

Short Review

Surgery for Advanced and Metastatic Pancreatic Cancer – Current State and Trends

MICHAEL F. NENTWICH, MAXIMILIAN BOCKHORN, ALEXANDRA KÖNIG,
JAKOB R. IZBICKI and GÜLLÜ CATALDEGIRMEN

*Department of General, Visceral and Thoracic Surgery,
University Medical Center of Hamburg-Eppendorf, Hamburg, Germany*

Abstract. *Due to the late onset of symptoms in pancreatic cancer, patients are often presented with an already advanced or metastatic state of disease. Only in a minority of patients is a tumor resection indicated, e.g. in general tumor encasement of major vessels, while the presence of metastatic disease excludes patients from curative-intended surgery. Limitations for pancreatic resections have been debated and re-thought after more experience has gained over time. This holds true for en-bloc vascular resections, total pancreatectomies, intentional R2 pancreatic resections and synchronous resection of liver metastases. These issues are addressed in this review.*

Although pancreatic adenocarcinoma has, for long, been in the focus of intense research, both in basic science as well as in clinical studies, generally the prognosis remains poor. Pancreatic adenocarcinoma is the fourth leading cause of cancer-related deaths in Germany for both genders with approximately 7.000 people developing pancreatic adenocarcinoma per year (1).

The only potentially curative therapeutic approach is resection of the tumor. Due to the late presentation of symptoms, the tumor stage is often already advanced, resulting in about 80% patients that are unsuitable for surgical resection. A literature review, published in 2006, reported median survival rates after resection ranging between 11-20 months, with a 5-year survival rate of 7-25%, and addressed local recurrence as well as hepatic metastasis

within 12 to 24 months after resection, as reasons for treatment failures. In cases of locally advanced or metastatic pancreatic cancer, median survival ranges between 10-12 months and 4-6 months, respectively (2). As mentioned above, only a minority of patients with pancreatic carcinoma are presented with a resectable disease. In the past, tumor encasement or infiltration on major vascular structures was seen as a contraindication for surgery as was the presence of distant metastases (3). Difficulties remain in the pre-surgical assessment of resectability as peritumoral inflammation may mimic true vessel involvement and its differentiation with imaging studies can be misleading. In recent years, limitations of resectability have been pushed backwards or at least are under debate. This holds true for locally advanced tumors with infiltration on portomesenteric vascular structures, as well as for total pancreatectomies, intentional R1/R2 resections, and concomitant resection of liver metastases. These issues are addressed followingly.

***En-bloc* Vascular Resection in Advanced Pancreatic Carcinoma**

In advanced local disease, pancreatic carcinoma, especially when localised in the pancreatic head, tends to involve vascular structures, mainly the portomesenteric vessels, as well as the celiac trunk and its branches. Several studies have compared the survival of patients who underwent pancreatoduodenectomy with or without combined resection of major venous vessels. Leach *et al.* (4) reported a series of 31 patients with resection of the superior mesenteric-portal vein and compared their survival to that of 44 patients without vascular resection; the median survival rates were 22 months *versus* 20 months without vessel resection. Another series by Harrison *et al.* included 58 patients with tumor-infiltrating portal vein and vascular resection. No significant difference in median survival was seen, with 13 months reported for the group of vascular-resected patients *versus* 17

Correspondence to: Michael F. Nentwich, Department of General, Visceral and Thoracic Surgery, University Medical Center of Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany. Tel: +49 40741052401, Fax: +49 40741044995, e-mail: m.nentwich@uke.uni-hamburg.de

Key Words: Advanced pancreatic carcinoma, surgery, trends, review.

months in patients without vascular resection (5). Tseng *et al.* reported on 110 patients with vascular resection and found no significant difference in median survival, with 23.4 *versus* 26.5 months in 181 patients without the need for vascular resections. Remarkably, even the higher R1-rate in vascular-resected patients found to be 22%, compared to 12% in patients without vascular resection, did not adversely affect the survival in this study (6). Our own group examined the long-term survival of 100 patients with pancreatic adenocarcinoma and vascular resection. As a result, median survival was 15 months for patients with vascular resection and evident tumor invasion *versus* 16 months for patients without vascular resection. In addition, a histologically confirmed vascular infiltration was seen in 77 patients, resulting in 23 patients with a tumor infiltration mimicking peritumoral inflammation (7).

This finding of similar survival in patients with venous vascular resection, compared to patients without vascular resection has been also reported in other series (8-15) as reviewed by Glanemann *et al.* (16) and Mann *et al.* (2). Broad evidence for similar results in patients in need of arterial resections, *e.g.* the superior mesenteric artery, the hepatic artery and the celiac trunk, is still lacking. A recently published study by our group evaluated the short- and long-term outcome of patients with advanced pancreatic malignant disease with arterial resection. Median survival was not significantly different in patients with arterial resection at 14.0 months *versus* 15.8 months in patients without arterial vessel resection and was superior to that of patients treated with palliative bypass surgery, with a median survival of 7.5 months. Yet high rates of post-surgical morbidity and mortality in patients who undergo arterial resections have huge impact on the achieved oncological benefits (17).

In conclusion, data suggest that survival after vascular resection in cases of suspected tumor infiltration of the portomesenteric veins is similar to that of patients without venous tumor infiltration, yet arterial resections have to be restricted to a group of highly selected patients.

Total Pancreatectomy

After the introduction of total pancreatectomy into general surgical practise in the mid-20th century, advantages in oncological, as well as in post-surgical, results were expected. Resection of the whole gland was assumed to achieve higher R0-resection rates and to better deal with suspected tumor multicentricity. As a secondary effect of total pancreatic resection, the formation of a possibly critical pancreatic anastomosis could be avoided. Yet neither were the oncological benefits shown to be superior to parenchyma-sparing resections, nor did the post-surgical morbidity rate decrease substantially. These findings, combined with the resulting exocrine and endocrine impairments that were difficult to

adequately treat, lead to a reduced number of performed total pancreatectomies (18). In recent times, total pancreatectomy has again become a therapeutic option in a widened range of indications, with acceptable morbidity and mortality rates. Supplementation of enzymes and insulin substitution nowadays sufficiently controls postsurgical impairments but with the risk of hypoglycaemic events (19, 20).

Examples of indications for total pancreatectomy are the presence of large tumor masses or main-duct intraductal papillary mucinous neoplasms (IPMNs) involving the whole pancreatic gland, as well as intraoperative positive resection margins with the need for extended resections to achieve an R0-status (21, 22). As reported in the review by Glanemann *et al.* (16), median survival varies in the presented studies, ranging from 7-21.9 months, with overall morbidity and mortality rates of 44.9% and 8.8%, respectively. Interestingly, in a study by Schmidt *et al.*, patients with total pancreatectomy, after initial isolated neck margin-positive R1-resection, had a prolonged survival compared to R0 resected patients after pancreatoduodenectomy (23).

Again, the question as to whether total pancreatectomy may be superior regarding oncological benefits over pancreatoduodenectomy, evidently, still cannot be answered. Therefore, total pancreatectomy has its indications in selected patients but does not represent the routine procedure for pancreatic malignancies.

Intentional R1/R2-Resection

As stated above, the pre-surgical assessment of resectability is complicated by possible desmoplastic changes of the pancreatic tissue mimicking true vascular infiltration. Therefore, in borderline resectable tumors, a thorough surgical exploration with a series of intraoperative frozen section specimens is performed in order to evaluate resectability. In some cases, the vascular involvement of the tumor is only visible after the pancreas has been transected. The anatomic triangle between the celiac trunk and the superior mesenteric artery has been reported to be the site that most commonly reveals unresectability (24). If the pancreas has been transected, resection has to be continued even though an R0-status will obviously not be achieved, and sometimes the procedure even ends up in an R2-resection. The influence on patients' survival of these R2-resections has been controversially discussed. A study by Köninger *et al.* compared patients after a R2 pancreatic resection with a group of patients that underwent surgical bypass palliation for advanced pancreatic cancer. Median survival was equal in both groups at 10.7 months (25). A study by Bockhorn *et al.*, with the same approach, demonstrated a survival benefit for R2-resected patients, with 11.5 months *versus* 7.5 months, respectively (24). This finding of prolonged survival in patients who had not undergone R0-resection has been

also shown in studies of the Johns Hopkins University (26) and the Amsterdam Medical Center (27). In contrast to the studies by Bockhorn *et al.* and Köninger *et al.*, these latter studies included both R1 and R2 resected patients in the group of palliative resections.

The studies examining the outcome of non-R0-resections in pancreatic cancer state that the primary intention of surgery was to perform an oncologically radical operation with intended R0-resection, instead of palliative tumor debulking and thus patient selection may possibly be biased regarding, for example, the tumor size and the patients' age. Additionally, a true comparison of tumor characteristics in resected and palliative bypass groups is not possible. Recently, our group published data on a series of 22 intentionally R2-resected patients and compared morbidity and mortality to these of a matched group of patients undergoing a palliative bypass. Results showed an increased morbidity and a longer hospital stay for intentionally R2-resected patients, without significant differences in overall survival (28).

If a pancreatic resection, intended to be radical, results as a non-R0 situation, it seems not to adversely affect median survival and might even be beneficial in individual cases compared to bypass procedures. Nevertheless, intentional palliative resection has not been proven to affect survival positively.

Synchronous resection of liver metastases

Due to the late presentation of pancreatic malignant disease, patients often harbor metastatic spread, mainly to the liver and the peritoneum. The general therapeutic approach towards metastatic pancreatic malignancy consists of chemotherapy and the option of palliative surgery. Yet a small group of patients are presented with limited metastatic disease in the liver and a resectable primary lesion. In this subset of patients, synchronous resection of both the primary tumor, as well as the liver metastases may be beneficial and improve the outcome.

A study by Gleisner *et al.* presented 22 patients with periampullary cancer (17 with pancreatic adenocarcinoma) that underwent simultaneous resection of liver metastases. Median survival in patients who underwent synchronous liver resection was 5.9 months compared to 5.6 months in patients who underwent a palliative bypass procedure alone (29). In the same manner, Seelig *et al.* reported on 20 patients with periampullary cancer and concomitant resection of lymph nodal, peritoneal and liver metastases. In 14 patients, liver metastases were synchronously resected. The mean survival was 11 months for combined pancreatic resection and liver metastasectomy, compared to a matched control group with a median survival of 15.6 months, not showing statistical significance (30). Shrikhande *et al.* retrospectively studied 29 patients who underwent pancreatic

resection with synchronous metastasectomy. In 11 patients, liver metastases were resected. The median survival for patients with liver metastases was 11.4 months which compares favorably to that for other palliative procedures, as stated in this paper (31).

Overall, no clear evidence exists that synchronous resection of liver metastases may have a survival benefit and it remains an individual approach for selected patients only. Controlled trials are required in order to clearly elucidate the best therapeutic approach towards low-volume metastatic pancreatic malignancy.

Conclusion

Although dedicated work has been carried out in the past decades, both in basic and in clinical research, the diagnosis of pancreatic malignancy is still associated with a negative prognosis. With the aim of increasing patients' survival, surgeons try to push the limits of resectability. Vascular resection in advanced disease is technically feasible and, with venous vessel involvement, might result in survival rates comparable to those of patients without vascular infiltration. Tumor involvement of the whole pancreatic gland can be addressed by total pancreatectomy with acceptable morbidity and mortality. The resulting endocrine and exocrine impairments are adequately controlled by enzyme and insulin substitution. The role of palliative tumor resection and the synchronous resection of liver metastases are still controversial and need further investigation in order for evidence to be gained on their implication in a multimodal treatment. The interdisciplinary approach to advanced and low-volume metastatic disease, in general, remains challenging for all involved physicians and needs to be discussed individually for each patient.

References

- 1 Husmann G, Kaatsch P, Katalinic A, Bertz J, Haberland J, Kraywinkel K and Wolf U: Krebs in Deutschland 2005/2006. Häufigkeiten und Trends. 7. Ausgabe. Berlin, Robert Koch Institut und die Gesellschaft der epidemiologischen Krebsregister in Deutschland e. V., 2010.
- 2 Mann O, Strate T, Schneider C, Yekebas EF and Izbicki JR: Surgery for advanced and metastatic pancreatic cancer – current state and perspectives. *Anticancer Res* 26: 681-686, 2006.
- 3 Ravichandran D and Johnson CD: Pancreatic adenocarcinoma: Why and when should it be resected? *Postgrad Med J* 73: 469-475, 1997.
- 4 Leach SD, Lee JE, Charnsangavej C, Cleary KR, Lowy AM, Fenoglio CJ, Pisters PW and Evans DB: Survival following pancreaticoduodenectomy with resection of the superior mesenteric-portal vein confluence for adenocarcinoma of the pancreatic head. *Br J Surg* 85: 611-617, 1998.
- 5 Harrison LE, Klimstra DS and Brennan MF: Isolated portal vein involvement in pancreatic adenocarcinoma. A contraindication for resection? *Ann Surg* 224: 342-347; discussion 347-349, 1996.

- 6 Tseng JF, Tamm EP, Lee JE, Pisters PW and Evans DB: Venous resection in pancreatic cancer surgery. *Best Pract Res Clin Gastroenterol* 20: 349-364, 2006.
- 7 Yekebas EF, Bogoevski D, Cataldegirmen G, Kunze C, Marx A, Vashist YK, Schurr PG, Liebl L, Thielges S, Gawad KA, Schneider C and Izbicki JR: *En bloc* vascular resection for locally advanced pancreatic malignancies infiltrating major blood vessels: perioperative outcome and long-term survival in 136 patients. *Ann Surg* 247: 300-309, 2008.
- 8 Siriwardana HP and Siriwardana AK: Systematic review of outcome of synchronous portal-superior mesenteric vein resection during pancreatectomy for cancer. *Br J Surg* 93: 662-673, 2006.
- 9 Riediger H, Makowiec F, Fischer E, Adam U and Hopt UT: Postoperative morbidity and long-term survival after pancreaticoduodenectomy with superior mesenteric-portal vein resection. *J Gastrointest Surg* 10: 1106-1115, 2006.
- 10 Al-Haddad M, Martin JK, Nguyen J, Pungpapong S, Raimondo M, Woodward T, Kim G, Noh K and Wallace MB: Vascular resection and reconstruction for pancreatic malignancy: a single-center survival study. *J Gastrointest Surg* 11: 1168-1174, 2007.
- 11 Fuhrman GM, Leach SD, Staley CA, Cusack JC, Charnsangavej C, Cleary KR, El-Naggar AK, Fenoglio CJ, Lee JE and Evans DB: Rationale for en bloc vein resection in the treatment of pancreatic adenocarcinoma adherent to the superior mesenteric-portal vein confluence. Pancreatic Tumor Study Group. *Ann Surg* 223: 154-162, 1996.
- 12 Bachellier P, Nakano H, Oussoultzoglou PD, Weber JC, Boudjema K, Wolf PD and Jaeck D: Is pancreaticoduodenectomy with mesentericoportal venous resection safe and worthwhile? *Am J Surg* 182: 120-129, 2001.
- 13 Nakagohri T, Kinoshita T, Konishi M, Inoue K and Takahashi S: Survival benefits of portal vein resection for pancreatic cancer. *Am J Surg* 186: 149-153, 2003.
- 14 Howard TJ, Villanustre N, Moore SA, DeWitt J, LeBlanc J, Maglente D and McHenry L: Efficacy of venous reconstruction in patients with adenocarcinoma of the pancreatic head. *J Gastrointest Surg* 7: 1089-1095, 2003.
- 15 Nakano H, Bachellier P, Weber JC, Oussoultzoglou E, Dieng M, Shimura H, Boudjema K, Wolf P and Jaeck D: Arterial and vena caval resections combined with pancreaticoduodenectomy in highly selected patients with periampullary malignancies. *Hepatogastroenterology* 49: 258-262, 2002.
- 16 Glanemann M, Shi B, Liang F, Sun XG, Bahra M, Jacob D, Neumann U and Neuhaus P: Surgical strategies for treatment of malignant pancreatic tumors: extended, standard or local surgery? *World J Surg Oncol* 6: 123, 2008.
- 17 Bockhorn M, Burdelski C, Bogoevski D, Sgourakis G, Yekebas EF and Izbicki JR: Arterial en bloc resection for pancreatic carcinoma. *Br J Surg* 98: 86-92, 2011.
- 18 Muller MW, Friess H, Kleeff J, Dahmen R, Wagner M, Hinz U, Breisch-Girbig D, Ceyhan GO and Buchler MW: Is there still a role for total pancreatectomy? *Ann Surg* 246: 966-974; discussion 974-965, 2007.
- 19 Casadei R, Monari F, Buscemi S, Laterza M, Ricci C, Rega D, D'Ambra M, Pezzilli R, Calculli L, Santini D and Minni F: Total pancreatectomy: indications, operative technique, and results: a single-centre experience and review of literature. *Updates Surg* 62: 41-46, 2010.
- 20 Parsaik AK, Murad MH, Sathananthan A, Moorthy V, Erwin PJ, Chari S, Carter RE, Farnell MB, Vege SS, Sarr MG and Kudva YC: Metabolic and target organ outcomes after total pancreatectomy: Mayo Clinic experience and meta-analysis of the literature. *Clin Endocrinol (Oxf)* 73: 723-731, 2010.
- 21 Janot MS, Belyaev O, Kersting S, Chromik AM, Seelig MH, Sulberg D, Mittelkotter U and Uhl WH: Indications and early outcomes for total pancreatectomy at a high-volume pancreas center. *HPB Surg* published online 2010: 686702, 2010.
- 22 Reddy S, Wolfgang CL, Cameron JL, Eckhauser F, Choti MA, Schulick RD, Edil BH and Pawlik TM: Total pancreatectomy for pancreatic adenocarcinoma: evaluation of morbidity and long-term survival. *Ann Surg* 250: 282-287, 2009.
- 23 Schmidt CM, Glant J, Winter JM, Kennard J, Dixon J, Zhao Q, Howard TJ, Madura JA, Nakeeb A, Pitt HA, Cameron JL, Yeo CJ and Lillemoe KD: Total pancreatectomy (R0 resection) improves survival over subtotal pancreatectomy in isolated neck margin positive pancreatic adenocarcinoma. *Surgery* 142: 572-578; discussion 578-580, 2007.
- 24 Bockhorn M, Cataldegirmen G, Kutup A, Marx A, Burdelski C, Vashist JK, Mann O, Liebl L, Konig A, Izbicki JR and Yekebas EF: Crossing the Rubicon: when pancreatic resection with curative intent ends in an R2 status. Impact of desmoplastic pseudo-pancreatitis and anatomical site of irresectability. *Ann Surg Oncol* 16: 1212-1221, 2009.
- 25 Koninger J, Wente MN, Muller-Stich BP, di Mola FF, Gutt CN, Hinz U, Muller MW, Friess H and Buchler MW: R2 resection in pancreatic cancer-Does it make sense? *Langenbecks Arch Surg* 393: 929-934, 2008.
- 26 Lillemoe KD, Cameron JL, Yeo CJ, Sohn TA, Nakeeb A, Sauter PK, Hruban RH, Abrams RA and Pitt HA: Pancreaticoduodenectomy. Does it have a role in the palliation of pancreatic cancer? *Ann Surg* 223: 718-725; discussion 725-718, 1996.
- 27 Reinders ME, Allema JH, van Gulik TM, Karsten TM, de Wit LT, Verbeek PC, Rauws EJ and Gouma DJ: Outcome of microscopically nonradical, subtotal pancreaticoduodenectomy (Whipple's resection) for treatment of pancreatic head tumors. *World J Surg* 19: 410-414; discussion 414-415, 1995.
- 28 Tachezy M, Bockhorn M, Gebauer F, Vashist YK, Kaifi JT and Izbicki JR: Bypass surgery *versus* intentionally incomplete resection in palliation of pancreatic cancer: Is resection the lesser evil? *J Gastrointest Surg* 15: 829-835, 2011.
- 29 Gleisner AL, Assumpcao L, Cameron JL, Wolfgang CL, Choti MA, Herman JM, Schulick RD and Pawlik TM: Is resection of periampullary or pancreatic adenocarcinoma with synchronous hepatic metastasis justified? *Cancer* 110: 2484-2492, 2007.
- 30 Seelig SK, Burkert B, Chromik AM, Tannapfel A, Uhl W and Seelig MH: Pancreatic resections for advanced M1-pancreatic carcinoma: the value of synchronous metastasectomy. *HPB Surg* 2010: 579672, 2010.
- 31 Shrikhande SV, Kleeff J, Reiser C, Weitz J, Hinz U, Esposito I, Schmidt J, Friess H and Buchler MW: Pancreatic resection for M1 pancreatic ductal adenocarcinoma. *Ann Surg Oncol* 14: 118-127, 2007.

Received February 13, 2012

Revised April 9, 2012

Accepted April 10, 2012