Diagnostic and Therapeutic Approach to Pancreatic Adenocarcinoma

Stylianos Germanos[1], Stavros Gourgiotis[2], Aglaia Stavrothanasopoulou[3], Periklis Alepas[4], Nikolaos Zampitis[5], Aikaterini Panteli[6]

1) Upper Gastrointestinal and General Surgery, Leighton Hospital, Mid Cheshire NHS Trust. 2) Division of General Surgery and Oncology, Royal Liverpool University Hospital, UK. 3) Department of Medicine, Patras University Hospital, Patras. 4) Surgical Department, 401 Military Hospital of Athens. 5) 1st Surgical Department, 'Evangelismos' General Hospital of Athens. 6) Surgical Department, General Panarcadic Hospital of Tripoli, Greece

Abstract

Pancreatic adenocarcinoma is the sixth leading cause of cancer-related death in Europe with survival rates remaining unchanged over the last three decades. Early diagnosis and accurate staging are essential due to the difficulty of curing this tumor in its advanced form. Endoscopic or laparoscopic ultrasonography and computed tomography are the preferred imaging and staging modalities for many patients with pancreatic adenocarcinoma. Morbidity and mortality are similar for pylorus-preserving and classic pancreaticoduodenectomy. Extended retroperitoneal lymphadenectomy does not improve survival and increases morbidity compared with standard pancreaticoduodenectomy, while adjuvant chemoradiotherapy prolongs survival in selected groups of patients. This article reviews the causes, risk factors, and clinical features of pancreatic adeno-carcinoma and discusses the methods of optimal diagnosis, staging and treatment.

Key words

Pancreas - adenocarcinoma - pancreatectomy - chemo-radiotherapy

Introduction

Pancreatic adenocarcinoma is the most common epithelial exocrine pancreatic neoplasm which accounts for up to 80-90% of all malignant pancreatic tumours. It was found that in series of surgical resections, 80-90% of tumours were located in the head of the pancreas (1). It is one of the most lethal human cancers and currently the fifth most common cause of cancer death in men, the sixth in women (2), and generally the sixth leading cause of cancer-related death all over Europe. The latest data from Europe show that the highest mortality rates are found in Hungary, Austria and the Czech Republic, while the lowest rates are found in Albania and Latvia (3).

Pancreatic adenocarcinoma is characterized by a late presentation which is responsible in part for the 5-year survival rate up to 4% (4). Recently, improvements in perioperative management have decreased the patients' morbidity and mortality after pancreatectomy but their prognosis remain unchanged. Between 10% and 20% of patients are candidates for curative resection with a 5-year survival rate of 7-25% (5). Although surgery remains the cornerstone for the management of pancreatic adeno-carcinoma and the only potential for cure, virtually all patients are dead within 7 years of surgery (1).

This study reviews the causes, risk factors, clinical symptoms and signs, diagnosis, staging and management of pancreatic adenocarcinoma. A Pubmed database search was performed. All abstracts were reviewed and every article and prospective randomized clinical trials of pancreatic adenocarcinoma was scrutinized. Further references were extracted by cross-referencing.

Causes and risk factors

Pancreatic adenocarcinoma is more prevalent in men than women and occurs in older age-groups, affecting individuals in their 60s and 80s (6). A family history of pancreatic cancer or a genetic defect is often present in patients with an early onset of this disease. Inherited genetic factors and environmental factors are known as the main causes of pancreatic adenocarcinoma (Table I).

Racial factors may influence the natural course of pancreatic adenocarcinoma. In a study that included more than 10,000 patients residing in the USA, Asian patients tended to have less aggressive tumors compared with white and black patients. There were no clear explanations for this finding, but it could be attributed both to genetic factors and to differences in environmental exposures (7).

J Gastrointestin Liver Dis
September 2006 Vol.15 No.3, 257-263
Address for correspondence: Stavros Gourgiotis MD PhD
21 Millersdale Road
Mossley Hill, L18 5HG
Liverpool, UK
E-mail: drsgourgiotis@tiscali.co.uk

Table I Risk factors for pancreatic adenocarcinoma

Environmental factors
Smoking
Exposure to carcinogens (formaldehyde, organochlorines, chlorinated hydrocarbons)
Fat content of the diet
Pre-existing diseases
Chronic pancreatitis (alcoholic, non-alcoholic, hereditary)
Diabetes
Morbid obesity
Hereditary factors
Hereditary pancreatitis
Familial breast cancer syndrome
Non-polyposis colorectal cancer syndrome (HNPCC)
Peutz-Jeghers syndrome
Familial multiple mole melanoma syndrome (FAMMM)
Cystic fibrosis

Tobacco smoking is an established risk factor for pancreatic adenocarcinoma (8). The relative risk ranges from 1.5- to 3-fold for smokers versus non smokers patients depending on the number of smoked cigarettes per day (9). Dietary factors, particularly the fat content in the diet, have most consistently been associated with pancreatic adenocarcinoma (10), while coffee and alcohol unlikely play a major role in pancreatic carcinomatosis (6). Jobs with exposure to several carcinogens such as formaldehyde, organochlorines, chlorinated hydrocarbons and various other substances, could result in an increased risk of pancreatic adenocarcinoma (11).

Pre-existing diseases such as chronic pancreatitis, diabetes, cholelithiasis, and morbid obesity are associated with increased risk for pancreatic adenocarcinoma. In patients with history of alcoholic and non-alcoholic chronic pancreatitis the increased relative risk for pancreatic adenocarcinoma varies from 10- to 20-fold, while the cumulative risk for patients with hereditary pancreatitis is with 30-40% higher than for any other known risk factor (12-13). However, only 3-4% of pancreatic adenocarcinomas may be attributed to chronic pancreatitis (14). In patients with type 2 diabetes the increased relative risk ranges from 1.3- to 2-fold for pancreatic adenocarcinoma, while the role of cholelithiasis in pancreatic carcinogenesis is uncertain (6). The estimated risk for pancreatic cancer among obese patients is 19% when compared with patients with normal body mass index (15).

Finally, up to 10% of cases of pancreatic adenocarcinoma are attributed to hereditary factors (16). The familial breast cancer syndrome, the hereditary non-polyposis colorectal cancer syndrome (HNPCC), the Peutz-Jeghers syndrome, and the familial multiple mole melanoma syndrome (FAMMM) are familial cancer syndromes associated with high incidence of pancreatic adenocarcinoma (6). The most important inherited germline disorder is BRCA2 which was found in 17% of patients with a strong family history of pancreatic adenocarcinoma (17). In addition, germline mutations of $p16^{INK4a}$ have been observed in families which have a combination of pancreatic adenocarcinoma and melanoma (18).

Clinical symptoms and signs

There are no specific early-warning symptoms of pancreatic adenocarcinoma. Symptoms often appear when the tumor grows large enough to interfere with the function of the stomach, liver, or other nearby organs. The first symptoms are usually abdominal pain and weight loss. The characteristic pain pattern is a vague epigastric pain that may radiate to the back. It is typically more severe in the supine position and is improved by leaning forwards. The presence of either abdominal or back pain is reported to be an ominous predictor of resectability and survival. Kelsen et al (19) observed that 55% of patients without pain had a resectable disease, while only 25% of the patients reporting pain were amenable to resection. Similarly the median survival among patients with resectable pancreatic adenocarcinoma without pain history was 21.9 months whereas in patients with pain history the reported median survival was only 9.2 months (19).

Late-onset diabetes mellitus or an unexplained attack of acute pancreatitis may be the first sign of pancreatic adenocarcinoma but only in rare cases (20-21). The presence of insulin-dependent diabetes before the age of fifty in a healthy, non-obese, and with no family history of diabetes patient, increases the possibility of pancreatic adenocarcinoma. About 80% of pancreatic adenocarcinomas occur in the head of the pancreas and can cause obstructive jaundice with pruritus, light-colored bowel movements, and slow digestion of food. A palpable Courvoisier's gallbladder may be also present. Dyspepsia due to delayed gastric emptying, and vomiting due to duodenal obstruction may be manifestations of late stage pancreatic adenocarcinoma. Changes in bowel habits and diarrhoea as a result of common bile duct obstruction may be another symptom. In rare cases a superficial migratory thrombophlebitis may be the first but a delayed symptom of the disease. Finally, clinical features such as rapid weight loss, ascites, abdominal mass, and supraclavicular lymphadenopathy usually indicate an irresectable tumour.

Diagnosis and staging

Improvement of imaging modalities has led to the diagnosis of small and early stage tumours but have failed to demonstrate small liver metastases or peritoneal dissemination found during laparotomy.

Contrast-enhanced computed tomography (CT), with arterial and postal venous phases, is considered to be the 'gold standard' modality for staging pancreatic adenocarcinoma. Its accuracy in predicting resectability is high (90-100%) (22), but it is much less accurate in identifying potentially resectable small tumours due to its poor accuracy in detecting lymph node metastases, microscopic local tumor extension, small hepatic metastases and pancreatic adenocarcinomas smaller than 1 cm in diameter. Helical CT is reported to be accurate in determining tumour resectability

in 83%, the extent of the primary tumour in 73%, regional extension in 74%, vascular invasion in 83%, and distant metastases in 88% (23).

Endoscopic ultrasonography (EUS) is the preferred imaging modality in many patients due to its efficiency for evaluation of the whole pancreas using the combination of stomach and duodenum scans and its ability to detect small lesions (24). Its accuracy for tumor staging ranges from 78% to 94% and for nodal staging ranges from 64% to 82% (24,25). EUS-guided fine needle aspiration (EUS-FNA) can achieve the histologic diagnosis of primary tumours, lymph node and distant metastases (24,26), but it should be avoided when the outcome of the EUS-FNA does not affect treatment strategy in order to prevent tumor dissemination. In comparison with CT, EUS is more accurate in determining tumor size and lymph node involvement and is considered to be the most cost effective test for resectable pancreatic adenocarcinoma (23).

Magnetic resonance imaging (MRI) is equal or superior to CT for the staging of pancreatic adenocarcinoma; its ability to detect liver metastases is higher when compared with CT while its accuracy for lymph node infiltration is similar to CT (27). Magnetic resonance cholangiopancreatography (MRCP) and magnetic resonance angiography also provide additional information for pancreato-biliary ductal abnormalities and invasion of vascular structures (27).

Endoscopic retrograde cholangiopancreatography (ERCP) can provide detailed pancreatograms of the main pancreatic duct and its branches revealing the morphologic changes in the ductal system as a result of histologic changes. It allows biopsy of the pancreatic duct, brush cytology and collection of pancreatic fluid for cytology, and gene analysis, while the introduction of ultrasonic probes and baby scopes into the pancreatic duct is helpful in diagnosis of small intraductal and intra-parenchymal lesions (28,29).

Staging laparoscopy can identify small peritoneal or liver metastases which have failed to be evidenced in preoperative staging (30,31) and in combination with laparoscopic ultrasound (LUS) and peritoneal cytology can identify occult metastatic lesions in the peritoneal cavity and the liver in 10-35% of instances that were not detected by other imaging modalities (32,33). John et al (34), in a series of 50 patients, reported 68% sensitivity and 100% specificity for predicting non resectability using LUS compared with 71% sensitivity and 47% specificity using CT.

No single best modality is available for diagnosis and staging of pancreatic adenocarcinoma. Even the combination of imaging modalities may miss over one third of patients with irresectable tumour (35-37). Avoiding the morbidity and the cost of an unnecessary laparotomy, the routine use of laparoscopy is justified for patients with the diagnosis of a resectable tumour during the preoperative work-up. Furthermore, in patients who underwent neoadjuvant chemoradiation and restaging, laparoscopy is necessary for identifying resectable tumours (38).

Standard pancreaticoduodenectomy versus extended lymphadenectomy

In the past, some non randomized retrospective studies suggested that extended lymphadenectomy (ELND) in patients with pancreatic adenocarcinoma could benefit longer-term survival rates (39-41). Since then, several centers have undertaken prospective randomized trials to compare the results of these two procedures (Table II).

In the first ever prospective multicenter study of 81 patients, Pedrazzoli et al (42) failed to demonstrate significant differences in survival between the standard pancreaticoduodenectomy (PD) and ELND in patients with pancreatic head adenocarcinoma. The patients were randomized in standard (n = 40) or extended (n = 41) lymphadenectomy and retroperitoneal tissue clearance groups. None of them received any postoperative adjuvant therapy. The number of lymph nodes resected in the PD group was 13.3 $\pm$ 8.3

Table II Evaluation of survival, morbidity and mortality of standard pancreaticoduodenectomy versus extended lymph-adenectomy

Study, year (ref.)	Study type (period)	No. of patients	PD	ELND	Results on mortality and morbidity	Results on survival
Pedrazzoli et al, 1998 (42)	Multicenter prospective trandomized (1991-1994)	81	40	41	NS	NS / Trend towards longer survival rates for patients with positive nodes in the ELND group
Farnell et al, 2005 (43)	Single institution prospective randomized (1997-2003)	79	40	39	NS	NS
Riall et al, 2005 (44)	Single institution prospective randomized (1996-2001)	162	80	82	29% morbidity in the PD group 43% morbidity in the ELND group	NS

PD: standard pancreaticoduodenectomy; ELND: extended lymphadenectomy; NS: not statistically significant

compared with 19.8 ± 15.1 of the ELND group. There was no statistical significance regarding mortality, morbidity, length of the operation, transfusion requirements, and hospital stay. There was no difference in the overall survival rate but the authors demonstrated that patients with positive nodes who underwent ELND appeared to have longer survival rates and might have benefitted from a more aggressive procedure such as ELND.

Similarly, a study by Farnell et al (43) showed no long-term survival in patients who underwent ELND. The trial involved 40 patients in the PD group and 39 patients in the ELND group. The median number of resected lymph nodes was 15 and 36, respectively. Both groups received adjuvant therapy consisting of 5-fluorouracil (5-FU) and external beam radiation. After a median follow-up of 4 years, the median survival was 19 and 26 months, respectively with 1-year, 3-year and 5-year survival consisting of 71%, 25%, and 16.5% in the PD group and 82%, 41%, and 16.4% in the ELND group. Morbidity and mortality were similar in the two groups.

A large study by Johns Hopkins Medical Institution (44,45) with an update on 5-year survival, reported no improvement in long-term survival and a higher complication rate. This study included 294 patients with periampullary cancer; 162 of them had pancreatic adenocarcinoma. Eighty patients were randomized in the PD group and 82 in the ELND group. The mean number of resected lymph nodes in the two groups was 17 and 28 respectively. 78% of patients in both groups underwent postoperative chemoradiation. After a median follow-up of 5.3 years, the 1- and 5-year survival for pancreatic adenocarcinoma was 75% and 13% respectively compared with 73% and 29% in the patients who underwent ELND. The authors reported that this difference was not statistically significant and they attributed the apparent difference in the 5-year survival to the fact that 21% of patients in the PD group had a margin positive resection compared with a 5% in the ELND group. The overall complication rate was 29% in the standard group compared with 43% in the radical group, with longer hospital stay, increased rate of pancreatic fistula, and delayed gastric emptying.

Recent prospective randomized studies were unable to demonstrate an improvement in survival when performing more radical operations. Morbidity was similar, while in some of the studies this remained higher during the radical procedures.

Standard pancreaticoduodenectomy versus pylorus preserving pancreaticoduodenectomy

The pylorus preserving pancreaticoduodenectomy (PPPD) was originally described by Watson in 1944 and popularized by Traverso and Longmire in the late 1970s (46). In the past, it was criticized for its radicalness when applied to patients with malignancy (47,48) and it was associated with a higher incidence of delayed gastric emptying (49).Several prospective randomized trials were undertaken investigating the effectiveness of PPPD towards PD for the treatment of pancreatic head adenocarcinoma (Table III).

In a prospective randomized multicenter analysis enrolling 134 patients with pancreatic adenocarcinoma and periampullary tumours, the two procedures were found equally effective in the treatment of pancreatic adenocarcinoma. The study included 68 patients (47 of them with pancreatic adenocarcinoma) who underwent PPPD and 66 patients (43 of them with pancreatic adenocarcinoma) who underwent PD. The duration of operation, blood loss, hospital stay, and postoperative weight loss were similar in these two groups. In the subgroup of patients with pancreatic adenocarcinoma the disease-free survival was 6 months in the PPPD group and 7 months in the PD group. The median survival was 12 and 11 months, respectively (50).

Table III Evaluation of survival, morbidity and mortality of standard pancreaticoduodenectomy versus pylorus preserving pancreaticoduodenectomy

Study, year (ref.)	Study type (period)	No. of patients	PD	PPPD	Results on mortality and morbidity	Results on survival
Tran et al, 2004 (50)	Multicenter prospective randomized (1992-2000)	134	66 (Pancreatic cancer n = 43)	68 (Pancreatic cancer n = 47)	NS	NS
Seiler et al, 2000, 2005 (51,52)	Multicenter prospective randomized (1996-2001)	110	57 (Pancreatic cancer n = 37)	53 (Pancreatic cancer n = 43)	Shorter operative time, less blood loss, earlier return to work after surgery in the PPPD group	NS
Lin and Lin 1999(53)	Single institution prospective randomized (1994-1997)	31	15 (Pancreatic cancer n = 3)	16 (Pancreatic cancer n = 2)	Delayed gastric emptying in the PPPD group with marginal statistical significance	NS

PD: standard pancreaticoduodenectomy; PPPD: pylorus preserving pancreaticoduodenectomy; NS: not statistically significant

A study by Seiler et al (51,52) enrolled 110 patients with proven pancreatic cancer; 53 patients in the PPPD group (37 with pancreatic adenocarcinoma) and 57 patients in the PD group (43 with pancreatic adeno-carcinoma). Both procedures were found to be equally ef-fective, while PPPD were found to be associated with shorter operative time, less blood loss, and an earlier return to work 6 months after surgery. There was no difference in terms of overall survival, tumour recurrence and quality of life. For the patients with pancreatic adenocarcinoma the median survival in the PPPD group was 49 months (lymph node-negative) and 15 months (lymph node-positive) compared with 39 and 18 months respectively, in the PD group.

In another small study with 31 patients, (16 patients in PPPD group and 15 patients in PD group), there was no significant difference in the term of operating time, blood loss and blood transfusion, while delayed gastric emptying was observed more frequently after PPPD with marginal statistical significance (53).

PPPD is as effective as PD for the treatment of the pancreatic head adenocarcinoma. It may be associated with shorter operating time and less blood loss, while there are conflicting results regarding the incidence of delayed gastric emptying. A possible explanation is that the incidence of delayed gastric emptying is not associated with the type of the procedure per se but is strongly correlated with the incidence of intra-abdominal complications (50-54).

Adjuvant therapy

Published data about the role of adjuvant therapy in pancreatic adenocarcinoma are not conclusive and the treatment strategies vary (5,55-59). In a study using the U.S. National Cancer Database in which a total of 100,313 patients with pancreatic cancer were enrolled, 9% (n = 9044) of them underwent pancreatectomy. Of these 9044 patients, 60% underwent pancreatectomy alone, 28% pancreatectomy and chemoradiation, and 12% pancreatectomy and radiation or chemotherapy. The overall five year survival rates in these three groups of patients were 23.3%, 17%, and 14.9% respectively (5).

The European Study Group for Pancreatic Cancer (ESPAC) 1 trial (55) used a two-by-two factorial design in which each patient was randomly assigned to receive chemoradiotherapy or chemotherapy, both, or no adjuvant treatment after the resection of the pancreatic adenocarcinoma. In this study, which randomized 289 patients from 11 European countries, the results showed that in terms of prolonged survival the standard care for resectable pancreatic adenocarcinoma should be a negative margin resection followed by systemic chemotherapy. Patients who were treated with postoperative chemotherapy had a median survival of 20.1 months compared with 15.5 months in the group of patients who were treated with surgical resection only. Surprisingly, chemoradiotherapy was found to reduce survival when it was performed before chemotherapy and did not show any benefit. Chemotherapy consisted of leucovorin and fluorouracil, while chemo-radiotherapy consisted of 20 Gy dose plus fluorouracil.

Neoadjuvant chemoradiotherapy may downstage patients with locally advanced irresectable pancreatic adenocarcinoma and permit surgical resection (60-63). In a group of 61 patients with locally advanced pancreatic adenocarcinoma, 23 (38%) patients had tumoral response and in 13 (21%) of them a Whipple procedure was performed. These patients received a total dose of 45 Gy of radiation therapy combined with infusion of fluorouracil and cisplatin. The median survival of the patients who underwent surgical resection was 20 months, which was similar to that of patients with initially resectable pancreatic adenocarcinoma (60).

Several studies showed a survival benefit of adjuvant chemotherapy (55,59) and adjuvant treatment was established in patients who had "curative" resection. The benefits of radiotherapy and neoadjuvant treatment on the other hand are still controversial.

Survival prognostic factors after resection

Previous reports have identified negative lymph node status, a small primary tumour diameter less than 2 cm, well or moderately differentiated tumour, negative resection margins and absence of vascular invasion as favourable prognostic factors (56,64,65) for pancreatic adenocarcinoma. Several other factors such as biological features, preoperative Ca 19.9 levels, centre specialization and administration of adjuvant therapy also influence prognosis (58,66-70). The ESPAC-1 trial reported that only tumour grade and lymph node status were identified as independent prognostic factors (1). The limits of surgery are defined by the low resectability rates on presentation and the aggressiveness of pancreatic adenocarcinoma. However, recurrence after 5 years remains likely despite the presence of favourable prognostic factors (71).

Conclusion

Pancreatic adenocarcinoma has dismal prognosis due to late diagnosis and tumor aggressiveness. Surgical resections provide the only influential chance of increased survival. Adjuvant treatment improves survival after onco-logical resection. The current standard of care of pancreatic adenocarcinoma is the combination of surgical resection and adjuvant chemotherapy. Current and future develop-ments in diagnosis, in epidemiology, in tumour behavior, in adjuvant and gene therapy may improve survival rates.

References

1. Alexakis N, Halloran C, Raraty M, Ghaneh P, Sutton R, Neoptolemos JP. Current standards of surgery for pancreatic cancer. Br J Surg 2004; 91: 1410-1427.
2. Matsuno S, Egawa S, Fukuyama S, et al. Pancreatic cancer

registry in Japan: 20 years of experience. Pancreas 2004; 28: 219-230.
3. Bray F, Sankila R, Ferlay J, Parkin DM. Estimates of cancer incidence and mortality in Europe in 1995. Eur J Cancer 2002; 38: 99-166.
4. Jemal A, Murray T, Samuels A, Ghafoor A, Ward E, Thun MJ. Cancer statistics, 2003. CA Cancer J Clin 2003; 53: 5-26.
5. Sener SF, Fremgen A, Menck HR, Winchester DP. Pancreatic cancer: a report of treatment and survival trends for 100,313 patients diagnosed from 1985-1995, using the National Cancer Database. J Am Coll Surg 1999; 189: 1-7.
6. Mishaud DS. Epidemiology of pancreatic cancer. Minerva Chir 2004; 59: 99-111.
7. Longnecker DS, Karagas MR, Tosteson TD, Mott LA. Racial differences in pancreatic cancer: comparison of survival and histologic types of pancreatic carcinoma in Asians, blacks and whites in the United States. Pancreas 2000; 21: 338-343.
8. Anderson KE, Potter JD, Mack TM. Pancreatic cancer. In: Schottenfeld and Fraumeni's, *Cancer epidemiology and prevention.* Oxford Univ Press, New York 1996, 725-771.
9. Ahigren JD. Epidemiology and risk factors in pancreatic cancer. Semin Oncol 1996; 23: 241-250.
10. Stolzenberg-Solomon RZ, Pietinen P, Taylor PR, Virtamo J, Albanes D. Prospective study of diet and pancreatic cancer in male smokers. Am J Epidemiol 2002; 155: 783-792.
11. Kauppinen T, Partanen T, Degerth R, Ojajarvi A. Pancreatic cancer and occupational exposures. Epidemiology 1995; 6 :498-502.
12. Lowenfels AB, Maisonneuve P, DiMagno EP, et al. Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group. J Natl Cancer Inst 1997; 89: 442-446.
13. Lowenfels AB, Maisonneuve P, Cavallini G, et al. Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group. N Engl J Med 1993; 328: 1433-1437.
14. Lowenfels AB, Maisonneuve P, Lankisch PG. Chronic pancreatitis and other risk factors for pancreatic cancer. Gastroenterol Clin North Am 1999; 28: 673-685.
15. Berrington de Gonzalez A, Sweetland S, Spencer E. A meta-analysis of obesity and risk of pancreatic cancer. Br J Cancer 2003; 89: 519-523.
16. Lynch HT, Smyrk T, Kern SE, et al. Familial pancreatic cancer: a review. Semin Oncol 1996; 23: 251-275.
17. Murphy KM, Brune KA, Griffin C, et al. Evaluation of candidate genes MAP2K4, MADH4, ACVR1B and BRCA2 in familial pancreatic cancer: deleterious BRCA2 mutation in 17%. Cancer Res 2002; 62: 3789-3793.
18. Bartsh DK, Sina-Frey M, Lang S, et al. CDKN2A germline mutations in familial pancreatic cancer. Ann Surg 2002; 236: 730-737.
19. Kelsen DP, Portenoy R, Thaler H, Tao Y, Brennan M. Pain as a predictor of outcome in patients with operable pancreatic carcinoma. Surgery 1997; 122: 53-59.
20. Murr MM, Sarr MG, Oishi AJ, van Heerden JA. Pancreatic cancer. CA Cancer J Clin 1994; 44: 304-318.
21. Mujica VR, Barkin JS, Go VL. Acute pancreatitis secondary to pancreatic carcinoma. Study Group Participants. Pancreas 2000; 21: 329-332.
22. McCarthy MJ, Evans J, Sagar G, Neoptolemos JP. Prediction of resectability of pancreatic malignancy by computed tomography. Br J Surg 1998; 85: 320-325.
23. Soriano A, Castells A, Ayuso JR, et al. Preoperative staging and tumor resectability assessment of pancreatic cancer: prospective study comparing endoscopic ultrasonography, helical computed tomography, magnetic resonance imaging and angiography. Am J Gastroenterol 2004; 99: 492-501.
24. Varadarajulu S, Wallace MB. Applications of endoscopic ultrasonography in pancreatic cancer. Cancer Control 2004; 11: 15-22.
25. Santo E. Pancreatic cancer imaging: Which method? JOP 2004; 5: 253-257.
26. Kahl S, Malfertheiner P. Role of endoscopic ultrasound in the diagnosis of patients with solid pancreatic masses. Dig Dis 2004; 22: 26-31.
27. Saisho H, Yamaguchi T. Diagnostic imaging for pancreatic cancer. Pancreas 2004; 28: 273-278.
28. Ishimaru S, Itoh M, Hanada K, Tsuchida A, Iwao T, Kajiyama G. Immunocytochemical detection of p53 protein from pancreatic duct brushings in patients with pancreatic carcinoma. Cancer 1996; 77: 2233-2239.
29. Nakaizumi A, Tatsuta M, Uehara H, et al. Effectiveness of the cytologic examination of pure pancreatic juice in the diagnosis of early neoplasia of the pancreas. Cancer 1995; 76: 750-757.
30. Cuschieri A, Hall CW, Clark J. Value of laparoscopy in the diagnosis and management of pancreatic cancer. Gut 1978; 19: 672-677.
31. Ellsmere J, Moltele K, Sahani D, et al. Does multidetector-row CT eliminate the role of diagnostic laparoscopy in assessing the resectability of pancreatic head adenocarcinoma? Surg Endosc 2005; 19: 369-373.
32. Minnard EA, Conlon KC, Hoos A, Dougherty EC, Hann LE, Brennan MF. Laparoscopic ultrasound enhances standard laparoscopy in the staging of pancreatic cancer. Ann Surg 1998; 228: 182-187.
33. Jimenez RE, Warshaw AL, Fernandez-Del Castillo C. Laparoscopy and peritoneal cytology in the staging of pancreatic cancer. J Hepatobiliary Pancreat Surg 2000; 7: 15-20.
34. John TG, Wright A, Allan PL, Paterson-Brown S, Carter DC, Garden OJ. Laparoscopy with laparoscopic ultrasonography in the TNM staging of pancreatic carcinoma. World J Surg 1999; 23: 870-881.
35. Kwon AH, Inui H, Kamiyama Y. Preoperative laparoscopic examination using surgical manipulation and ultrasonography for pancreatic lesions. Endoscopy 2002; 34: 464-468.
36. Conlon KC, Dougherty E, Klimstra DS, Coit DG, Turnbull AD, Brennan MF. The value of minimal access surgery in the staging of patients with potentially resectable peripancreatic malignancy. Ann Surg 1996; 223: 134-140.
37. Schachter PP, Avni Y, Shimonov M, Gvirtz G, Rosen A, Czerniak A. The impact of laparoscopy and laparoscopic ultrasonography on the management of pancreatic cancer. Arch Surg 2000; 135: 1303-1307.
38. White RR, Paulson EK, Freed KS, et al. Staging of pancreatic cancer before and after neoadjuvant chemoradiation. J Gastrointest Surg 2001; 5: 6239.
39. Satake K, Nishiwaki H, Yokomatsu H, et al. Surgical curability and prognosis for standard versus extended resections for T1 carcinoma of the pancreas. Surg Gynecol Obstet 1992; 175: 259-265.
40. Ishikawa O, Ohhigashi H, Sasaki Y, et al. Practical usefulness of lymphatic and connective tissue clearance for the carcinoma of the pancreatic head. Ann Surg 1988; 208: 215-220.6-633.

41. Kayahara M, Nagakawa T, Ueno K, Ohta T, Tsukioka Y, Miyazaki I. Surgical strategy for carcinoma of the pancreas head area based on clinicopathologic analysis of nodal involvement and plexus invasion. Surgery 1995; 117: 616-623.
42. Pedrazzoli S, DiCarlo V, Dionigi R, 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; 228: 508-517.
43. Farnell MB, Pearson RK, Sarr MG, et al; Pancreas Cancer Working Group. A prospective randomized trial comparing standard pancreaticoduodenectomy with extended lymphadenectomy in respectable pancreatic head adenocarcinoma. Surgery 2005; 138: 618-630.
44. Riall TS, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma - part 3: update on 5-years survival. J Gastrointest Surg 2005; 9: 1191-1206.
45. Yeo CJ, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma - part 2: randomized controlled trial evaluating survival, morbidity, and mortality. Ann Surg 2002; 236: 355-368.
46. Traverso LW, Longmire WP. Preservation of the pylorus in pancreaticoduodenectomy. Surg Gynecol Obstet 1978; 146: 959-962.
47. Sharp KW, Ross CB, Halter SA, et al. Pancreaticoduodenectomy with pyloric preservation for carcinoma of the pancreas: a cautionary note. Surgery 1989; 105: 645-653.
48. Roder JD, Stein HJ, Huttl W, Siewert JR. Pylorus preserving versus standard pancreaticoduodenectomy: an analysis of 110 pancreatic and periampullary carcinomas. Br J Surg 1992; 79: 152-155.
49. Kobayashi I, Miyachi M, Kanai M, et al. Different gastric emptying of solid and liquid meals after pylorus-preserving pancreatoduodenectomy. Br J Surg 1998; 85: 927-930.
50. Tran KT, Smeenk HG, van Eijck CH, et al. Pylorus preserving pancreaticoduodenectomy versus standard Whipple procedure. A prospective, randomized, multicenter analysis of 170 patients with pancreatic and periampullary tumors. Ann Surg 2004; 240: 738-745.
51. Seiler CA, Wagner M, Sadowski C, Kulli C, Buchler MW. Randomized prospective trial of pylorus-preserving vs. classic duodenopancreatectomy (Whipple procedure): initial clinical results. J Gastrointest Surg 2000; 4: 443-452.
52. Seiler CA, Wagner M, Bachmann T, et al. Randomized clinical trial of pylorus-preserving duodenopancreatectomy versus classical Whipple resection - long term results. Br J Surg 2005; 92: 547-556.
53. Lin PW, Lin YJ. Prospective randomized comparison between pylorus-preserving and standard pancreaticoduodenectomy. Br J Surg 1999; 86: 603-607.
54. van Berge Henegouwen MI, van Gulik TM, DeWit LT, et al. Delayed gastric emptying after standard pancreaticoduodenectomy versus pylorus-preserving pancreaticoduodenectomy: an analysis of 200 consecutive patients. J Am Coll Surg 1997; 185: 373-379.
55. Neoptolemos JP, Stocken DD, Friess H, et al; European Study Group for Pancreatic Cancer. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med 2004; 350: 1200-1210.
56. Sohn TA, Yeo CJ, Cameron JL, et al. Resected adenocarcinoma of the pancreas - 616 patients: results, outcomes, and prognostic indicators. J Gastrointest Surg 2000; 4: 567-579.
57. O'Connor JK, Sause WT, Hazard LJ, Belnap LP, Noyes RD. Survival after attempted surgical resection and intraoperative radiation therapy for pancreatic and periampullary adenocarcinoma. Int J Radiation Oncology Biol Phys 2005; 63: 1060-1066.
58. Ahmad NA, Lewis JD, Ginsberg GG, et al. Long term survival after pancreatic resection for pancreatic adenocarcinoma. Am J Gastroenterol 2001; 96: 2609-2615.
59. Beger HG, Rau B, Gansauge F, Poch B, Link KH. Treatment of pancreatic cancer: challenge of the facts. World J Surg 2003; 27: 1075-1084.
60. Sa Cunha A, Rault A, Laurent C, et al. Surgical resection after radiochemotherapy in patients with unresectable adenocarcinoma of the pancreas. J Am Coll Surg 2005; 201: 359-365.
61. Wanedo HJ, Glicksman AS, Vezeridis MP, et al. Preoperative chemotherapy, radiotherapy and surgical resection of locally advanced pancreatic cancer. Arch Surg 2000; 135: 81-87.
62. Breslin TM, Hess KR, Harbison DB, et al. Neoadjuvant chemoradiotherapy for adenocarcinoma of the pancreas: treatment variables and survival duration. Ann Surg Oncol 2001; 8: 123-132.
63. Neoptolemos JP, Cunningham D, Friess H, et al. Adjuvant therapy in pancreatic cancer: historical and current prospectives. Ann Oncol 2003; 14: 675-692.
64. Baumel H, Huguier M, Manderscheid JC, Fabre JM, Houry S, Fagot H. Results of resection for cancer of the exocrine pancreas: a study from the French Association of Surgery. Br J Surg 1994; 81: 102-107
65. Kuhlmann KF, De Castro SM, Wesseling JG, et al. Surgical treatment of pancreatic adenocarcinoma: actual survival and prognostic factors in 343 patients. Eur J Cancer 2004; 40: 549-558.
66. Birkmeyer JD, Warshaw AL, Finlayson SR, Grove MR, Tosteson AN. Relationship between hospital volume and late survival after pancreaticoduodenectomy. Surgery 1999; 126: 178-183.
67. Birkmeyer JD, Finlayson SR, Tostason AN, Sharp SM, Warshaw AL, Fisher ES. Effect of hospital volume on in-hospital mortality with pancreaticoduodenectomy. Surgery 1999; 125: 250-256.
68. Geer RJ, Brennan M. Resection of pancreatic adenocarcinoma: prognostic indicators for survival. Am J Surg 1993; 165: 68-73.
69. Berger AC, Meszoely IM, Ross EA, Watson JC, Hoffman JP. Undetectable preoperative levels of serum Ca 19.9 correlate with improved survival for patients with resectable pancreatic adenocarcinoma. Ann Surg Oncol 2004; 11: 644-649.
70. Schlieman MG, Ho HS, Bold RJ. Utility of tumor markers in determining resectability of pancreatic cancer. Arch Surg 2003; 138: 951-956.
71. Kawesha A, Ghaneh P, Andren-Sandberg A, et al. K-ras oncogene subtype mutations are associated with survival but not the expression of p53, $p16^{INK4a}$, p21 (WAF-1), cyclin D1, erbB-2 and erbB-3 in resected pancreatic ductal adenocarcinoma. Int J Cancer 2000; 89: 469-474.