Randomized Clinical Trials in Pancreatic Adenocarcinoma

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KEYWORDS

• Pancreas cancer • Randomized controlled trials
• Literature review • Level Ia evidence

The authors of this article have identified 107 prospective, randomized controlled trials (RCT) for pancreatic adenocarcinoma through a standard MEDLINE literature search strategy that were published between 2000 and 2008. The articles are critically reviewed and ranked according to a standardized, previously published 3-tiered system (Ia, Ib, and Ic).[1] All trials included in this article are Ia or Ib.

Overall, there was a near 2-fold increase in RCT published per year on pancreas cancer compared with the previous study period (1977–2000). This surge was due mostly to an increase for advanced disease trials, the increased reporting of endoscopic stent trials, and advances in targeted molecular therapies.

RANDOMIZED CONTROLLED TRIALS IN PANCREAS CANCER BETWEEN 1977 AND 2000

The authors previously reported surgical trials conducted within this time period with the largest impact on clinical practice.[2] These trials included studies of the role of extended retroperitoneal lymphadenectomy for periampullary cancers, the type of pancreaticoenteric reconstruction after pancreaticoduodenectomy, and the use of prophylactic gastrojejunostomy for unresectable pancreatic cancer.[3–5] There was no evidence that a distal gastrectomy with perigastric and extensive retroperitoneal lymphadenectomy improved outcome,[3] and there was no advantage for pancreaticogastrostomy versus pancreaticojejunostomy following pancreaticoduodenectomy.[4] Although the randomized trial on prophylactic gastrojejunostomy for unresectable periampullary cancer indicated a decrease in the incidence of late gastric outlet obstruction and related complications in the prophylactic bypass group, the authors alluded to the emerging role of duodenal stents that would diminish the role of this procedure in the palliation of unresectable pancreas cancer in the near future.[5]

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There were 2 landmark chemotherapy/chemoradiation trials during this period, including a small randomized trial of gemcitabine use in advanced pancreas cancer.[6] Quality of life was improved in the gemcitabine arm compared with the 5-fluorouracil (5-FU) arm (24% vs 5%; $P = .002$), and there were also improvements in median survival (5.7 vs 4.4 months; $P = .003$), time to disease progression (9 vs 4 weeks; $P = .002$), and 12-month survival (18% vs 2% for the gemcitabine arm; $P = .0025$). Although the results were limited because of the single-blinded design of the study, they represent the first implications of superior clinical efficacy of gemcitabine-based systemic chemotherapy.[6] The EORTC GTCCG trial was a small study that observed a trend toward improved survival ($P = .09$) in patients who were randomized to adjuvant radiation therapy and 5-FU after surgery.[7] Randomized trials investigating nutritional interventions and the prophylactic use of octreotide to prevent pancreatic fistulas did not demonstrate any advantage in outcome in the intervention groups.[8–11]

SURGERY

There were 14 surgical trials reported, of which three compared pylorus preserving pancreaticoduodenectomy (PPPD) to a standard Whipple procedure (**Table 1**).[12–16] Both procedures were shown to be equally effective for the treatment of pancreatic and periampullary cancers, with similar overall long-term and disease-free survival rates. Both procedures were associated with comparable operating time, blood loss, hospital stay, mortality (5.3%), morbidity, positive resection margins, and quality of life (QOL). The two largest trials reported similar rates of delayed gastric emptying between groups, and only a minor postoperative increase in capacity to work at 6 months in the PPPD group (56 vs 77%; $P = .019$).[12,13] Previous findings of reduced blood loss and operating time in the PPPD group were not confirmed by these larger trials. These studies demonstrate the long-term oncologic equivalency of the two procedures and suggest only minor short-term advantages associated with PPPD.

Two trials evaluated the extent of lymphadenectomy at the time of pancreatectomy.[17,18] In both studies extended pancreaticoduodenectomy (PD) was performed with similar perioperative mortality but increased morbidity compared with standard pancreaticoduodenal resection. The overall complication rates were 29% for the standard group versus 43% for the extended group ($P = .01$).[17,19] Extended retroperitoneal lymphadenectomy was associated with longer hospital stay (11.3 vs 14.3 days; $P = .003$), increased rates of pancreatic fistula (13% vs 6%; $P = .05$), delayed gastric emptying (16% vs 6%; $P = .006$), and decreased early QOL.[18,19] There were no long-term differences in quality of life or overall survival (75% and 13% vs 73% and 29%; $P = .13$ for 1- and 5-year survival).[19,20] A consequent feasibility study to address this question concluded that more than 200,000 patients would be required to adequately power a trial that would detect any overall survival benefit, and will not be completed.[21,22]

Four trials examined various types of pancreaticoenteric reconstruction. Two studies examined the effect of pancreatic duct occlusion with fibrin glue versus standard pancreaticoenteric anastomosis after PD.[23,24] Duct occlusion without pancreaticojejunostomy was associated with significantly higher fistula rates (17% vs 5%) and a marked increase in the occurrence of diabetes mellitus. Of note, there were similar rates of exocrine insufficiency, as measured by the use of pancreatic enzyme substitution, between the study groups at 1-year follow-up (58 vs 59%).[23] Temporary duct occlusion with a pancreaticoenteric anastomosis did not decrease the rate or severity of intra-abdominal complications, including pancreatic fistula rates, after resection.[24] Pancreaticoenteric anastomosis remains the standard after PD.