimamoto T, et al. Prognostic factors for long-term survival in patients with locally invasive pancreatic cancer. J Hepatobiliary Pancreat Surg. 2007;14(6):545-50.
[135] Butturini G, Stocken DD, Wente MN, Jeekel H, Klinkenbijl JHG, Bakkevold KE, et al. Influence of resection margins and treatment on survival in patients with pancreatic cancer: meta-analysis of randomized controlled trials. Arch Surg. 2008 Jan;143(1):75-83; discussion
[136] Westgaard A, Tafjord S, Farstad IN, Cvancarova M, Eide TJ, Mathisen O, et al. Resectable adenocarcinomas in the pancreatic head: the retroperitoneal resection margin is an independent prognostic factor. BMC Cancer. 2008;8:5.
[137] House MG, Gonen M, Jarnagin WR, D'Angelica M, DeMatteo RP, Fong Y, et al. Prognostic significance of pathologic nodal status in patients with resected pancreatic cancer. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2007 Nov;11(11):1549-55.
[138] Pawlik TM, Gleisner AL, Cameron JL, Winter JM, Assumpcao L, Lillemoe KD, et al. Prognostic relevance of lymph node ratio following pancreaticoduodenectomy for pancreatic cancer. Surgery. 2007 May;141(5):610-8.
[139] Slidell MB, Chang DC, Cameron JL, Wolfgang C, Herman JM, Schulick RD, et al. Impact of total lymph node count and lymph node ratio on staging and survival after pancreatectomy for pancreatic adenocarcinoma: a large, population-based analysis. Ann Surg Oncol. 2008 Jan;15(1):165-74.
[140] Schwarz RE, Smith DD. Extent of lymph node retrieval and pancreatic cancer survival: information from a large US population database. Ann Surg Oncol. 2006 Sep;13(9):1189-200.
[141] Tomlinson JS, Jain S, Bentrem DJ, Sekeris EG, Maggard MA, Hines OJ, et al. Accuracy of staging node-negative pancreas cancer: a potential quality measure. Arch Surg. 2007 Aug;142(8):767-23; discussion 73-4.
[142] Garcea G, Neal CP, Pattenden CJ, Steward WP, Berry DP. Molecular prognostic markers in pancreatic cancer: a systematic review. 2005 Oct;41(15):2213-36.
[143] Doucas H, Neal CP, O'Reilly K, Dennison AR, Berry DP. Frozen section diagnosis of pancreatic malignancy: a sensitive diagnostic technique. Pancreatology. 2006;6(3):210-3; discussion 4.
[144] Lechago J. Frozen section examination of liver, gallbladder, and pancreas. Arch Pathol Lab Med. 2005 Dec;129(12):1610-8.
[145] Hruban RH, Takaori K, Klimstra DS, Adsay NV, Albores-Saavedra J, Biankin AV, et al. An illustrated consensus on the classification of pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. The American journal of surgical pathology. 2004 Aug;28(8):977-87.
[146] UICC. Classification of Malignant Tumours. 6th ed. New York: Wiley-Liss 2002.
[147] Japan Pancreas Society. Classification of Pancreatic Carcinoma. 2nd English ed. Tokyo: JCS 2003.
[148] Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial.[see comment]. 2007 Jan 17;297(3):267-77.
[149] Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. Arch Surg. 1985 Aug;120(8):899-903.
[150] Neoptolemos JP, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer.[see comment][erratum appears in N Engl J Med. 2004 Aug 12;351(7):726]. 2004 Mar 18;350(12):1200-10.
[151] Kosuge T, Kiuchi T, Mukai K, Kakizoe T, Japanese Study Group of Adjuvant Therapy for Pancreatic C. A multicenter randomized controlled trial to evaluate the effect of adjuvant cisplatin and 5-fluorouracil therapy after curative resection in cases of pancreatic cancer. 2006 Mar;36(3):159-65.
[152] Van Laethem J, Van Cutsem E, Hammel P, Mornex F, Azria D, Van Tienhoven G, et al. Adjuvant chemotherapy alone versus chemoradiation after curative resection for pancreatic cancer : feasibility results of a randomised EORTC/FFCD/GERCOR phase II/III study (40013/22012/0304). ASCO Meeting Abstracts. 2008 May 20, 2008;26(15_suppl):4514-.
[153] Maeda A, Boku N, Fukutomi A, Kondo S, Kinoshita T, Nagino M, et al. Randomized phase III trial of adjuvant chemotherapy with gemcitabine versus S-1 in patients with resected pancreatic cancer: Japan Adjuvant Study Group of Pancreatic Cancer (JASPAC-01). 2008 Mar;38(3):227-9.
[154] Brasiuniene B, Juozaityte E. The effect of combined treatment methods on survival and toxicity in patients with pancreatic cancer. Medicina. 2007;43(9):716-25.
[155] Regine WF, Winter KA, Abrams RA, Safran H, Hoffman JP, Konski A, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial.[see comment]. 2008 Mar 5;299(9):1019-26.
[156] Kim JK, Ha HK, Han DJ, Auh YH. CT analysis of postoperative tumor recurrence patterns in periampullary cancer. Abdom Imaging. 2003 May-Jun;28(3):384-91.
[157] Coombs RJ, Zeiss J, Howard JM, Thomford NR, Merrick HW. CT of the abdomen after the Whipple procedure: value in depicting postoperative anatomy, surgical

complications, and tumor recurrence. AJR American journal of roentgenology. 1990 May;154(5):1011-4.
[158] Ruf J, Lopez Hanninen E, Oettle H, Plotkin M, Pelzer U, Stroszczynski C, et al. Detection of recurrent pancreatic cancer: comparison of FDG-PET with CT/MRI. Pancreatology. 2005;5(2-3):266-72.
[159] Banfi G, Bravi S, Ardemagni A, Zerbi A. CA 19.9, CA 242 and CEA in the diagnosis and follow-up of pancreatic cancer. The International journal of biological markers. 1996 Apr-Jun;11(2):77-81.
[160] Beretta E, Malesci A, Zerbi A, Mariani A, Carlucci M, Bonato C, et al. Serum CA 19-9 in the postsurgical follow-up of patients with pancreatic cancer. Cancer. 1987 Nov 15;60(10):2428-31.
[161] Micke O, Bruns F, Schafer U, Kurowski R, Horst E, Willich N. CA 19-9 in the therapy monitoring and follow-up of locally advanced cancer of the exocrine pancreas treated with radiochemotherapy. Anticancer Res. 2003 Mar-Apr;23(2A):835-40.
[162] Sultana A, Smith CT, Cunningham D, Starling N, Neoptolemos JP, Ghaneh P. Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer. 2007 Jun 20;25(18):2607-15.
[163] Yip D, Karapetis C, Strickland A, Steer CB, Goldstein D. Chemotherapy and radiotherapy for inoperable advanced pancreatic cancer. Cochrane Database Syst Rev. 2006;3.
[164] Andersen JR, Friis-Moller A, Hancke S, Roder O, Steen J, Baden H. A controlled trial of combination chemotherapy with 5-FU and BCNU in pancreatic cancer. Scandinavian journal of gastroenterology. 1981;16(8):973-5.
[165] Boeck S, Hinke A, Wilkowski R, Heinemann V. Importance of performance status for treatment outcome in advanced pancreatic cancer. World J Gastroenterol. 2007 Jan 14;13(2):224-7.
[166] Ychou M, Desseigne F, Guimbaud R, Ducreux M, Bouche O, Becouarn Y, et al. Randomized phase II trial comparing folfirinox (5FU/leucovorin [LV], irinotecan [I] and oxaliplatin [O]) vs gemcitabine (G) as first-line treatment for metastatic pancreatic adenocarcinoma (MPA). First results of the ACCORD 11 trial. ASCO Meeting Abstracts. 2007 June 20, 2007;25(18_suppl):4516-.
[167] Heinemann V, Boeck S, Hinke A, Labianca R, Louvet C. Meta-analysis of randomized trials: evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer. BMC Cancer. 2008;8(82).
[168] Bria E, Milella M, Gelibter A, Cuppone F, Pino MS, Ruggeri EM, et al. Gemcitabine-based combinations for inoperable pancreatic cancer: have we made real progress? A meta-analysis of 20 phase 3 trials. 2007 Aug 1;110(3):525-33.
[169] Banu E, Banu A, Fodor A, Landi B, Rougier P, Chatellier G, et al. Meta-analysis of randomised trials comparing gemcitabine-based doublets versus gemcitabine alone in patients with advanced and metastatic pancreatic cancer. Drugs & Aging. 2007;24(10):865-79.
[170] Xie DR, Liang HL, Wang Y, Guo SS. Meta-analysis of inoperable pancreatic cancer: gemcitabine combined with cisplatin versus gemcitabine alone. Chin J Dig Dis. 2006;7(1):49-54.
[171] Germond C, Maroun J, Moore M, Zwaal C, Wong S, and members of the Gastrointestinal Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care. Use of Gemcitabine in the Treatment of Advanced Pancreatic Adenocarcinoma. Practice Guideline Report #2-10. Ottawa, Ontario: CCO 2005.
[172] Yang Q, Xie DR, Liang HL, Jiang ZM, Bi ZF, Chen SL. A meta-analysis of randomized controlled trials comparing gemcitabine (GEM)-based combination chemotherapy with gemcitabine alone in advanced pancreatic cancer: An updated subgroup analysis of overall survival. ASCO Meeting Abstracts. 2008 May 20, 2008;26(15_suppl):15661-.
[173] Herrmann R, Bodoky G, Ruhstaller T, Glimelius B, Bajetta E, Schuller J, et al. Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group.[see comment]. 2007 Jun 1;25(16):2212-7.
[174] Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group.[see comment]. 2007 May 20;25(15):1960-6.
[175] Richards DA, Boehm KA, Waterhouse DM, Wagener DJ, Krishnamurthi SS, Rosemurgy A, et al. Gemcitabine plus CI-994 offers no advantage over gemcitabine alone in the treatment of patients with advanced pancreatic cancer: results of a phase II randomized, double-blind, placebo-controlled, multicenter study. 2006 Jul;17(7):1096-102.
[176] Kindler HL, Niedzwiecki D, Hollis D, Oraefo E, Schrag D, Hurwitz H, et al. A double-blind, placebo-controlled, randomized phase III trial of gemcitabine (G) plus bevacizumab (B) versus gemcitabine plus placebo (P) in patients (pts) with advanced pancreatic cancer (PC): A preliminary analysis of Cancer and Leukemia Group B (CALGB. ASCO Meeting Abstracts. 2007 June 20, 2007;25(18_suppl):4508-.

[177] Philip PA, Benedetti J, Fenoglio-Preiser C, Zalupski M, Lenz H, O'Reilly E, et al. Phase III study of gemcitabine [G] plus cetuximab [C] versus gemcitabine in patients [pts] with locally advanced or metastatic pancreatic adenocarcinoma [PC]: SWOG S0205 study. ASCO Meeting Abstracts. 2007 June 20, 2007;25(18_suppl):LBA4509-.

[178] Spano J, Chodkiewicz C, Maurel J, Wong RP, Wasan HS, Pithavala YK, et al. A randomized phase II study of axitinib (AG-013736) and gemcitabine versus gemcitabine in advanced pancreatic cancer, preceded by a phase I component. ASCO Meeting Abstracts. 2007 June 20, 2007;25(18_suppl):4551-.

[179] Tuinmann G, Mueller L, Hossfeld D, Bokemeyer C. A randomised phase II study of gemcitabine versus mitomycin C versus gemcitabine/mitomycin C in patients with advanced pancreatic cancer. ASCO Meeting Abstracts. 2008 May 20, 2008;26(15_suppl):15658-.

[180] Wright JA, Osterlee J, Fekete S, Lee Y, Young AH. A phase III trial of virulizin plus gemcitabine vs. gemcitabine alone in advanced pancreatic cancer: Results of subgroup analysis. ASCO Meeting Abstracts. 2006 June 20, 2006;24(18_suppl):4116-.

[181] Van Cutsem E, Verslype C, Grusenmeyer PA. Lessons learned in the management of advanced pancreatic cancer. J Clin Oncol. 2007 May 20;25(15):1949-52.

[182] Cunningham D, Chau I, Stocken D, Davies C, Dunn J, Valle J, et al. Phase III randomised comparison of gemcitabine (GEM) versus gemcitabine plus capecitabine (GEM-CAP) in patients with advanced pancreatic cancer. Eur J Cancer Suppl. 2005;3(4):4 (PS11).

[183] Ducreux M, Mitry E, Ould-Kaci M, Boige V, Seitz JF, Bugat R, et al. Randomized phase II study evaluating oxaliplatin alone, oxaliplatin combined with infusional 5-FU, and infusional 5-FU alone in advanced pancreatic carcinoma patients.[see comment]. 2004 Mar;15(3):467-73.

[184] Levi FA, Tubiana-Mathieu N, Focan C, Brezault-Bonnet C, Coudert B, Carvalho C, et al. Chronomodulated (Chrono) vs constant (Cst) rate infusional 5-fluorouracil (FU) with or without cisplatin (CDDP) in patients with advanced or metastatic pancreatic cancer. A multicenter randomized trial of the Chronotherapy Group of the European Organisation for Research and Treatment of Cancer (EORTC 05962). ASCO Meeting Abstracts. 2004 July 15, 2004;22(14_suppl):4117-.

[185] Boeck S, Hoehler T, Seipelt G, Mahlberg R, Wein A, Hochhaus A, et al. Capecitabine plus oxaliplatin (CapOx) versus capecitabine plus gemcitabine (CapGem) versus gemcitabine plus oxaliplatin (mGemOx): final results of a multicenter randomized phase II trial in advanced pancreatic cancer. 2008 Feb;19(2):340-7.

[186] Lutz MP, Van Cutsem E, Wagener T, Van Laethem J-L, Vanhoefer U, Wils JA, et al. Docetaxel plus gemcitabine or docetaxel plus cisplatin in advanced pancreatic carcinoma: randomized phase II study 40984 of the European Organisation for Research and Treatment of Cancer Gastrointestinal Group. 2005 Dec 20;23(36):9250-6.

[187] Alberts SR, Foster NR, Morton RF, Kugler J, Schaefer P, Wiesenfeld M, et al. PS-341 and gemcitabine in patients with metastatic pancreatic adenocarcinoma: a North Central Cancer Treatment Group (NCCTG) randomized phase II study. 2005 Oct;16(10):1654-61.

[188] Kulke MH, Niedzwiecki D, Tempero MA, Hollis DR, Mayer RJ. A randomized phase II study of gemcitabine/cisplatin, gemcitabine fixed dose rate infusion, gemcitabine/docetaxel, or gemcitabine/irinotecan in patients with metastatic pancreatic cancer (CALGB 89904). ASCO Meeting Abstracts. 2004 July 15, 2004;22(14_suppl):4011-.

[189] Cheverton P, Friess H, Andras C, Salek T, Geddes C, Bodoky G, et al. Phase III results of exatecan (DX-8951f) versus gemcitabine (Gem) in chemotherapy-naive patients with advanced pancreatic cancer (APC). ASCO Meeting Abstracts. 2004 July 15, 2004;22(14_suppl):4005-.

[190] Reni M, Cereda S, Passoni P, Rognone A, Mazza E, Nicoletti R, et al. A randomized phase II trial of PEXG (cisplatin, epirubicin, capecitabine, gemcitabine) or PDXG (docetaxel) regimen in advanced pancreatic adenocarcinoma. ASCO Meeting Abstracts. 2007 June 20, 2007;25(18_suppl):4628-.

[191] Andre T, Afchain P, Lledo G, Nguyen S, Paitel J, Mineur L, et al. First-line simplified GEMOX (D1-D1) versus classical GEMOX (D1-D2) in metastatic pancreatic adenocarcinoma (MPA). A GERCOR randomized phase II study. ASCO Meeting Abstracts. 2007 June 20, 2007;25(18_suppl):4592-.

[192] Mitry E, Dahan L, Ychou M, Arthaud J, Gasmi M, Raoul J, et al. LV5FU2-cisplatin followed by gemcitabine or the reverse sequence in metastatic pancreatic cancer: Preliminary results of a randomized phase III trial (FFCD 0301). ASCO Meeting Abstracts. 2008 May 20, 2008;26(15_suppl):4513-.

[193] Cascinu S, Berardi R, Labianca R, Siena S, Falcone A, Aitini E, et al. Cetuximab plus gemcitabine and cisplatin compared with gemcitabine and cisplatin alone in patients with advanced pancreatic cancer: a randomised, multicentre, phase II trial.[see comment]. 2008 Jan;9(1):39-44.

[194] Astsaturov IA, Meropol NJ, Alpaugh RK, Cheng JD, Lewis NL, Beard M, et al. A randomized phase II and coagulation study of bevacizumab alone or with docetaxel in patients with previously treated metastatic pancreatic adenocarcinoma. ASCO Meeting Abstracts. 2007 June 20, 2007;25(18_suppl):4556-.

[195] Ebert M, Nitsche B, Roecken C, Fahlke J, Hosius C, Gschaidmeier H, et al. A prospective and randomised clinical trial of the tyrosine kinase inhibitor imatinib mesylate as an initial therapy of advanced pancreatic cancer. ASCO Meeting Abstracts. 2004 July 15, 2004;22(14_suppl):4151-.

[196] Kindler HL, Bylow KA, Hochster HS, Friberg G, Micetich K, Locker G, et al. A randomized phase II study of bevacizumab (B) and gemcitabine (G) plus cetuximab (C) or erlotinib (E) in patients (pts) with advanced pancreatic cancer (PC): A preliminary analysis. ASCO Meeting Abstracts. 2006 June 20, 2006;24(18_suppl):4040-.

[197] Kindler HL, Gangadhar T, Karrison T, Hochster HS, Moore MJ, Micetich K, et al. Final analysis of a randomized phase II study of bevacizumab (B) and gemcitabine (G) plus cetuximab (C) or erlotinib (E) in patients (pts) with advanced pancreatic cancer (PC). ASCO Meeting Abstracts. 2008 May 20, 2008;26(15_suppl):4502-.

[198] Vervenne W, Bennouna J, Humblet Y, Gill S, Moore MJ, Van Laethem J, et al. A randomized, double-blind, placebo (P) controlled, multicenter phase III trial to evaluate the efficacy and safety of adding bevacizumab (B) to erlotinib (E) and gemcitabine (G) in patients (pts) with metastatic pancreatic cancer. ASCO Meeting Abstracts. 2008 May 20, 2008;26(15_suppl):4507-.

[199] Earle CC, Agboola O, Maroun J, Zuraw L, Cancer Care Ontario Practice Guidelines Initiative's Gastrointestinal Cancer Disease Site G. The treatment of locally advanced pancreatic cancer: a practice guideline. 2003 Mar;17(3):161-7.

[200] Sultana A, Tudur Smith C, Cunningham D, Starling N, Tait D, Neoptolemos JP, et al. Systematic review, including meta-analyses, on the management of locally advanced pancreatic cancer using radiation/combined modality therapy. 2007 Apr 23;96(8):1183-90.

[201] Shinchi H, Takao S, Noma H, Matsuo Y, Mataki Y, Mori S, et al. Length and quality of survival after external-beam radiotherapy with concurrent continuous 5-fluorouracil infusion for locally unresectable pancreatic cancer. 2002 May 1;53(1):146-50.

[202] Moertel CG, Frytak S, Hahn RG, O'Connell MJ, Reitemeier RJ, Rubin J, et al. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: The Gastrointestinal Tumor Study Group. Cancer. 1981 Oct 15;48(8):1705-10.

[203] Loehrer PJ, Sr., Powell ME, Cardenes HR, Wagner L, Brell JM, Ramanathan RK, et al. A randomized phase III study of gemcitabine in combination with radiation therapy versus gemcitabine alone in patients with localized, unresectable pancreatic cancer: E4201. ASCO Meeting Abstracts. 2008 May 20, 2008;26(15_suppl):4506-.

[204] Li C-P, Chao Y, Chi K-H, Chan W-K, Teng H-C, Lee R-C, et al. Concurrent chemoradiotherapy treatment of locally advanced pancreatic cancer: gemcitabine versus 5-fluorouracil, a randomized controlled study.[see comment]. 2003 Sep 1;57(1):98-104.

[205] Radiation therapy combined with Adriamycin or 5-fluorouracil for the treatment of locally unresectable pancreatic carcinoma. Gastrointestinal Tumor Study Group. Cancer. 1985 Dec 1;56(11):2563-8.

[206] Earle JD, Foley JF, Wieand HS, Kvols LK, McKenna PJ, Krook JE, et al. Evaluation of external-beam radiation therapy plus 5-fluorouracil (5-FU) versus external-beam radiation therapy plus hycanthone (HYC) in confined, unresectable pancreatic cancer. Int J Radiat Oncol Biol Phys. 1994 Jan 1;28(1):207-11.

[207] McCracken JD, Ray P, Heilbrun LK, Vaitkevicius VK, Saiki JH, Rivkin SE, et al. 5-Fluorouracil, methyl-CCNU, and radiotherapy with or without testolactone for localized adenocarcinoma of the exocrine pancreas: a Southwest Oncology Group Study. Cancer. 1980 Oct 1;46(7):1518-22.

[208] Wilkowski R, Thoma M, Bruns C, Wagner A, Heinemann V. Chemoradiotherapy with gemcitabine and continuous 5-FU in patients with primary inoperable pancreatic cancer. Jop. 2006;7(4):349-60.

[209] Huguet F, Andre T, Hammel P, Artru P, Balosso J, Selle F, et al. Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. J Clin Oncol. 2007 Jan 20;25(3):326-31.

[210] Moss AC, Morris E, Leyden J, MacMathuna P. Do the benefits of metal stents justify the costs? A systematic review and meta-analysis of trials comparing endoscopic stents for malignant biliary obstruction. Eur J Gastroenterol Hepatol. 2007 Dec;19(12):1119-24.

[211] Moss AC, Morris E, Mac Mathuna P. Palliative biliary stents for obstructing pancreatic carcinoma. Cochrane Database Syst Rev. 2006(1):CD004200.

[212] Hammarstrom L-E. Role of palliative endoscopic drainage in patients with malignant biliary obstruction. Dig Surg. 2005;22(5):295-304; discussion 5.

[213] Taylor MC, McLeod RS, Langer B. Biliary stenting versus bypass surgery for the palliation of malignant distal bile duct obstruction: a meta-analysis. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2000 May;6(3):302-8.

[214] Artifon ELA, Sakai P, Cunha JEM, Dupont A, Filho FM, Hondo FY, et al. Surgery or endoscopy for palliation of biliary obstruction due to metastatic pancreatic cancer. 2006 Sep;101(9):2031-7.
[215] Nieveen van Dijkum EJM, Romijn MG, Terwee CB, de Wit LT, van der Meulen JHP, Lameris HS, et al. Laparoscopic staging and subsequent palliation in patients with peripancreatic carcinoma. 2003 Jan;237(1):66-73.
[216] Date RS, Siriwardena AK. Current status of laparoscopic biliary bypass in the management of non-resectable peri-ampullary cancer. Pancreatology. 2005;5(4-5):325-9.
[217] Navarra G, Musolino C, Venneri A, De Marco ML, Bartolotta M. Palliative antecolic isoperistaltic gastrojejunostomy: a randomized controlled trial comparing open and laparoscopic approaches. 2006 Dec;20(12):1831-4.
[218] Van Heek NT, De Castro SMM, van Eijck CH, van Geenen RCI, Hesselink EJ, Breslau PJ, et al. The need for a prophylactic gastrojejunostomy for unresectable periampullary cancer: a prospective randomized multicenter trial with special focus on assessment of quality of life. Ann Surg. 2003 Dec;238(6):894-902; discussion -5.
[219] Yilmaz S, Kirimlioglu V, Katz DA, Kayaalp C, Caglikulekci M, Ara C. Randomised clinical trial of two bypass operations for unresectable cancer of the pancreatic head. Eur J Surg. 2001 Oct;167(10):770-6.
[220] Shyr YM, Su CH, King KL, Wang HC, Lo SS, Wu CW, et al. Randomized trial of three types of gastrojejunostomy in unresectable periampullary cancer. Surgery. 1997 May;121(5):506-12.
[221] Katsinelos P, Paikos D, Kountouras J, Chatzimavroudis G, Paroutoglou G, Moschos I, et al. Tannenbaum and metal stents in the palliative treatment of malignant distal bile duct obstruction: a comparative study of patency and cost effectiveness. 2006 Oct;20(10):1587-93.
[222] Soderlund C, Linder S. Covered metal versus plastic stents for malignant common bile duct stenosis: a prospective, randomized, controlled trial.[see comment]. 2006 Jun;63(7):986-95.
[223] Goonetilleke KS, Siriwardena AK. Systematic review of peri-operative nutritional supplementation in patients undergoing pancreaticoduodenectomy. Jop. 2006;7(1):5-13.
[224] Giger U, Buchler M, Farhadi J, Berger D, Husler J, Schneider H, et al. Preoperative immunonutrition suppresses perioperative inflammatory response in patients with major abdominal surgery-a randomized controlled pilot study. Ann Surg Oncol. 2007 Oct;14(10):2798-806.
[225] Braga M, Gianotti L, Radaelli G, Vignali A, Mari G, Gentilini O, et al. Perioperative immunonutrition in patients undergoing cancer surgery: results of a randomized double-blind phase 3 trial.[see comment]. Arch Surg. 1999 Apr;134(4):428-33.
[226] Braga M, Gianotti L, Gentilini O, Parisi V, Salis C, Di Carlo V. Early postoperative enteral nutrition improves gut oxygenation and reduces costs compared with total parenteral nutrition.[see comment]. Crit Care Med. 2001 Feb;29(2):242-8.
[227] Braga M, Gianotti L, Vignali A, Cestari A, Bisagni P, Di Carlo V. Artificial nutrition after major abdominal surgery: impact of route of administration and composition of the diet.[see comment]. Crit Care Med. 1998 Jan;26(1):24-30.
[228] Di Carlo V, Gianotti L, Balzano G, Zerbi A, Braga M. Complications of pancreatic surgery and the role of perioperative nutrition. Dig Surg. 1999;16(4):320-6.
[229] Gianotti L, Braga M, Vignali A, Balzano G, Zerbi A, Bisagni P, et al. Effect of route of delivery and formulation of postoperative nutritional support in patients undergoing major operations for malignant neoplasms. Arch Surg. 1997 Nov;132(11):1222-9; discussion 9-30.
[230] Fish J, Sporay G, Beyer K, Jones J, Kihara T, Kennedy A, et al. A prospective randomized study of glutamine-enriched parenteral compared with enteral feeding in postoperative patients. Am J Clin Nutr. 1997 Apr;65(4):977-83.
[231] Klek S, Kulig J, Sierzega M, Szczepanek K, Szybinski P, Scislo L, et al. Standard and immunomodulating enteral nutrition in patients after extended gastrointestinal surgery--a prospective, randomized, controlled clinical trial. Clin Nutr. 2008 Aug;27(4):504-12.
[232] Lobo DN, Williams RN, Welch NT, Aloysius MM, Nunes QM, Padmanabhan J, et al. Early postoperative jejunostomy feeding with an immune modulating diet in patients undergoing resectional surgery for upper gastrointestinal cancer: a prospective, randomized, controlled, double-blind study. Clin Nutr. 2006 Oct;25(5):716-26.
[233] Jo S, Choi S-H, Heo J-S, Kim E-M, Min M-S, Choi D-W, et al. Missing effect of glutamine supplementation on the surgical outcome after pancreaticoduodenectomy for periampullary tumors: a prospective, randomized, double-blind, controlled clinical trial. World Journal of Surgery. 2006 Nov;30(11):1974-82; discussion 83-4.
[234] Heller AR, Rossel T, Gottschlich B, Tiebel O, Menschikowski M, Litz RJ, et al. Omega-3 fatty acids improve liver and pancreas function in postoperative cancer patients. International Journal of Cancer. 2004 Sep 10;111(4):611-6.
[235] Topal B, Peeters G, Vandeweyer H, Aerts R, Penninckx F. Hospital cost-categories of pancreaticoduodenectomy. Acta Chir Belg. 2007 Jul-Aug;107(4):373-7.

[236] Major P, Figueredo A, Tandan V, Bramwell V, Charette M, Oliver T, et al. The Role of Octreotide in the Management of Patients with Cancer. Practice Guideline Report #12-7. Ontario: CCO 2003.
[237] Hesse UJ, DeDecker C, Houtmeyers P, Demetter P, Ceelen W, Pattyn P, et al. Prospectively randomized trial using perioperative low-dose octreotide to prevent organ-related and general complications after pancreatic surgery and pancreatico-jejunostomy.[erratum appears in World J Surg. 2006 Apr;30(4):641]. World Journal of Surgery. 2005 Oct;29(10):1325-8.
[238] Shan Y-S, Sy ED, Lin P-W. Role of somatostatin in the prevention of pancreatic stump-related morbidity following elective pancreaticoduodenectomy in high-risk patients and elimination of surgeon-related factors: prospective, randomized, controlled trial. World Journal of Surgery. 2003 Jun;27(6):709-14.
[239] Gouillat C, Chipponi J, Baulieux J, Partensky C, Saric J, Gayet B. Randomized controlled multicentre trial of somatostatin infusion after pancreaticoduodenectomy. British Journal of Surgery. 2001 Nov;88(11):1456-62.
[240] Sarr MG, Pancreatic Surgery G. The potent somatostatin analogue vapreotide does not decrease pancreas-specific complications after elective pancreatectomy: a prospective, multicenter, double-blinded, randomized, placebo-controlled trial. J Am Coll Surg. 2003 Apr;196(4):556-64; discussion 64-5; author reply 65.
[241] Bruno MJ. Maldigestion and Exocrine Pancreatic Insufficiency after Pancreatic Resection for Malignant Disease. Pancreatology. 2001;1, suppl.1:55-61.
[242] Safdi M, Bekal PK, Martin S, Saeed ZA, Burton F, Toskes PP. The effects of oral pancreatic enzymes (Creon 10 capsule) on steatorrhea: a multicenter, placebo-controlled, parallel group trial in subjects with chronic pancreatitis. Pancreas. 2006 Aug;33(2):156-62.
[243] Stern RC, Eisenberg JD, Wagener JS, Ahrens R, Rock M, doPico G, et al. A comparison of the efficacy and tolerance of pancrelipase and placebo in the treatment of steatorrhea in cystic fibrosis patients with clinical exocrine pancreatic insufficiency. Am J Gastroenterol. 2000 Aug;95(8):1932-8.
[244] Bruno MJ, Haverkort EB, Tijssen GP, Tytgat GN, van Leeuwen DJ. Placebo controlled trial of enteric coated pancreatin microsphere treatment in patients with unresectable cancer of the pancreatic head region. Gut. 1998 Jan;42(1):92-6.
[245] American Society of Anesthesiologists Task Force on Acute Pain M. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology. 2004 Jun;100(6):1573-81.
[246] Barzoi G, Carluccio S, Bianchi B, Vassia S, Colucci G, Mangiante GL. Morphine plus bupivacaine vs. morphine peridural analgesia in abdominal surgery: the effects on postoperative course in major hepatobiliary surgery. HPB Surg. 2000 Aug;11(6):393-9.
[247] Ravasco P, Monteiro-Grillo I, Camilo ME. Does nutrition influence quality of life in cancer patients undergoing radiotherapy? Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2003 May;67(2):213-20.
[248] Capra S, Bauer J, Davidson W, Ash S. Nutritional therapy for cancer-induced weight loss. Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition. 2002 Aug;17(4):210-3.
[249] Davidson W, Ash S, Capra S, Bauer J, Cancer Cachexia Study G. Weight stabilisation is associated with improved survival duration and quality of life in unresectable pancreatic cancer. Clin Nutr. 2004 Apr;23(2):239-47.
[250] Fearon KCH, Von Meyenfeldt MF, Moses AGW, Van Geenen R, Roy A, Gouma DJ, et al. Effect of a protein and energy dense N-3 fatty acid enriched oral supplement on loss of weight and lean tissue in cancer cachexia: a randomised double blind trial.[see comment]. Gut. 2003 Oct;52(10):1479-86.
[251] Bauer J, Capra S, Battistutta D, Davidson W, Ash S, Cancer Cachexia Study G. Compliance with nutrition prescription improves outcomes in patients with unresectable pancreatic cancer. Clin Nutr. 2005 Dec;24(6):998-1004.
[252] Moses AWG, Slater C, Preston T, Barber MD, Fearon KCH. Reduced total energy expenditure and physical activity in cachectic patients with pancreatic cancer can be modulated by an energy and protein dense oral supplement enriched with n-3 fatty acids. British Journal of Cancer. 2004 Mar 8;90(5):996-1002.
[253] Yan BM, Myers RP. Neurolytic celiac plexus block for pain control in unresectable pancreatic cancer. Am J Gastroenterol. 2007 Feb;102(2):430-8.
[254] Zhang C-L, Zhang T-J, Guo Y-N, Yang L-Q, He M-W, Shi J-Z, et al. Effect of neurolytic celiac plexus block guided by computerized tomography on pancreatic cancer pain. Dig Dis Sci. 2008 Mar;53(3):856-60.
[255] Ischia S, Ischia A, Polati E, Finco G. Three posterior percutaneous celiac plexus block techniques. A prospective, randomized study in 61 patients with pancreatic cancer pain. Anesthesiology. 1992 Apr;76(4):534-40.
[256] Suleyman Ozyalcin N, Talu GK, Camlica H, Erdine S. Efficacy of coeliac plexus and splanchnic nerve blockades in body and tail located pancreatic cancer pain. Eur J Pain. 2004 Dec;8(6):539-45.
[257] Gress F, Schmitt C, Sherman S, Ikenberry S, Lehman G. A prospective randomized comparison of endoscopic ultrasound- and computed tomography-guided celiac plexus block for managing chronic pancreatitis pain.[see comment]. Am J Gastroenterol. 1999 Apr;94(4):900-5.

[258] Kuchler T, Bestmann B, Rappat S, Henne-Bruns D, Wood-Dauphinee S. Impact of psychotherapeutic support for patients with gastrointestinal cancer undergoing surgery: 10-year survival results of a randomized trial.[see comment][erratum appears in J Clin Oncol. 2007 Sep 20;25(27):4328]. J Clin Oncol. 2007 Jul 1;25(19):2702-8.

[259] Meyers MO, Meszoely IM, Hoffman JP, Watson JC, Ross E, Eisenberg BL. Is reporting of recurrence data important in pancreatic cancer? Ann Surg Oncol. 2004 Mar;11(3):304-9.

[260] Wilkowski R, Thoma M, Bruns C, Duhmke E, Heinemann V. Combined chemoradiotherapy for isolated local recurrence after primary resection of pancreatic cancer. Jop. 2006;7(1):34-40.

[261] Kleeff J, Reiser C, Hinz U, Bachmann J, Debus J, Jaeger D, et al. Surgery for recurrent pancreatic ductal adenocarcinoma. Ann Surg. 2007 Apr;245(4):566-72.

[262] Miura F, Takada T, Amano H, Yoshida M, Isaka T, Toyota N, et al. Repeated pancreatectomy after pancreatoduodenectomy. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2007 Feb;11(2):179-86.

[263] Nakeeb A, Lillemoe KD, Cameron JL. The role of pancreaticoduodenectomy for locally recurrent or metastatic carcinoma to the periampullary region. J Am Coll Surg. 1995 Feb;180(2):188-92.

[264] Moriya T, Kimura W, Hirai I, Mizutani M, Yamamoto T, Toya R, et al. Twelve years survival with repeated hepatectomy and lung resection for metastasis from carcinoma of the papilla of Vater after pancreaticoduodenectomy. Hepatogastroenterology. 2007 Sep;54(78):1652-4.

Searched guideline websites and websites of oncologic organisations	
Alberta Heritage Foundation For Medical Research (AHFMR)	http://www.ahfmr.ab.ca/
American Society of Clinical Oncology (ASCO)	http://www.asco.org/
American College of Surgeons (ACS)	http://www.facs.org/cancer/coc/
Cancer Care Ontario	http://www.cancercare.on.ca/english/home/
CMA Infobase	http://mdm.ca/cpgsnew/cpgs/index.asp
Guidelines International Network (GIN)	http://www.g-i-n.net/
National Comprehensive Cancer Network (NCCN)	http://www.nccn.org/
National Guideline Clearinghouse	http://www.guideline.gov/
National Cancer Institute	http://www.cancer.gov/
Haute Autorité de Santé (HAS)	http://bfes.has-sante.fr/HTML/indexBFES_HAS.html
BC Cancer Agency	http://www.bccancer.bc.ca/default.htm
Institute for Clinical Systems Improvement (ICSI)	http://www.icsi.org/index.asp
National Health and Medical Research Council (NHMRC)	http://www.nhmrc.gov.au/
Scottish Intercollegiate Guidelines Network (SIGN)	http://www.sign.ac.uk/
New Zealand Guidelines Group (NZGG)	http://www.nzgg.org.nz/
Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC)	http://www.fnclcc.fr/sor/structure/index-sorspecialistes.html
National Institute for Health and Clinical Excellence (NICE)	http://www.nice.org.uk/

Grade of Recommendation/ Description	Benefit vs. Risk and Burdens	Methodological Quality of Supporting Evidence	Implications
1A/ Strong recommendation, high quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B/ Strong recommendation, moderate quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C/ Strong recommendation, low quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation, but may change when higher quality evidence becomes available
2A/ Weak recommendation, high quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B/ Weak recommendation, moderate quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C/ Weak recommendation, low quality evidence	Benefits closely balanced with risks and burden	Observational studies or case series	Very weak recommendation, other alternatives may be equally reasonable

PANCREATIC CANCER

Number	Name	Number	Name
1	Right cardiac	13	**Posterior pancreaticoduodenal**
2	Left cardiac	13a	Superior to ampulla of Vater
3	Gastric lesser curve	13b	Inferior to ampulla of Vater
4	Gastric greater curve	14	**Proximal mesenteric lymph nodes**
5	Superior pyloric	14a	Origin of SMA
6	Inferior pyloric	14b	Right side of SMA
7	Left gastric artery	14c	Anterior SMA at middle colic artery
8	**Common hepatic artery**	14d	Left side of SMA at first jejunal branch
8a	Anterosuperior	14v	SMV nodes
8p	Posterior	15	Middle colic vessels
9	Celiac origin	16	**Aorta-caval nodes**
10	Splenic hilum	16a1	Aortic hiatus of diaphragm
11	Splenic artery	16a2	Celiac to left renal vein
12	**Hepatoduodenal ligament**	16b1	Left renal vein to IMA
12a1	Along hepatic artery, superior	16b2	IMA to aortic bifurcation
12a2	Along hepatic artery, inferior	17	**Anterior pancreaticoduodenal**
12b1	Along bile duct, superior	17a	Superior to ampulla of Vater
12b2	Along bile duct, inferior	17b	Inferior to ampulla of Vater
12c	Around cystic duct	18	Inferior border of pancreatic body and tail
12h	Hepatic hilum		
12p1	Retro portal vein, superior		
12p2	Retro portal vein, inferior		

(source: Japanese Pancreas Society [JCS] classification [147])

T Primary Tumour	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour limited to the pancreas, 2 cm or less in greatest dimension
T2	Tumour limited to the pancreas, more than 2 cm in greatest dimension
T3	Tumour extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4	Tumour involves the celiac axis or the superior mesenteric artery (unresectable primary tumour)
N Regional Lymph Nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes metastasis.
N1	Regional lymph node metastasis
M Distant Metastasis	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage 0 (Tis N0 M0)	The tumor is confined to the top layers of pancreatic duct cells and has not invaded deeper tissues. It has not spread outside of the pancreas. These tumors are sometimes referred to as pancreatic carcinoma in situ or pancreatic intraepithelial neoplasia III (PanIn III).
Stage IA (T1 N0 M0)	The tumor is confined to the pancreas and is less than 2 cm in size. It has not spread to nearby lymph nodes or distant sites.
Stage IB (T2 N0 M0)	The tumor is confined to the pancreas and is larger than 2 cm in size. It has not spread to nearby lymph nodes or distant sites.
Stage IIA (T3 N0 M0)	The tumor is growing outside the pancreas but not into large blood vessels. It has not spread to nearby lymph nodes or distant sites.
Stage IIB (T1-3 N1 M0)	The tumor is either confined to the pancreas or growing outside the pancreas but not into nearby large blood vessels or major nerves. It has spread to nearby lymph nodes but not distant sites.
Stage III (T4, any N, M0)	The tumor is growing outside the pancreas into nearby large blood vessels or major nerves. It may or may not have spread to nearby lymph nodes. It has not spread to distant sites.
Stage IV (any T, any N, M1)	The cancer has spread to distant sites.

T categories	T1: Tumour size 0 – 2 cm. T2: Tumour size 2.1 – 4 cm. T3: Tumour size 4.1 – 6 cm. T4: Tumour size >6 cm.
N categories	N0: No lymph node involvement. N1: Involvement of regional lymph nodes close to the primary tumour. N2: Involvement of regional lymph nodes distant from the primary tumour. N3: Involvement of lymph nodes other than regional.
Invasion of peripancreatic tissues	Rp-S-PV 0: Absence of retroperitoneal serosal – portal vein system invasion Rp-S-PV 1: Suspected retroperitoneal serosal – portal vein system invasion Rp-S-PV 2: Definite retroperitoneal serosal – portal vein system invasion Rp-S-PV 3: Severe retroperitoneal serosal – portal vein system invasion
Stage grouping for pancreatic cancer	The most advanced factor determines the stage. Distant metastasis is stage IV. Stage I: T1 and N0 and Rp0 and S0 and PV0 Stage II: T2 and/or N1 and/or Rp1 and/or S1 and/or PV1 Stage III: T3 and/or N2 and/or Rp2 and/or S2 and/or PV2 Stage IV: T4 and/or N3 and/or Rp3 and/or S3 and/or PV3

WHO DEFINITION OF INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS (IPMNS) [145]

An intraductal papillary mucin-producing neoplasm, arising in the main pancreatic duct or its major branches. The papillary epithelial component and the degree of mucin secretion, cystic dilatation, and invasiveness are variable. Intraductal papillary-mucinous neoplasms are divided into benign, borderline, and malignant noninvasive or invasive lesions.

WHO GRADING OF INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS (IPMNS) [145]

IPMN adenoma: The epithelium is comprised of tall columnar mucin-containing cells that show slight or no dysplasia (i.e. the epithelium maintains a high degree of differentiation in adenomas).

IPMN borderline: IPMNs with moderate dysplasia are placed in the borderline category. The epithelium shows no more than moderate loss of polarity, nuclear crowding, nuclear enlargement, pseudostratification, and nuclear hyperchromatism. Papillary areas maintain identifiable stromal cores, but pseudopapillary structures may be present.

Intraductal papillary mucinous carcinoma: IPMNs with severe dysplastic epithelial change (carcinoma in situ) are designated as carcinoma even in the absence of invasion. They can be papillary or micropapillary. Cribriform growth and budding of small clusters of epithelial cells into the lumen support the diagnosis of carcinoma in situ. Severe dysplasia is manifest cytologically as loss of polarity, loss of differentiated cytoplasmic features including diminished mucin content, cellular and nuclear pleomorphism, nuclear enlargement, and the presence of mitoses (especially if suprabasal or luminal). Severely dysplastic cells may lack mucin.

