

- Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin* 2013;63:11–30.
- American Cancer Society. *Cancer Facts & Figures*. Atlanta: American Cancer Society; 2013.
- Riall TS, Nealon WH, Goodwin JS, et al. Pancreatic cancer in the general population: Improvements in survival over the last decade. *J Gastrointest Surg* 2006;10:1212–1223.
- Worni M, Guller U, White RR, et al. Modest improvement in overall survival for patients with metastatic pancreatic cancer: a trend analysis using the Surveillance, Epidemiology, and End Results Registry From 1988 to 2008. *Pancreas* 2013;42:1157–1163.
- Winter JM, Brennan MF, Tang LH, et al. Survival after resection of pancreatic adenocarcinoma: results from a single institution over three decades. *Ann Surg Oncol* 2012;19:169–175.
- Edge SE, Byrd DR. *AJCC Cancer Staging Manual*. New York: Springer; 2009.
- Billimoria KY, Bentrem DJ, Ko CY, et al. Validation of the 6th edition AJCC Pancreatic Cancer Staging System: report from the National Cancer Database. *Cancer* 2007;110:738–744.
- National Cancer Institute. SEER Stat Fact Sheets: Pancreas Cancer. <http://seer.cancer.gov/statfacts/html/pancreas.html>.
- Solomon S, Das S, Brand R, et al. Inherited pancreatic cancer syndromes. *Cancer J* 2012;18:485–491.
- Klein AP, Brune KA, Petersen GM, et al. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. *Cancer Res* 2004;64:2634–2638.
- Klein AP. Genetic susceptibility to pancreatic cancer. *Mol Carcinog* 2012; 51:14–24.
- Iodice S, Gandini S, Maisonneuve P, et al. Tobacco and the risk of pancreatic cancer: a review and meta-analysis. *Langenbecks Arch Surg* 2008; 393:535–545.
- Bosetti C, Lucenteforte E, Silverman DT, et al. Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (PanC4). *Ann Oncol* 2012;23:1880–1888.
- Silverman DT, Schiffman M, Everhart J, et al. Diabetes mellitus, other medical conditions and familial history of cancer as risk factors for pancreatic cancer. *Br J Cancer* 1999;80:1830–1837.
- Schenk M, Schwartz AG, O'Neal E, et al. Familial risk of pancreatic cancer. *J Natl Cancer Inst* 2001;93:640–644.
- Bertuccio P, La Vecchia C, Silverman DT, et al. Cigar and pipe smoking, smokeless tobacco use and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (PanC4). *Ann Oncol* 2011;22:1420–1426.
- Zhou J, Wellenius GA, Michaud DS. Environmental tobacco smoke and the risk of pancreatic cancer among non-smokers: a meta-analysis. *Occup Environ Med* 2012;69:853–857.
- Chuang SC, Gallo V, Michaud D, et al. Exposure to environmental tobacco smoke in childhood and incidence of cancer in adulthood in never smokers in the European Prospective Investigation into Cancer and Nutrition. *Cancer Causes Control* 2011;22:487–494.
- Hecht SS. Tobacco carcinogens, their biomarkers and tobacco-induced cancer. *Nat Rev Cancer* 2003;3:733–744.
- Andreotti G, Silverman DT. Occupational risk factors and pancreatic cancer: a review of recent findings. *Mol Carcinog* 2012;51:98–108.
- Lucenteforte E, La Vecchia C, Silverman D, et al. Alcohol consumption and pancreatic cancer: a pooled analysis in the International Pancreatic Cancer Case-Control Consortium (PanC4). *Ann Oncol* 2012;23:374–382.
- Duell EJ, Lucenteforte E, Olson SH, et al. Pancreatitis and pancreatic cancer risk: a pooled analysis in the International Pancreatic Cancer Case-Control Consortium (PanC4). *Ann Oncol* 2012;23:2964–2970.
- Bracci PM. Obesity and pancreatic cancer: overview of epidemiologic evidence and biologic mechanisms. *Mol Carcinog* 2012;51:53–63.
- Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A, et al. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *Br J Cancer* 2005;92:2076–2083.
- Ben Q, Xu M, Ning X, et al. Diabetes mellitus and risk of pancreatic cancer: A meta-analysis of cohort studies. *Eur J Cancer* 2011;47:1928–1937.
- Klimstra DS, Pitman MB, Hruban RH. An algorithmic approach to the diagnosis of pancreatic neoplasms. *Arch Pathol Lab Med* 2009;133:454–464.
- Winter JM, Cameron JL, Campbell KA, et al. 1423 pancreaticoduodenectomies for pancreatic cancer: A single-institution experience. *J Gastrointest Surg* 2006;10:1199–1210.
- Winter JM, Maitra A, Yeo CJ. Genetics and pathology of pancreatic cancer. *HPB (Oxford)* 2006;8:324–336.
- Neesse A, Michl P, Frese KK, et al. Stromal biology and therapy in pancreatic cancer. *Gut* 2011;60:861–868.
- Anderson AR, Weaver AM, Cummings PT, et al. Tumor morphology and phenotypic evolution driven by selective pressure from the microenvironment. *Cell* 2006;127:905–915.
- Izuiishi K, Kato K, Ogura T, et al. Remarkable tolerance of tumor cells to nutrient deprivation: possible new biochemical target for cancer therapy. *Cancer Res* 2000;60:6201–6207.
- Cho KR, Vogelstein B. Genetic alterations in the adenoma–carcinoma sequence. *Cancer* 1992;70:1727–1731.
- Kozuka S, Sassa R, Taki T, et al. Relation of pancreatic duct hyperplasia to carcinoma. *Cancer* 1979;43:1418–1428.
- Biankin AV, Waddell N, Kassahn KS, et al. Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes. *Nature* 2012;491:399–405.
- Jones S, Zhang X, Parsons DW, et al. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. *Science* 2008;321: 1801–1806.
- Caldas C, Kern SE. K-ras mutation and pancreatic adenocarcinoma. *Int J Pancreatol* 1995;18:1–6.
- Smit VT, Boot AJ, Smits AM, et al. KRAS codon 12 mutations occur very frequently in pancreatic adenocarcinomas. *Nucleic Acids Res* 1988; 16:7773–7782.
- Suda K, Tomizawa K, Mitsudomi T. Biological and clinical significance of KRAS mutations in lung cancer: an oncogenic driver that contrasts with EGFR mutation. *Cancer Metastasis Rev* 2010;29:49–60.
- Baines AT, Xu D, Der CJ. Inhibition of Ras for cancer treatment: the search continues. *Future Med Chem* 2011;3:1787–1808.
- Schleger C, Arens N, Zentgraf H, et al. Identification of frequent chromosomal aberrations in ductal adenocarcinoma of the pancreas by comparative genomic hybridization (CGH). *J Pathol* 2000;191:27–32.
- Calhoun ES, Hucl T, Gallmeier E, et al. Identifying allelic loss and homozygous deletions in pancreatic cancer without matched normals using high-density single-nucleotide polymorphism arrays. *Cancer Res* 2006;66: 7920–7928.
- Caldas C, Hahn SA, da Costa LT, et al. Frequent somatic mutations and homozygous deletions of the p16 (MTS1) gene in pancreatic adenocarcinoma. *Nat Genet* 1994;8:27–32.
- Schutte M, Hruban RH, Gerads J, et al. Abrogation of the Rb/p16 tumor-suppressive pathway in virtually all pancreatic carcinomas. *Cancer Res* 1997;57:3126–3130.
- Scarpa A, Capelli P, Mukai K, et al. Pancreatic adenocarcinomas frequently show p53 gene mutations. *Am J Pathol* 1993;142:1534–1543.
- Schmitt CA, Fridman JS, Yang M, et al. Dissecting p53 tumor suppressor functions in vivo. *Cancer Cell* 2002;1:289–298.
- Yu X, Vazquez A, Levine AJ, et al. Allele-specific p53 mutant reactivation. *Cancer Cell* 2012;21:614–625.
- Meng X, Laidler LL, Kosmacek EA, et al. Induction of mitotic cell death by overruling G2/M checkpoint in endometrial cancer cells with non-functional p53. *Gynecol Oncol* 2013;128:461–469.
- Hahn SA, Schutte M, Hoque AT, et al. DPC4, a candidate tumor suppressor gene at human chromosome 18q21.1. *Science* 1996;271:350–353.
- Iacobuzio-Donahue CA, Fu B, Yachida S, et al. DPC4 gene status of the primary carcinoma correlates with patterns of failure in patients with pancreatic cancer. *J Clin Oncol* 2009;27:1806–1813.
- Shi C, Hong SM, Lim P, et al. KRAS2 mutations in human pancreatic acinar-ductal metaplastic lesions are limited to those with PanIN: implications for the human pancreatic cancer cell of origin. *Mol Cancer Res* 2009; 7:230–236.
- van Heek NT, Meeker AK, Kern SE, et al. Telomere shortening is nearly universal in pancreatic intraepithelial neoplasia. *Am J Pathol* 2002;161: 1541–1547.
- Rosty C, Gerads J, Sato N, et al. p16 Inactivation in pancreatic intraepithelial neoplasias (PanINs) arising in patients with chronic pancreatitis. *Am J Surg Pathol* 2003;27:1495–1501.
- McCarthy DM, Brat DJ, Wilentz RE, et al. Pancreatic intraepithelial neoplasia and infiltrating adenocarcinoma: analysis of progression and recurrence by DPC4 immunohistochemical labeling. *Hum Pathol* 2001;32:638–642.
- Wilentz RE, Iacobuzio-Donahue CA, Argani P, et al. Loss of expression of Dpc4 in pancreatic intraepithelial neoplasia: evidence that DPC4 inactivation occurs late in neoplastic progression. *Cancer Res* 2000;60:2002–2006.
- Baumgart M, Werther M, Bockholt A, et al. Genomic instability at both the base pair level and the chromosomal level is detectable in earliest PanIN lesions in tissues of chronic pancreatitis. *Pancreas* 2010;39:1093–1103.
- Hong SM, Vincent A, Kanda M, et al. Genome-wide somatic copy number alterations in low-grade PanINs and IPMNs from individuals with a family history of pancreatic cancer. *Clin Cancer Res* 2012;18:4303–4312.
- Luttges J, Gallehdari H, Brocker V, et al. Allelic loss is often the first hit in the biallelic inactivation of the p53 and DPC4 genes during pancreatic carcinogenesis. *Am J Pathol* 2001;158:1677–1683.
- Yachida S, Iacobuzio-Donahue CA. Evolution and dynamics of pancreatic cancer progression. *Oncogene* 2013;32:5253–5260.
- Roberts NJ, Jiao Y, Yu J, et al. ATM mutations in patients with hereditary pancreatic cancer. *Cancer Discov* 2012;2:41–46.
- Canto MI, Hruban RH, Fishman EK, et al. Frequent detection of pancreatic lesions in asymptomatic high-risk individuals. *Gastroenterology* 2012;142:796–804.
- Canto MI, Harinck F, Hruban RH, et al. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. *Gut* 2013;62:339–347.
- Peréz-Mancera PA, Guerra C, Barbacid M, et al. What we have learned about pancreatic cancer from mouse models. *Gastroenterology* 2012;142: 1079–1092.

63. Seth AK, Argani P, Campbell KA, et al. Acinar cell carcinoma of the pancreas: an institutional series of resected patients and review of the current literature. *J Gastrointest Surg* 2008;12:1061–1067.
64. Jiao Y, Yonescu R, Offerhaus CJ, et al. Whole exome sequencing of pancreatic neoplasms with acinar differentiation. *J Pathol* 2014;232:428–435.
65. Salman B, Brat G, Yoon YS, et al. The diagnosis and surgical treatment of pancreatoblastoma in adults: a case series and review of the literature. *J Gastrointest Surg* 2013;17:2153–2161.
66. Shi C, Hruban RH. Intraductal papillary mucinous neoplasm. *Hum Pathol* 2012;43:1–16.
67. Laffan TA, Horton KM, Klein AP, et al. Prevalence of unsuspected pancreatic cysts on MDCT. *AJR Am J Roentgenol* 2008;191:802–807.
68. Tanaka M, Chari S, Adsay V, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. *Pancreatol* 2006;6:17–32.
69. Poultsides GA, Reddy S, Cameron JL, et al. Histopathologic basis for the favorable survival after resection of intraductal papillary mucinous neoplasm-associated invasive adenocarcinoma of the pancreas. *Ann Surg* 2010;251:470–476.
70. Wu J, Jiao Y, Dal Molin M, et al. Whole-exome sequencing of neoplastic cysts of the pancreas reveals recurrent mutations in components of ubiquitin-dependent pathways. *Proc Natl Acad Sci U S A* 2011;108:21188–21193.
71. Reddy S, Cameron JL, Scudiere J, et al. Surgical management of solid-pseudopapillary neoplasms of the pancreas (Franz or Hamoudi tumors): a large single-institutional series. *J Am Coll Surg* 2009;208:950–957.
72. Ellison TA, Wolfgang CL, Shi C, et al. A single institution's 26-year experience with nonfunctional pancreatic neuroendocrine tumors: a validation of current staging systems and a new prognostic nomogram. *Ann Surg* 2014;259:204–212.
73. Klimstra DS, Modlin IR, Coppola D, et al. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. *Pancreas* 2010;39:707–712.
74. Phan GQ, Yeo CJ, Hruban RH, et al. Surgical experience with pancreatic and peripancreatic neuroendocrine tumors: review of 125 patients. *J Gastrointest Surg* 1998;2:472–482.
75. Kimura W, Kuroda A, Morioka Y. Clinical pathology of endocrine tumors of the pancreas. Analysis of autopsy cases. *Dig Dis Sci* 1991;36:933–942.
76. Whipple AO. The surgical therapy of hyperinsulinism. *J Int Chir* 1938;3:237–276.
77. Jiao Y, Shi C, Edil BH, et al. DAXX/ATRX, MEN1, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors. *Science* 2011;331:1199–1203.
78. Falconi M, Bartsch DK, Eriksson B, et al. ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms of the digestive system: well-differentiated pancreatic non-functioning tumors. *Neuroendocrinology* 2012;95:120–134.
79. Pannala R, Basu A, Petersen GM, et al. New-onset diabetes: a potential clue to the early diagnosis of pancreatic cancer. *Lancet Oncol* 2009;10:88–95.
80. Fong ZV, Tan WP, Lavu H, et al. Preoperative imaging for resectable periampullary cancer: clinicopathologic implications of reported radiographic findings. *J Gastrointest Surg* 2013;17:1098–1106.
81. Callery MP, Chang KJ, Fishman EK, et al. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. *Ann Surg Oncol* 2009;16:1727–1733.
82. Evans DB, Erickson BA, Ritch P. Borderline resectable pancreatic cancer: definitions and the importance of multimodality therapy. *Ann Surg Oncol* 2010;17:2803–2805.
83. Varadhachary GR, Tamm EP, Abbruzzese JL, et al. Borderline resectable pancreatic cancer: definitions, management, and role of preoperative therapy. *Ann Surg Oncol* 2006;13:1035–1046.
84. Evans DB, Varadhachary GR, Crane CH, et al. Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. *J Clin Oncol* 2008;26:3496–3502.
85. Katz MH, Fleming JB, Bhosale P, et al. Response of borderline resectable pancreatic cancer to neoadjuvant therapy is not reflected by radiographic indicators. *Cancer* 2012;118:5749–5756.
86. van der Gaag NA, Rauws EA, van Eijck CH, et al. Preoperative biliary drainage for cancer of the head of the pancreas. *N Engl J Med* 2010;362:129–137.
87. Kooby DA, Hawkins WG, Schmidt CM, et al. A multicenter analysis of distal pancreatectomy for adenocarcinoma: is laparoscopic resection appropriate? *J Am Coll Surg* 2010;210:779–785.
88. Venkat R, Edil BH, Schulick RD, et al. Laparoscopic distal pancreatectomy is associated with significantly less overall morbidity compared to the open technique: a systematic review and meta-analysis. *Ann Surg* 2012;255:1048–1059.
89. Kendrick ML. Laparoscopic and robotic resection for pancreatic cancer. *Cancer J* 2012;18:571–576.
90. Bassi C, Dervenis C, Butturini G, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery* 2005;138:8–13.
91. Wente MN, Bassi C, Dervenis C, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 2007;142:761–768.
92. Wente MN, Veit JA, Bassi C, et al. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. *Surgery* 2007;142:20–25.
93. Shukla PJ, Barreto SG, Fingerhut A, et al. Toward improving uniformity and standardization in the reporting of pancreatic anastomoses: a new classification system by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 2010;147:144–153.
94. Burkhardt RA, Relles D, Pineda DM, et al. Defining treatment and outcomes of hepaticojejunostomy failure following pancreaticoduodenectomy. *J Gastrointest Surg* 2013;17:451–460.
95. Doi R, Imamura M, Hosotani R, et al. Surgery versus radiochemotherapy for resectable locally invasive pancreatic cancer: final results of a randomized multi-institutional trial. *Surg Today* 2008;38:1021–1028.
96. Bloechle C, Broering DC, Latuske C, et al. Prospective randomized study to evaluate quality of life after partial pancreateoduodenectomy according to whipple versus pylorus preserving pancreateoduodenectomy according to longmire-traverso for periampullary carcinoma. *Deutsche Gesellschaft Chir* 1999;Suppl 1:661–664.
97. Karanicolas PJ, Davies E, Kunz R, 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. *Ann Surg Oncol* 2007;14:1825–1834.
98. Lin PW, Shan YS, Lin YJ, et al. Pancreaticoduodenectomy for pancreatic head cancer: PPPD versus Whipple procedure. *Hepatogastroenterology* 2005;52:1601–1604.
99. Paquet KJ. Comparison of Whipples pancreaticoduodenectomy with the pylorus-preserving pancreaticoduodenectomy—a prospectively controlled, randomized long-term trial. *Chir Gastroenterol* 1998;14:54–58.
100. 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.
101. 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.
102. Wenger FA, Jacobi CA, Haubold K, et al. [Gastrointestinal quality of life after duodenopancreatectomy in pancreatic carcinoma. Preliminary results of a prospective randomized study: pancreaticoduodenectomy or pylorus-preserving pancreaticoduodenectomy]. *Chirurg* 1999;70:1454–1459.
103. Imamura N, Chijiwa K, Ohuchida J, et al. Prospective randomized clinical trial of a change in gastric emptying and nutritional status after a pylorus-preserving pancreaticoduodenectomy: comparison between an antecolic and a vertical retrocolic duodenojejunostomy. *HPB (Oxford)* 2014;16:382–394.
104. Gangavathiker R, Pal S, Javed A, et al. Effect of antecolic or retrocolic reconstruction of the gastro/duodenojejunostomy on delayed gastric emptying after pancreaticoduodenectomy: a randomized controlled trial. *J Gastrointest Surg* 2011;15:843–852.
105. Eshuis WJ, van Eijck CH, Gerhards MF, et al. Antecolic versus retrocolic route of the gastroenteric anastomosis after pancreaticoduodenectomy: a randomized controlled trial. *Ann Surg* 2014;259:45–51.
106. Tamandl D, Sahara K, Prucker J, et al. Impact of the reconstruction method on delayed gastric emptying after pylorus-preserving pancreaticoduodenectomy: a prospective randomized study. *World J Surg* 2014;38:465–475.
107. Tani M, Terasawa H, Kawai M, et al. Improvement of delayed gastric emptying in pylorus-preserving pancreaticoduodenectomy: results of a prospective, randomized, controlled trial. *Ann Surg* 2006;243:316–320.
108. Winter JM, Cameron JL, Yeo CJ, et al. Biochemical markers predict morbidity and mortality after pancreaticoduodenectomy. *J Am Coll Surg* 2007;204:1029–1036.
109. Mathur A, Pitt HA, Marine M, et al. Fatty pancreas: a factor in postoperative pancreatic fistula. *Ann Surg* 2007;246:1058–1064.
110. Lillemoe KD, Cameron JL, Kim MP, et al. Does fibrin glue sealant decrease the rate of pancreatic fistula after pancreaticoduodenectomy? Results of a prospective randomized trial. *J Gastrointest Surg* 2004;8:766–772.
111. Martin I, Au K. Does fibrin glue sealant decrease the rate of anastomotic leak after a pancreaticoduodenectomy? Results of a prospective randomized trial. *HPB (Oxford)* 2013;15:561–566.
112. Yeo CJ, Cameron JL, Lillemoe KD, et al. Does prophylactic octreotide decrease the rates of pancreatic fistula and other complications after pancreaticoduodenectomy? Results of a prospective randomized placebo-controlled trial. *Ann Surg* 2000;232:419–429.
113. Beguiristain A, Espi A, Balen E, et al. [Somatostatin prophylaxis following cephalic duodenopancreatectomy]. *Rev Esp Enferm Dig* 1995;87:221–224.
114. Fernandez-Cruz L, Jimenez Chavarria E, Taura P, et al. Prospective randomized trial of the effect of octreotide on pancreatic juice output after pancreaticoduodenectomy in relation to histological diagnosis, duct size and leakage. *HPB (Oxford)* 2013;15:392–399.
115. Gouillat C, Chipponi J, Baulieux J, et al. Randomized controlled multicentre trial of somatostatin infusion after pancreaticoduodenectomy. *Br J Surg* 2001;88:1456–1462.
116. Kollmar O, Moussavian MR, Richter S, et al. Prophylactic octreotide and delayed gastric emptying after pancreaticoduodenectomy: results of a prospective randomized double-blind placebo-controlled trial. *Eur J Surg Oncol* 2008;34:868–875.
117. Shan YS, Sy ED, Lin PW. 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 J Surg* 2003;27:709–714.

118. Wang W, Tian B, Babu SR, et al. Randomized, placebo-controlled study of the efficacy of preoperative somatostatin administration in the prevention of postoperative complications following pancreaticoduodenectomy. *Hepato-gastroenterology* 2013;60:400–405.
119. Klempa I, Baca I, Menzel J, et al. [Effect of somatostatin on basal and stimulated exocrine pancreatic secretion after partial duodenopancreatectomy. A clinical experimental study]. *Chirurg* 1991;62:293–299.
120. He T, Zhao Y, Chen Q, et al. Pancreaticojejunostomy versus pancreaticogastrostomy after pancreaticoduodenectomy: a systematic review and meta-analysis. *Dig Surg* 2013;30:56–69.
121. Amaud JP, Tuech JJ, Cervi C, et al. Pancreaticogastrostomy compared with pancreaticojejunostomy after pancreaticoduodenectomy. *Eur J Surg* 1999;165:357–362.
122. Bassi C, Falconi M, Molinari E, et al. Reconstruction by pancreaticojejunostomy versus pancreaticogastrostomy following pancreatectomy: results of a comparative study. *Ann Surg* 2005;242:767–771.
123. Duffas JP, Suc B, Msika S, et al. A controlled randomized multicenter trial of pancreaticogastrostomy or pancreaticojejunostomy after pancreatoduodenectomy. *Am J Surg* 2005;189:720–729.
124. Fernandez-Cruz L, Cosa R, Blanco L, et al. Pancreatogastrostomy with gastric partition after pylorus-preserving pancreatoduodenectomy versus conventional pancreaticojejunostomy: a prospective randomized study. *Ann Surg* 2008;248:930–938.
125. Takano S, Ito Y, Watanabe Y, et al. Pancreaticojejunostomy versus pancreaticogastrostomy in reconstruction following pancreaticoduodenectomy. *Br J Surg* 2000;87:423–427.
126. Yeo CJ, Cameron JL, Maher MM, et al. A prospective randomized trial of pancreaticogastrostomy versus pancreaticojejunostomy after pancreaticoduodenectomy. *Ann Surg* 1995;222:580–588.
127. Berger AC, Howard TJ, Kennedy EP, et al. Does type of pancreaticojejunostomy after pancreaticoduodenectomy decrease rate of pancreatic fistula? A randomized, prospective, dual-institution trial. *J Am Coll Surg* 2009;208:738–747.
128. Peng SY, Wang JW, Lau WY, et al. Conventional versus binding pancreaticojejunostomy after pancreaticoduodenectomy: a prospective randomized trial. *Ann Surg* 2007;245:692–698.
129. Pessaux P, Sauvanet A, Mariette C, et al. External pancreatic duct stent decreases pancreatic fistula rate after pancreaticoduodenectomy: prospective multicenter randomized trial. *Ann Surg* 2011;253:879–885.
130. Poon RT, Fan ST, Lo CM, et al. External drainage of pancreatic duct with a stent to reduce leakage rate of pancreaticojejunostomy after pancreaticoduodenectomy: a prospective randomized trial. *Ann Surg* 2007;246:425–433.
131. Motoi F, Egawa S, Rikiyama T, et al. Randomized clinical trial of external stent drainage of the pancreatic duct to reduce postoperative pancreatic fistula after pancreaticojejunostomy. *Br J Surg* 2012;99:524–531.
132. Imaizumi T, Harada N, Hatori T, et al. Stenting is unnecessary in duct-to-mucosa pancreaticojejunostomy even in the normal pancreas. *Pancreatol* 2002;2:116–121.
133. Ke S, Ding XM, Gao J, et al. A prospective, randomized trial of Roux-en-Y reconstruction with isolated pancreatic drainage versus conventional loop reconstruction after pancreaticoduodenectomy. *Surgery* 2013;153:743–752.
134. Svoronos C, Tsooufas G, Katsourakis A, et al. Role of extended lymphadenectomy in the treatment of pancreatic head adenocarcinoma: review and meta-analysis. *ANZ J Surg* 2013 [Epub ahead of print].
135. Farnell MB, Pearson RK, Sarr MG, et al. A prospective randomized trial comparing standard pancreaticoduodenectomy with pancreatoduodenectomy with extended lymphadenectomy in resectable pancreatic head adenocarcinoma. *Surgery* 2005;138:618–628.
136. 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.
137. 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-year survival. *J Gastrointest Surg* 2005;9:1191–1204.
138. Brennan MF, Pisters PW, Posner M, et al. A prospective randomized trial of total parenteral nutrition after major pancreatic resection for malignancy. *Ann Surg* 1994;220:436–441.
139. Conlon KC, Labow D, Leung D, et al. Prospective randomized clinical trial of the value of intraperitoneal drainage after pancreatic resection. *Ann Surg* 2001;234:487–493.
140. Van Buren C, Bloomston M, Hughes SJ, et al. A randomized prospective multicenter trial of pancreaticoduodenectomy with and without routine intraperitoneal drainage. *Ann Surg* 2014;259:605–612.
141. Diener MK, Seiler CM, Rossion I, et al. Efficacy of stapler versus hand-sewn closure after distal pancreatectomy (DISPACT): a randomised, controlled multicentre trial. *Lancet* 2011;377:1514–1522.
142. Carter TI, Fong ZV, Hyslop T, et al. A dual-institution randomized controlled trial of remnant closure after distal pancreatectomy: does the addition of a falciform patch and fibrin glue improve outcomes? *J Gastrointest Surg* 2013;17:102–109.
143. Montorsi M, Zerbi A, Bassi C, et al. Efficacy of an absorbable fibrin sealant patch (TachoSil) after distal pancreatectomy: a multicenter, randomized, controlled trial. *Ann Surg* 2012;256:853–859.
144. Suzuki Y, Fujino Y, Tanioka Y, et al. Randomized clinical trial of ultrasonic dissector or conventional division in distal pancreatectomy for non-fibrotic pancreas. *Br J Surg* 1999;86:608–611.
145. Glazer ES, Hornbrook MC, Krouse RS. A meta-analysis of randomized trials: immediate stent placement vs. surgical bypass in the palliative management of malignant biliary obstruction. *J Pain Symptom Manage* 2014;47:307–314.
146. Lillemoe KD, Cameron JL, Hardacre JM, et al. Is prophylactic gastrojejunostomy indicated for unresectable periampullary cancer? A prospective randomized trial. *Ann Surg* 1999;230:322–328.
147. Van Heek NT, De Castro SM, van Eijck CH, 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;238:894–902.
148. Lillemoe KD, Cameron JL, Kaufman HS, et al. Chemical splanchnicectomy in patients with unresectable pancreatic cancer. A prospective randomized trial. *Ann Surg* 1993;217:447–455.
149. Katz MH, Merchant NB, Brower S, et al. Standardization of surgical and pathologic variables is needed in multicenter trials of adjuvant therapy for pancreatic cancer: results from the ACOSOG Z5031 trial. *Ann Surg Oncol* 2011;18:337–344.
150. Maithel SK, Maloney S, Winston C, et al. Preoperative CA 19-9 and the yield of staging laparoscopy in patients with radiographically resectable pancreatic adenocarcinoma. *Ann Surg Oncol* 2008;15:3512–3520.
151. Barton JG, Bois JP, Sarr MC, et al. Predictive and prognostic value of CA 19-9 in resected pancreatic adenocarcinoma. *J Gastrointest Surg* 2009;13:2050–2058.
152. Hartwig W, Hackert T, Hinz U, et al. Pancreatic cancer surgery in the new millennium: better prediction of outcome. *Ann Surg* 2011;254:311–319.
153. Marrelli D, Caruso S, Pedrazzani C, et al. CA19-9 serum levels in obstructive jaundice: clinical value in benign and malignant conditions. *Am J Surg* 2009;198:333–339.
154. Berger AC, Garcia M Jr, Hoffman JP, et al. Postresection CA 19-9 predicts overall survival in patients with pancreatic cancer treated with adjuvant chemoradiation: a prospective validation by RTOG 9704. *J Clin Oncol* 2008;26:5918–5922.
155. Narimatsu H, Iwasaki H, Nakayama F, et al. Lewis and secretor gene dosages affect CA19-9 and DU-PAN-2 serum levels in normal individuals and colorectal cancer patients. *Cancer Res* 1998;58:512–518.
156. Tempero MA, Uchida E, Takasaki H, et al. Relationship of carbohydrate antigen 19-9 and Lewis antigens in pancreatic cancer. *Cancer Res* 1987;47:5501–5503.
157. National Comprehensive Cancer Network. NCCN Guidelines. Pancreatic Adenocarcinoma. http://www.nccn.org/professionals/physician_gls/PDF/pancreatic.pdf.
158. Boeck S, Ankerst DP, Heinemann V. The role of adjuvant chemotherapy for patients with resected pancreatic cancer: systematic review of randomized controlled trials and meta-analysis. *Oncology* 2007;72:314–321.
159. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *JAMA* 2007;297:267–277.
160. Winter JM, Tang LH, Klimstra DS, et al. Failure patterns in resected pancreatic adenocarcinoma: lack of predicted benefit to smad4 expression. *Ann Surg* 2013;258:331–335.
161. Crane CH, Varadhachary GR, Yordy JS, et al. Phase II trial of cetuximab, gemcitabine, and oxaliplatin followed by chemoradiation with cetuximab for locally advanced (T4) pancreatic adenocarcinoma: correlation of Smad4(Dpc4) immunostaining with pattern of disease progression. *J Clin Oncol* 2011;29:3037–3043.
162. Winter JM, Tang LH, Klimstra DS, et al. A novel survival-based tissue microarray of pancreatic cancer validates MUC1 and mesothelin as biomarkers. *PLoS One* 2012;7:e40157.
163. Smeenk HG, van Eijck CH, Hop WC, et al. Long-term survival and metastatic pattern of pancreatic and periampullary cancer after adjuvant chemoradiation or observation: long-term results of EORTC trial 40891. *Ann Surg* 2007;246:734–740.
164. Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. *JAMA* 2013;310:1473–1481.
165. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med* 2004;350:1200–1210.
166. Neoptolemos JP, Stocken DD, Bassi C, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. *JAMA* 2010;304:1073–1081.
167. Kosuge T, Kiuchi T, Mukai K, et al. A multicenter randomized controlled trial to evaluate the effect of adjuvant cisplatin and 5-fluorouracil therapy after curative resection in cases of pancreatic cancer. *Jpn J Clin Oncol* 2006;36:159–165.
168. Kalsner MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. *Arch Surg* 1985;120:899–903.

169. Bakkevold KE, Amesjo B, Dahl O, et al. Adjuvant combination chemotherapy (AMF) following radical resection of carcinoma of the pancreas and papilla of Vater—results of a controlled, prospective, randomised multicentre study. *Eur J Cancer* 1993;29A:698–703.
170. Regine WF, Winter KA, Abrams R, et al. Fluorouracil-based chemoradiation with either gemcitabine or fluorouracil chemotherapy after resection of pancreatic adenocarcinoma: 5-year analysis of the U.S. Intergroup/RTOG 9704 phase III trial. *Ann Surg Oncol* 2011;18:1319–1326.
171. Burris HA 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997;15:2403–2413.
172. Regine WF, Winter KA, Abrams RA, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial. *JAMA* 2008;299:1019–1026.
173. Abrams RA, Winter KA, Regine WF, et al. Failure to adhere to protocol specified radiation therapy guidelines was associated with decreased survival in RTOG 9704—a phase III trial of adjuvant chemotherapy and chemoradiotherapy for patients with resected adenocarcinoma of the pancreas. *Int J Radiat Oncol Biol Phys* 2012;82:809–816.
174. Herrmann R, Bodoky C, Ruhstaller B, et al. Gemcitabine (G) plus capecitabine (C) versus G alone in locally advanced or metastatic pancreatic cancer. A randomized phase III study of the Swiss Group for Clinical Cancer Research (SAKK) and the Central European Cooperative Oncology Group (CECOG). *J Clin Oncol* 2005;23: LBA4010.
175. Moore MJ, Goldstein D, Hamm J, 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. *J Clin Oncol* 2007;25:1960–1966.
176. O'Reilly EM. Evolving panorama of treatment for metastatic pancreas adenocarcinoma. *J Clin Oncol* 2013;31:1621–1623.
177. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011;364:1817–1825.
178. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013;369:1691–1703.
179. O'Reilly EM, Lowery MA. Postresection surveillance for pancreatic cancer performance status, imaging, and serum markers. *Cancer J* 2012;18:609–613.
180. Sheffield KM, Crowell KT, Lin YL, et al. Surveillance of pancreatic cancer patients after surgical resection. *Ann Surg Oncol* 2012;19:1670–1677.
181. Locker GY, Hamilton S, Harris J, et al. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. *J Clin Oncol* 2006;24:5313–5327.
182. Arnaoutakis GJ, Rangachari D, Laheru DA, et al. Pulmonary resection for isolated pancreatic adenocarcinoma metastasis: an analysis of outcomes and survival. *J Gastrointest Surg* 2011;15:1611–1617.
183. Fitzgerald TL, Seymore NM, Kachare SD, et al. Measuring the impact of multidisciplinary care on quality for pancreatic surgery: transition to a focused, very high-volume program. *Am Surg* 2013;79:775–780.
184. Cai S, Hong TS, Goldberg SI, et al. Updated long-term outcomes and prognostic factors for patients with unresectable locally advanced pancreatic cancer treated with intraoperative radiotherapy at the Massachusetts General Hospital, 1978 to 2010. *Cancer* 2013;119:4196–4204.
185. Ikeda M, Okada S, Tokuyue K, et al. Prognostic factors in patients with locally advanced pancreatic carcinoma receiving chemoradiotherapy. *Cancer* 2001;91:490–495.
186. Krishnan S, Rana V, Janjan NA, et al. Prognostic factors in patients with unresectable locally advanced pancreatic adenocarcinoma treated with chemoradiation. *Cancer* 2006;107:2589–2896.
187. Rudra S, Narang AK, Pawlik TM, et al. Evaluation of predictive variables in locally advanced pancreatic adenocarcinoma patients receiving definitive chemoradiation. *Pract Radiat Oncol* 2012;2:77–85.
188. Dickler A, Abrams RA. Radiochemotherapy in the management of pancreatic cancer—part II: use in adjuvant and locally unresectable settings. *Semin Radiat Oncol* 2005;15:235–244.
189. Oshima M, Okano K, Muraki S, et al. Immunohistochemically detected expression of 3 major genes (CDKN2A/p16, TP53, and SMAD4/DPC4) strongly predicts survival in patients with resectable pancreatic cancer. *Ann Surg* 2013;258:336–346.
190. Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. Gastrointestinal Tumor Study Group. *J Natl Cancer Inst* 1988;80:751–755.
191. Chauffert B, Mornez F, Bonnetain F, et al. Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000-01 FFCDS/FRO study. *Ann Oncol* 2008;19:1592–1599.
192. Klaassen DJ, MacIntyre JM, Catton GE, et al. Treatment of locally unresectable cancer of the stomach and pancreas: a randomized comparison of 5-fluorouracil alone with radiation plus concurrent and maintenance 5-fluorouracil—an Eastern Cooperative Oncology Group study. *J Clin Oncol* 1985;3:373–378.
193. Loehrer PJ, Sr., Feng Y, Cardenes H, et al. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an Eastern Cooperative Oncology Group trial. *J Clin Oncol* 2011;29:4105–4112.
194. Hammel P, Florence H, Van Lathem J, et al. Comparison of chemoradiotherapy (CRT) and chemotherapy (CT) in patients with a locally advanced pancreatic cancer (LAPC) controlled after 4 months of gemcitabine with or without erlotinib: Final results of the international phase III LAP 07 study. *J Clin Oncol* 2013;31:suppl; abstr LBA4003.
195. Brunner TB, Tinkl D, Grabenbauer GG, et al. Maintenance chemotherapy after chemoradiation improves survival of patients with locally advanced pancreatic carcinoma: a retrospective analysis of prospectively recruited patients. *Strahlenther Onkol* 2006;182:210–215.
196. Crane CH, Wolff RA, Abbruzzese JL, et al. Combining gemcitabine with radiation in pancreatic cancer: understanding important variables influencing the therapeutic index. *Semin Oncol* 2001;28:25–33.
197. Ben-Josef E, Schipper M, Francis IR, et al. A phase I/II trial of intensity modulated radiation (IMRT) dose escalation with concurrent fixed-dose rate gemcitabine (FDR-G) in patients with unresectable pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2012;84:1166–1171.
198. Murphy JD, Adusumilli S, Griffith KA, et al. Full-dose gemcitabine and concurrent radiotherapy for unresectable pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2007;68:801–808.
199. Small W Jr, Berlin J, Freedman GM, et al. Full-dose gemcitabine with concurrent radiation therapy in patients with nonmetastatic pancreatic cancer: a multicenter phase II trial. *J Clin Oncol* 2008;26:942–947.
200. Wolff RA, Evans DB, Gravel DM, et al. Phase I trial of gemcitabine combined with radiation for the treatment of locally advanced pancreatic adenocarcinoma. *Clin Cancer Res* 2001;7:2246–2253.
201. Kim HJ, Czischke K, Brennan MF, et al. Does neoadjuvant chemoradiation downstage locally advanced pancreatic cancer? *J Gastrointest Surg* 2002;6:763–769.
202. Crane CH, Abbruzzese JL, Evans DB, et al. Is the therapeutic index better with gemcitabine-based chemoradiation than with 5-fluorouracil-based chemoradiation in locally advanced pancreatic cancer? *Int J Radiat Oncol Biol Phys* 2002;52:1293–1302.
203. Zhu CP, Shi J, Chen YX, et al. Gemcitabine in the chemoradiotherapy for locally advanced pancreatic cancer: a meta-analysis. *Radiother Oncol* 2011;99:108–113.
204. Van Cutsem E, Hoff PM, Harper P, et al. Oral capecitabine vs intravenous 5-fluorouracil and leucovorin: integrated efficacy data and novel analyses from two large, randomised, phase III trials. *Br J Cancer* 2004;90:1190–1197.
205. Kim YJ, Lee WJ, Woo SM, et al. Comparison of capecitabine and 5-fluorouracil in chemoradiotherapy for locally advanced pancreatic cancer. *Radiat Oncol* 2013;8:160.
206. Jackson AS, Jain P, Watkins GR, et al. Efficacy and tolerability of limited field radiotherapy with concurrent capecitabine in locally advanced pancreatic cancer. *Clin Oncol (R Coll Radiol)* 2010;22:570–577.
207. Mukherjee S, Hurt CN, Bridgewater J, et al. Gemcitabine-based or capecitabine-based chemoradiotherapy for locally advanced pancreatic cancer (SCALOP): a multicentre, randomised, phase 2 trial. *Lancet Oncol* 2013;14:317–326.
208. Huguet F, Andre T, Hammel P, 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;25:326–331.
209. Krishnan S, Rana V, Janjan NA, et al. Induction chemotherapy selects patients with locally advanced, unresectable pancreatic cancer for optimal benefit from consolidative chemoradiation therapy. *Cancer* 2007;110:47–55.
210. Conroy T, Paillot B, Francois E, et al. Irinotecan plus oxaliplatin and leucovorin-modulated fluorouracil in advanced pancreatic cancer—a Groupe Tumeurs Digestives of the Federation Nationale des Centres de Lutte Contre le Cancer study. *J Clin Oncol* 2005;23:1228–1236.
211. Festa V, Andriulli A, Valvano MR, et al. Neoadjuvant chemo-radiotherapy for patients with borderline resectable pancreatic cancer: a meta-analytical evaluation of prospective studies. *JOP* 2013;14:618–625.
212. Katz MH, Pisters PW, Evans DB, et al. Borderline resectable pancreatic cancer: the importance of this emerging stage of disease. *J Am Coll Surg* 2008;206:833–846.
213. Seo Y, Kim MS, Yoo S, et al. Stereotactic body radiation therapy boost in locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2009;75:1456–1461.
214. Rwigema JC, Parikh SD, Heron DE, et al. Stereotactic body radiotherapy in the treatment of advanced adenocarcinoma of the pancreas. *Am J Clin Oncol* 2011;34:63–69.
215. Mahadevan A, Jain S, Goldstein M, et al. Stereotactic body radiotherapy and gemcitabine for locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2010;78:735–742.
216. Hansen R, Quebbeman E, Ritch P, et al. Continuous 5-fluorouracil (5FU) infusion in carcinoma of the pancreas: a phase II study. *Am J Med Sci* 1988;295:91–93.
217. Sebastiani V, Ricci F, Rubio-Viqueira B, et al. Immunohistochemical and genetic evaluation of deoxycytidine kinase in pancreatic cancer: relationship to molecular mechanisms of gemcitabine resistance and survival. *Clin Cancer Res* 2006;12:2492–2497.

218. Mini E, Nobili S, Caciagli B, et al. Cellular pharmacology of gemcitabine. *Ann Oncol* 2006;17 Suppl 5:v7-v12.
219. Tempero M, Plunkett W, Ruiz Van Haperen V, et al. Randomized phase II comparison of dose-intense gemcitabine: thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. *J Clin Oncol* 2003;21:3402-3408.
220. Poplin E, Feng Y, Berlin J, et al. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2009;27:3778-3785.
221. Abou-Alfa GK, Letourneau R, Harker G, et al. Randomized phase III study of exatecan and gemcitabine compared with gemcitabine alone in untreated advanced pancreatic cancer. *J Clin Oncol* 2006;24:4441-4447.
222. Berlin JD, Catalano P, Thomas JP, et al. Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group Trial E2297. *J Clin Oncol* 2002;20:3270-3275.
223. Colucci G, Giuliani F, Gebbia V, et al. Gemcitabine alone or with cisplatin for the treatment of patients with locally advanced and/or metastatic pancreatic carcinoma: a prospective, randomized phase III study of the Gruppo Oncologia dell'Italia Meridionale. *Cancer* 2002;94:902-910.
224. Cunningham D, Chau I, Stocken DD, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. *J Clin Oncol* 2009;27:5513-5518.
225. Heinemann V, Quietzsch D, Gieseler F, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. *J Clin Oncol* 2006;24:3946-3952.
226. Louvet C, Labianca R, Hammel P, et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. *J Clin Oncol* 2005;23:3509-3516.
227. Rocha Lima CM, Green MR, Roche R, et al. Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. *J Clin Oncol* 2004;22:3776-3783.
228. Stathopoulos GP, Syrigos K, Aravantinos G, et al. A multicenter phase III trial comparing irinotecan-gemcitabine (IG) with gemcitabine (G) monotherapy as first-line treatment in patients with locally advanced or metastatic pancreatic cancer. *Br J Cancer* 2006;95:587-592.
229. Bramhall SR, Schulz J, Nemunaitis J, et al. A double-blind placebo-controlled, randomised study comparing gemcitabine and marimastat with gemcitabine and placebo as first line therapy in patients with advanced pancreatic cancer. *Br J Cancer* 2002;87:161-167.
230. Kindler HL, Ioka T, Richel DJ, et al. Axitinib plus gemcitabine versus placebo plus gemcitabine in patients with advanced pancreatic adenocarcinoma: a double-blind randomised phase 3 study. *Lancet Oncol* 2011;12:256-262.
231. Kindler HL, Niedzwiecki D, Hollis D, et al. Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: phase III trial of the Cancer and Leukemia Group B (CALGB 80303). *J Clin Oncol* 2010;28:3617-3622.
232. Philip PA, Benedetti J, Corless CL, et al. Phase III study comparing gemcitabine plus cetuximab versus gemcitabine in patients with advanced pancreatic adenocarcinoma: Southwest Oncology Group-directed intergroup trial S0205. *J Clin Oncol* 2010;28:3605-3610.
233. Van Cutsem E, van de Velde H, Karasek P, et al. Phase III trial of gemcitabine plus tipifarnib compared with gemcitabine plus placebo in advanced pancreatic cancer. *J Clin Oncol* 2004;22:1430-1438.
234. da Cunha Santos G, Dhani N, Tu D, et al. Molecular predictors of outcome in a phase 3 study of gemcitabine and erlotinib therapy in patients with advanced pancreatic cancer: National Cancer Institute of Canada Clinical Trials Group Study PA.3. *Cancer* 2010;116:5599-5607.
235. Xiong HQ, Rosenberg A, LoBuglio A, et al. Cetuximab, a monoclonal antibody targeting the epidermal growth factor receptor, in combination with gemcitabine for advanced pancreatic cancer: a multicenter phase II Trial. *J Clin Oncol* 2004;22:2610-2616.
236. Ciliberto D, Botta C, Correale P, et al. Role of gemcitabine-based combination therapy in the management of advanced pancreatic cancer: a meta-analysis of randomised trials. *Eur J Cancer* 2013;49:593-603.
237. Sun C, Ansari D, Andersson R, et al. Does gemcitabine-based combination therapy improve the prognosis of unresectable pancreatic cancer? *World J Gastroenterol* 2012;18:4944-4958.
238. Tam VC, Ko YJ, Mittmann N, et al. Cost-effectiveness of systemic therapies for metastatic pancreatic cancer. *Curr Oncol* 2013;20:e90-e106.
239. Karapatis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med* 2008;359:1757-1765.
240. Van Cutsem E, Vervenne WL, Bonnaun J, et al. Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. *J Clin Oncol* 2009;27:2231-2237.
241. Yardley DA. nab-Paclitaxel mechanisms of action and delivery. *J Control Release* 2013;170:365-372.
242. Miele E, Spinelli GP, Tomao F, et al. Albumin-bound formulation of paclitaxel (Abraxane ABI-007) in the treatment of breast cancer. *Int J Nanomedicine* 2009;4:99-105.
243. Neesse A, Frese KK, Chan DS, et al. SPARC independent drug delivery and antitumor effects of nab-paclitaxel in genetically engineered mice. *Cut* 2014;63:974-983.
244. Von Hoff DD, Ramanathan RK, Borad MJ, et al. Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. *J Clin Oncol* 2011;29:4548-4554.
245. Ychou M, Conroy T, Seitz JF, et al. An open phase I study assessing the feasibility of the triple combination: oxaliplatin plus irinotecan plus leucovorin/5-fluorouracil every 2 weeks in patients with advanced solid tumors. *Ann Oncol* 2003;14:481-489.
246. Ychou M, Desseigne F, Guimbaud R, et al. Randomized phase II trial comparing folfoxin (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. *J Clin Oncol* 2007;25:4516.
247. Gourgou-Bourgade S, Bascoul-Mollevis C, Desseigne F, et al. Impact of FOLFIRINOX compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer: results from the PRODIGE 4/ACCORD 11 randomized trial. *J Clin Oncol* 2013;31:23-29.
248. Ueno H, Ioka T, Ikeda M, et al. Randomized phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: GEST study. *J Clin Oncol* 2013;31:1640-1648.
249. Hamad N, Heilbrun LK, Philip PA, et al. CA19-9 as a predictor of tumor response and survival in patients with advanced pancreatic cancer treated with gemcitabine based chemotherapy. *Asia Pac J Clin Oncol* 2010;6:98-105.
250. Heinemann V, Schermuly MM, Stieber P, et al. CA19-9: a predictor of response in pancreatic cancer treated with gemcitabine and cisplatin. *Anticancer Res* 1999;19:2433-2435.
251. Maisey NR, Norman AR, Hill A, et al. CA19-9 as a prognostic factor in inoperable pancreatic cancer: the implication for clinical trials. *Br J Cancer* 2005;93:740-743.
252. Wong D, Ko AH, Hwang J, et al. Serum CA19-9 decline compared to radiographic response as a surrogate for clinical outcomes in patients with metastatic pancreatic cancer receiving chemotherapy. *Pancreas* 2008;37:269-274.
253. Ziske C, Schlie C, Gorschluter M, et al. Prognostic value of CA 19-9 levels in patients with inoperable adenocarcinoma of the pancreas treated with gemcitabine. *Br J Cancer* 2003;89:1413-1417.
254. Rhim AD, Mirek ET, Aiello NM, et al. EMT and dissemination precede pancreatic tumor formation. *Cell* 2012;148:349-361.
255. Yachida S, Jones S, Bozic I, et al. Distant metastasis occurs late during the genetic evolution of pancreatic cancer. *Nature* 2010;467:1114-1117.
256. Andea A, Sarkar F, Adsay VN. Clinicopathological correlates of pancreatic intraepithelial neoplasia: a comparative analysis of 82 cases with and 152 cases without pancreatic ductal adenocarcinoma. *Mod Pathol* 2003;16:996-1006.
257. Diehl F, Li M, Dressman D, et al. Detection and quantification of mutations in the plasma of patients with colorectal tumors. *Proc Natl Acad Sci U S A* 2005;102:16368-16373.
258. Stravford JK, Brentem DJ, Anderson JM, et al. A six-gene signature predicts survival of patients with localized pancreatic ductal adenocarcinoma. *PLoS Med* 2010;7:e1000307.
259. Farrell JJ, Elsah H, Garcia M, et al. Human equilibrative nucleoside transporter 1 levels predict response to gemcitabine in patients with pancreatic cancer. *Gastroenterology* 2009;136:187-195.
260. Poplin E, Wasan H, Rolfe L, et al. Randomized, multicenter, phase II study of co-101 versus gemcitabine in patients with metastatic pancreatic ductal adenocarcinoma: including a prospective evaluation of the role of hent1 in gemcitabine or co-101 sensitivity. *J Clin Oncol* 2013;31:4453-4461.
261. Costantino CL, Witkiewicz AK, Kuwano Y, et al. The role of HuR in gemcitabine efficacy in pancreatic cancer: HuR Up-regulates the expression of the gemcitabine metabolizing enzyme deoxycytidine kinase. *Cancer Res* 2009;69:4567-4572.
262. Richards NG, Rittenhouse DW, Freydn B, et al. HuR status is a powerful marker for prognosis and response to gemcitabine-based chemotherapy for resected pancreatic ductal adenocarcinoma patients. *Ann Surg* 2010;252:499-505.
263. Sutherland RM. Cell and environment interactions in tumor microregions: the multicell spheroid model. *Science* 1988;240:177-184.
264. Chaika NV, Yu F, Purohit V, et al. Differential expression of metabolic genes in tumor and stromal components of primary and metastatic loci in pancreatic adenocarcinoma. *PLoS One* 2012;7:e32996.
265. Faratin D, Christiansen J, Gustavson M, et al. Heterogeneity mapping of protein expression in tumors using quantitative immunofluorescence. *J Vis Exp* 2011:e3334.
266. Showalter SL, Huang YH, Witkiewicz A, et al. Nanoparticulate delivery of diphtheria toxin DNA effectively kills Mesothelin expressing pancreatic cancer cells. *Cancer Biol Ther* 2008;7:1584-1590.
267. Erkan M, Hausmann S, Michalski CW, et al. The role of stroma in pancreatic cancer: diagnostic and therapeutic implications. *Nat Rev Gastroenterol Hepatol* 2012;9:454-467.
268. Olive KP, Jacobetz MA, Davidson CJ, et al. Inhibition of Hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. *Science* 2009;324:1457-1461.

269. Provenzano PP, Cuevas C, Chang AE, et al. Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. *Cancer Cell* 2012;21:418–429.
270. Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science* 2009;324:1029–1033.
271. Ying H, Kimmelman AC, Lyssiotis CA, et al. Oncogenic Kras maintains pancreatic tumors through regulation of anabolic glucose metabolism. *Cell* 2012;149:656–670.
272. Son J, Lyssiotis CA, Ying H, et al. Glutamine supports pancreatic cancer growth through a KRAS-regulated metabolic pathway. *Nature* 2013;496:101–105.
273. Comisso C, Davidson SM, Soydaner-Azeloglu RG, et al. Macropinocytosis of protein is an amino acid supply route in Ras-transformed cells. *Nature* 2013;497:633–637.
274. Burkhardt RA, Pineda DM, Chand SN, et al. HuR is a post-transcriptional regulator of core metabolic enzymes in pancreatic cancer. *RNA Biol* 2013;10:1312–1323.
275. Couzin-Frankel J. Breakthrough of the year 2013. Cancer immunotherapy. *Science* 2013;342:1432–1433.
276. Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med* 2011;364:2517–2526.
277. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012;366:2443–2454.
278. Hinrichs CS, Rosenberg SA. Exploiting the curative potential of adoptive T-cell therapy for cancer. *Immunol Rev* 2014;257:56–71.
279. Beatty GL, Torigian DA, Chiorean EG, et al. A phase I study of an agonist CD40 monoclonal antibody (CP-870,893) in combination with gemcitabine in patients with advanced pancreatic ductal adenocarcinoma. *Clin Cancer Res* 2013;19:6286–6295.
280. Hardacre JM, Mulcahy M, Small W, et al. Addition of algenpantucel-L immunotherapy to standard adjuvant therapy for pancreatic cancer: a phase 2 study. *J Gastrointest Surg* 2012;17:94–100.
281. Fischer M, Matsuo K, Gonen M, et al. Relationship between intraoperative fluid administration and perioperative outcome after pancreaticoduodenectomy: results of a prospective randomized trial of acute normovolemic hemodilution compared with standard intraoperative management. *Ann Surg* 2010;252:952–958.
282. Uemura K, Murakami Y, Hayashidani Y, et al. Randomized clinical trial to assess the efficacy of ulinastatin for postoperative pancreatitis following pancreaticoduodenectomy. *J Surg Oncol* 2008;98:309–313.
283. Jo S, Choi SH, Heo JS, 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 J Surg* 2006;30:1974–1982.
284. Bassi C, Molinari E, Malleo G, et al. Early versus late drain removal after standard pancreatic resections: results of a prospective randomized trial. *Ann Surg* 2010;252:207–214.
285. Kuroki T, Tajima Y, Kitasato A, et al. Stenting versus non-stenting in pancreaticojejunostomy: a prospective study limited to a normal pancreas without fibrosis sorted by using dynamic MRI. *Pancreas* 2011;40:25–29.
286. Kamoda Y, Fujino Y, Matsumoto I, et al. Usefulness of performing a pancreaticojejunostomy with an internal stent after a pancreatoduodenectomy. *Surg Today* 2008;38:524–528.
287. Tani M, Onishi H, Kinoshita H, et al. The evaluation of duct-to-mucosal pancreaticojejunostomy in pancreaticoduodenectomy. *World J Surg* 2005;29:76–79.
288. Reissman P, Perry Y, Cuenca A, et al. Pancreaticojejunostomy versus controlled pancreaticocutaneous fistula in pancreaticoduodenectomy for peripapillary carcinoma. *Am J Surg* 1995;169:585–588.
289. Tran K, Van Eijck C, Di Carlo V, et al. Occlusion of the pancreatic duct versus pancreaticojejunostomy: a prospective randomized trial. *Ann Surg* 2002;236:422–428.
290. Bassi C, Falconi M, Molinari E, et al. Duct-to-mucosa versus end-to-side pancreaticojejunostomy reconstruction after pancreaticoduodenectomy: results of a prospective randomized trial. *Surgery* 2003;134:766–771.
291. Yeo CJ, Barry MK, Sauter PK, et al. Erythromycin accelerates gastric emptying after pancreaticoduodenectomy. A prospective, randomized, placebo-controlled trial. *Ann Surg* 1993;218:229–237.
292. McCracken JD, Ray P, Heilbrun LK, 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;46:1518–1522.
293. Moertel CG, Frytak S, Hahn RG, 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;48:1705–1710.
294. Radiation therapy combined with Adriamycin or 5-fluorouracil for the treatment of locally unresectable pancreatic carcinoma. Gastrointestinal Tumor Study Group. *Cancer* 1985;56:2563–2568.
295. Earle JD, Foley JF, Wieand HS, 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;28:207–211.
296. Cohen SJ, Dobelbower R, Jr., Lipsitz S, et al. A randomized phase III study of radiotherapy alone or with 5-fluorouracil and mitomycin-C in patients with locally advanced adenocarcinoma of the pancreas: Eastern Cooperative Oncology Group study E8282. *Int J Radiat Oncol Biol Phys* 2005;62:1345–1350.
297. Richards DA, Kindler HL, Oettle H, et al. A randomized phase III study comparing gemcitabine + pemetrexed versus gemcitabine in patients with locally advanced and metastatic pancreas cancer. *J Clin Oncol* 2004;22:4007.