## Current management of localised pancreatic cancer

## M.W. Büchler

Department of General Surgery, University of Heidelberg, Heidelberg, Germany

Pancreatic cancer remains – with an overall long-term survival rate of less than 1% – one of the most difficult cancers to treat. It is the fourth leading cause of cancer related mortality in the Western world and is responsible for around 30,000 deaths per year in the USA [1] and 40,000 per year in Europe.

In only 10-20% of pancreatic cancer patients is potentially curative surgery possible, and even in these patients, the median survival is only 10-18 months with 5-year survival rates of approximately 20-25% [2–5]. Nonetheless, surgery remains the only treatment option with the chance of cure. Pancreatic surgery has significantly changed during the past years. Irrespectively, pancreatic resection remains an intervention of particular significance, often technically challenging and with logistic demands for preoperative diagnostics and perioperative management. Recently, the value of centralisation of pancreatic surgery in 'high volume institutions' has been demonstrated [6,7]. The current mortality rates following pancreatic resections are well below 5% in specialised surgical centres [8,9]. Pancreaticoduodenectomy is the surgical option for tumours of the pancreatic head, which account for the majority of pancreatic cancers. Tumours in the body or tail of the pancreas are treated by pancreatic left resection or occasionally by total pancreatectomy. Organ preserving resection procedures such as pancreatic segmental resection are performed more frequently for selected cases [10]. In this context, pylorus-preserving pancreaticoduodenectomy has been proven to be equal to the classical pancreaticoduodenectomy in terms of tumour recurrence or long-term survival, and should therefore be considered the standard procedure for tumours of the pancreatic head [11]. Various forms of radical lymphadenectomies for pancreatic cancer do not improve the long-term survival but might compromise quality of life according to randomised controlled trials [12-16]. Resections for recurrent pancreatic cancer as well as resections for metastasised tumours remain controversial despite recent reports that suggest a benefit in selected cases [17,18]. Novel neoadjuvant treatment strategies have been employed using radiotherapy often in conjunction

with chemotherapy. Early reports suggest increasing resectability rates (and therefore potentially higher cure rates). Nonetheless, randomised controlled trials are needed to definitely judge the value of neoadjuvant therapy in pancreatic cancer [19].

The role of adjuvant treatment in pancreatic cancer had previously been based on a small number of poorly powered studies. In the ESPAC-1 study, the role of adjuvant chemoradiation and chemotherapy was assessed [20]. Patients were randomised into a 2×2 factorial design (observation, chemoradiation, chemotherapy or combination) or into one of the main treatment comparisons (i.e. chemoradiotherapy versus no chemoradiotherapy or chemotherapy versus no chemotherapy). Overall results showed no benefit for chemoradiation, but a significant survival benefit for chemotherapy (5-FU). The benefit of adjuvant chemotherapy has recently also been demonstrated for gemcitabine [21]. The current ESPAC-3 trial will answer the question whether either drug (5-FU versus gemcitabine) is superior. In addition, more aggressive approaches, i.e. adjuvant immunotherapy plus radiochemotherapy are being evaluated.

In conclusion, pancreatic resections can be performed with considerable safety and low pancreas-specific complication rates. However, even since pancreatic surgery remains the only treatment with curative potential, the long-term survival for pancreatic cancer is not more than 20–25% after radical resection. Since there is a benefit for adjuvant chemotherapy, patients undergoing pancreatic cancer resection should receive this therapy. In the future, these results can hopefully be significantly improved by novel multimodal treatment concepts (including neoadjuvant, adjuvant, and 'targeted' therapies) for pancreatic malignancies.

## Conflict of interest statement

None declared.

## References

- 1 Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin 2007, 57(1), 43-66.
- 2 Lim JE, Chien MW, Earle CC. Prognostic factors following curative resection for pancreatic adenocarcinoma: a populationbased, linked database analysis of 396 patients. *Ann Surg* 2003, 237(1), 74–85.
- 3 Richter A, Niedergethmann M, Sturm JW, Lorenz D, Post S, Trede M. Long-term results of partial pancreaticoduodenectomy for ductal adenocarcinoma of the pancreatic head: 25-year experience. World J Surg 2003, 27(3), 324–329.
- 4 Wagner M, Redaelli C, Lietz M, Seiler CA, Friess H, Buchler MW. Curative resection is the single most important factor determining outcome in patients with pancreatic adenocarcinoma. *Br J Surg* 2004, **91**(5), 586–594.
- 5 Yeo CJ, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy for cancer of the head of the pancreas. 201 patients. Ann Surg 1995, 221(6), 721–731.
- 6 Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. N Engl J Med 2002, 346(15), 1128–1137.
- 7 van Heek NT, Kuhlmann KF, Scholten RJ, et al. Hospital volume and mortality after pancreatic resection: a systematic review and an evaluation of intervention in the Netherlands. Ann Surg 2005, 242(6), 781–788, discussion.
- 8 Buchler MW, Wagner M, Schmied BM, Uhl W, Friess H, Z'graggen K. Changes in morbidity after pancreatic resection: toward the end of completion pancreatectomy. *Arch Surg* 2003, **138**(12), 1310–1314.
- 9 Cameron JL, Riall TS, Coleman J, Belcher KA. One thousand consecutive pancreaticoduodenectomies. *Ann Surg* 2006, 244(1), 10–15
- 10 Muller MW, Friess H, Kleeff J, et al. Middle segmental pancreatic resection: An option to treat benign pancreatic body lesions. Ann Surg 2006, 244(6), 909–918.
- 11 Diener MK, Knaebel HP, Heukaufer C, Antes G, Buchler MW, Seiler CM. A systematic review and meta-analysis of pylorus-preserving versus classical pancreaticoduodenectomy for surgical treatment of periampullary and pancreatic carcinoma. *Ann Surg* 2007, 245(2), 187–200.

- 12 Farnell MB, Pearson RK, Sarr MG, et al. A prospective randomized trial comparing standard pancreatoduodenectomy with pancreatoduodenectomy with extended lymphadenectomy in resectable pancreatic head adenocarcinoma. Surgery 2005, 138(4), 618–628.
- 13 Michalski CW, Kleeff J, Wente MN, Diener MK, Buchler MW, Friess H. Systematic review and meta-analysis of standard and extended lymphadenectomy in pancreaticoduodenectomy for pancreatic cancer. Br J Surg 2007, 94(3), 265–273.
- 14 Nimura Y, Nagino M, Kato H, et al. Standard versus Extended Lymphadenectomy for Pancreatic Cancer: A Multicenter, Randomized Controlled Trial. Pancreatology 2004, 4, 274.
- 15 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(4), 508– 517
- 16 Yeo CJ, Cameron JL, Sohn TA, et al. Pancreaticoduodenectomy with or without extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma: comparison of morbidity and mortality and short-term outcome. Ann Surg 1999, 229(5), 613– 622.
- 17 Kleeff J, Reiser C, Hinz U, et al. Surgery for recurrent pancreatic ductal adenocarcinoma. Ann Surg 2007, 245(4), 566–572.
- 18 Shrikhande SV, Kleeff J, Reiser C, et al. Pancreatic resection for M1 pancreatic ductal adenocarcinoma. Ann Surg Oncol 2007, 14(1), 118–127.
- 19 Kleeff J, Friess H, Buchler MW. Neoadjuvant therapy for pancreatic cancer. Br J Surg 2007, 94(3), 261–262.
- 20 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(12), 1200–1210.
- 21 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(3), 267–277.