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Extended pancreatectomy in pancreatic ductal adenocarcinoma: definition and consensus of the International Study Group for Pancreatic Surgery (ISGPS)

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ABSTRACT

Background: Complete macroscopic tumor resection is one of the most relevant predictors of long-term survival in pancreatic ductal adenocarcinoma. Because locally advanced pancreatic tumors can involve adjacent organs, “extended” pancreatectomy which includes the resection of additional organs may be needed to achieve this goal. Our aim was to develop a common consistent terminology to be used in centers reporting results of pancreatic resections for cancer.

Methods: An international panel of pancreatic surgeons working in well-known, high-volume centers reviewed the literature on extended pancreatectomies and worked together to establish a consensus on the definition and the role of extended pancreatectomy in pancreatic cancer.

Results: Macroscopic (R1) and microscopic (R0) complete tumor resection can be achieved in patients with locally advanced disease by extended pancreatectomy. Operative time, blood loss, need for blood transfusions, duration of stay in the intensive care unit and hospital, morbidity, and possibly also perioperative mortality are increased with extended resections. Long-term survival is similar compared to standard resections but appears to be better compared to bypass surgery or nonsurgical palliative chemotherapy or chemoradiotherapy. It was not possible to identify any clear prognostic criteria based on the specific additional organ resected.

Conclusions: Despite increased perioperative morbidity, extended pancreatectomy is warranted in locally advanced disease to achieve long-term survival in pancreatic ductal adenocarcinoma if macroscopic clearance can be achieved. Definitions of extended pancreatectomies for locally advanced disease (and not distant metastatic disease) are established which are crucial for comparison of results of future trials across different practices and countries, in particular for those utilizing neoadjuvant therapy.

INTRODUCTION

Despite recent improvements in diagnosis and therapy, ductal adenocarcinoma of the pancreas is among the five most frequent causes of cancer-related death in Europe and the US, with overall 5-year survival rates of 5-6% [1,2]. Complete surgical resection of the pancreatic cancer is the only potential hope of cure and is the most relevant predictor of long-term survival [3-6]. Unfortunately, only around 30% of all patients with pancreatic adenocarcinoma have localized or regional disease amenable to surgical resection [7]. Due to the locoregional growth pattern and the early systemic spread of pancreatic ductal adenocarcinoma, local invasion of surrounding vessels and organs or evidence of distant metastasis, primarily to the liver, often limit resectability.

Macroscopic (R1) or ideally microscopic (R0) margin-free tumor resection is considered a prerequisite for favorable survival in pancreatic cancer [4,6,8]. Locally advanced pancreatic tumors may appear unresectable because of tumor spread to nearby vessels and organs beyond the peripancreatic fat. Neoadjuvant therapy may occasionally allow for tumor regression, increasing the reported resectability rates in patients with otherwise unresectable disease to approximately 30% [9]. Extended pancreatectomies, which, loosely defined, include the resections of adjacent organs or vascular structures, and eventually combined with neoadjuvant protocols, represent an option to achieve the complete resection of advanced tumors; however, well organized, randomized controlled trials on extended pancreatectomy or on neoadjuvant therapy are not yet available.

The present position statement of the International Study Group of Pancreatic Surgery (ISGPS) provides a consensus on the definition and value of extended pancreatectomy in pancreatic ductal adenocarcinoma which hopefully will allow better collaboration and understanding internationally of classification of pancreatic resections similar to other ISGPS classifications of pancreatic fistula [10], delayed gastric emptying [11], and postoperative hemorrhage [12].

METHODS

A computerized search of the PubMed database was made using the following terms: ”pancreatic cancer“, “pancreatic adenocarcinoma”, “extended resection”, “multivisceral resection”, “additional organ resection”, “morbidity”, “mortality”, and ”survival“. The reference list of relevant articles was screened for further eligible studies. Selected studies were rated according to descending levels of evidence: systematic reviews and meta-analyses of randomized controlled trials, prospective randomized controlled trials, systematic reviews of cohort studies, prospective/retrospective cohort studies, and existing consensus reports. All studies were categorized according to the evidence level of individual studies as per the recommendations of the Centre for Evidence-Based Medicine, Oxford, UK (http://www.cebm.net/). Only studies published in English were included. Studies of fewer than 10 patients were not included. The last search was done on February 28th, 2013.

All relevant literature and a summary of the extracted data were reviewed by the study group (WH, CMV, AF, CJY, JPN, MWB) of the International Study Group of Pancreatic Surgery (ISGPS) which resulted in a first draft of the consensus definition and preparation of the statement. During the Consensus Meeting that was held in Garda/Verona, Italy from April 23rd – 24th, 2013 and attended by members of the ISGPS, the first draft was discussed. A final consensus statement on the definition of standard lymphadenectomy in pancreatic surgery was formulated and agreed by all cosignatories using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines [13].

DEFINITIONS AND CONSENSUS STATEMENTS

Definition

The available literature on extended pancreatectomy is heterogeneous, and the authors analyzed pancreatectomies combined with the resection of various adjacent organs. **Table 1** summarizes the relevant literature on extended pancreatectomy [14-27].

A partial colectomy is required occasionally because of the proximity of pancreatic tumors to the transverse colon and/or mesocolic root. Several studies have assessed the role of additional colonic resection, either by including only patients with pancreatectomy and additional colectomy [18] or by identifying the role of additional colectomy in uni-or multivariate analysis regarding the perioperative risk and its long-term prognosis [14,15,17,24,26]

Likewise, vascular resections are performed increasingly frequently in extended resections of the pancreatic head or body. Beyond venous resections, arterial resections can involve the celiac trunk, the hepatic artery, and/or the superior mesenteric artery. Because of the technical expertise necessary for resections of these organ-essential arteries, the increased potential morbidity and a possibly impaired long-term prognosis, the malignant involvement of the celiac axis or superior mesenteric artery is usually regarded as non-resectable disease and is staged as AJCC/UICC stage III (7^{th} edition)[28,29]. Several studies and one meta-analysis [30] focused on arterial resections in pancreatectomies or assessed their perioperative risk and prognosis within the analysis of extended pancreatectomies [14,24].

Similar to arterial resections, patients undergoing resection of the portal or superior mesenteric vein have been included in many studies on extended pancreatectomy. Because the evidence of whether porto-mesenteric vein resection negatively affects short- and long-term prognosis of pancreatectomies is inhomogenous [31-33], some studies excluded porto-mesenteric vein resections in the definition of extended pancreatectomy [24,26]. In contrast, our ISGPS consensus recommends that pancreatectomy with concomitant portal or superior mesenteric vein resection should be classified as an extended pancreatectomy in future studies.

The literature on concomitant liver resection in extended pancreatectomy requires critical appraisal. Seemingly few patients during pancreatectomy require liver resection because of direct tumor infiltration into the liver. Instead, most patients included in the available reports on extended or multivisceral pancreatectomies underwent liver resections for distant metastases. Importantly, in the studies by Klempnauer, Hartwig, and Burdelski and colleagues [14,24,26], 28% to 38% of patients with multivisceral resections had concomitant distant metastasis. However, to identify the role of extended resections in locally advanced pancreatic cancer, the ISGPS recommends that patients undergoing resection of metastatic disease to the liver should be reported separately and not be considered as an extended pancreatectomy for locally advanced disease.

The oncologic necessity of adrenalectomy in distal pancreatectomy for pancreatic cancer is controversial. Strasberg et al. included the left adrenal gland in their posterior, radical, antegrade modular pancreatosplenectomy (RAMPS) procedure to achieve R0 resection regardless of whether the gland is involved grossly with tumor infiltration [20,27]. While this type of extension of distal pancreatectomy appears to be necessary for larger body or tail tumors, it is not always the case in standard resections of smaller tumors. Therefore, the consensus of the ISGPS is to include left adrenalectomy as part of an extended distal pancreatectomy.

Extended lymphadenectomy combined with pancreatic resection has often been called an extended pancreatectomy. Based on four, randomized controlled trials [34-37] and two meta-analyses [38,39], no survival advantage has been demonstrated for any extended lymphadenectomy. Currently, a form of standard radical lymphadenectomy is recommended by the ISGPS in pancreatectomy (reference ISGPS consensus on lymphadenectomy, also submitted to Surgery), although extended lymphadenectomy may be warranted in patients with obviously enlarged interaortocaval or paraaortic lymph nodes. Because the term “extended pancreatectomy” focuses to the resection of locally advanced tumors, the ISGPS consensus is that the performance of an extended lymphadenectomy alone in pancreatectomy should not be called an extended pancreatectomy, but categorized separately as an extended lymphadenectomy.

Because of the limited comparability of presently available studies mainly due to inhomogeneous inclusion criteria, the ISGPS highlights the need to establish a consensus definition of standard and extended pancreatectomy. Based on tumor location and the type of pancreatectomy, the definitions put forth by this ISGPS consensus are as follows:

Consensus (strong recommendation):

Standard pancreatoduodenectomy

- head of the pancreas and uncinate process
- duodenum and first segment of jejunum
- common bile duct and gallbladder
- lymphadenectomy (as defined in the ISGPS consensus statement lymphadenectomy (reference ISGPS consensus on lymphadenectomy, also submitted to Surgery)
- sometimes pylorus and/or antrum of stomach
- sometimes elements of the transverse mesocolon exclusive of relevant vasculature (e.g. limited soft tissue contiguous to the tumor, but not including the colon itself)

Standard distal pancreatectomy

- body and/or tail of the pancreas
- spleen including splenic vessels
- lymphadenectomy (as defined in the ISGPS consensus statement lymphadenectomy) (reference ISGPS consensus on lymphadenectomy, also submitted to Surgery)
- sometimes fascia of Gerota
- sometimes elements of the transverse mesocolon exclusive of relevant vasculature (e.g. limited soft tissue contiguous to the tumor, but not including the colon itself)

Standard total pancreatectomy:

- head, neck, body, and tail of the pancreas
- duodenum and first segment of jejunum
- common bile duct and gallbladder
- spleen including splenic vessels
- lymphadenectomy (as defined in the ISGPS consensus statement lymphadenectomy) (reference ISGPS consensus on lymphadenectomy, also submitted to Surgery)
- sometimes pylorus and/or antrum of stomach
- sometimes fascia of Gerota
- sometimes elements of the transverse mesocolon exclusive of relevant vasculature (e.g. limited soft tissue contiguous to the tumor, but not including the colon itself)

Extended pancreatoduodenectomy:

Standard pancreatoduodenectomy as defined above plus any of the following organs involved in continuity:

- more than the antrum or distal half of the stomach
- colon and/or mesocolon with relevant vascular structures of the transverse mesocolon (ileocolic, right, or middle colic vessels)
- small bowel beyond the first jejuna segment
- portal, superior mesenteric, and/or inferior mesenteric vein (type I-IV as defined by the ISGPS consensus statement on borderline resectable tumors)(reference ISGPS consensus on borderline resecable tumors, also submitted to Surgery)
- hepatic artery, celiac trunk, and/or superior mesenteric artery

- inferior vena cava
- right adrenal gland
- right kidney and/or its vasculature
- liver
- diaphragmatic crura

Extended distal pancreatectomy:

Standard distal pancreatectomy as defined above plus any of the following organs involved in continuity:

- any type of gastric resection
- colon and/or relevant vascular structures of the transverse mesocolon (middle or left colic vessels)
- small bowel
- portal, superior mesenteric, and/or inferior mesenteric vein (type I-IV as defined by the ISGPS consensus statement on borderline resectable tumors)(reference ISGPS consensus on borderline resecable tumors, also submitted to Surgery)
- hepatic artery, celiac axis, and/or superior mesenteric artery
- inferior vena cava
- left adrenal gland
- left kidney and/or its vasculature
- diaphragmatic crura and/or diaphragm
- liver

Extended total pancreatectomy:

Standard total pancreatectomy as defined above plus any of the following organs involved in continuity:

- more than the antrum or distal half of the stomach
- colon and/or relevant vascular structures of the transverse mesocolon (ileocolic, right, middle, or left colic vessels)
- small bowel beyond the first jejunal segment
- portal, superior mesenteric, and/or inferior mesenteric vein (type I-IV as defined by the ISGPS consensus statement on borderline resectable tumors)(reference ISGPS consensus on borderline resecable tumors, also submitted to Surgery)
- hepatic artery, celiac trunk and/or superior mesenteric artery
- inferior vena cava
- right and/or left adrenal gland
- kidney and/or its vasculature
- diaphragmatic crura and/or diaphragm
- liver

<u>For all types of extended pancreatectomy:</u>

To facilitate the comparability of studies, a partial pancreatectomy which needs to be extended to the left or the right because of a positive pancreatic margin on frozen section should not be called an “extended pancreatectomy”. In reports on extended pancreatectomy, the resection of the hepatic artery, celiac trunk, and/or superior mesenteric artery should be analyzed separately because of their potentially critical effects on short and long-term outcome. After vascular resections, adequate organ perfusion must be ensured by vascular reconstruction or via spontaneous or iatrogenically induced collaterals (e.g. adequate liver perfusion after resection of aberrant liver arteries or preoperative embolization of the common hepatic artery; adequate colon perfusion after resection of mesocolon

including the central colic vessels). The panel recommends that tumor resection in extended pancreatectomy should be performed "en-bloc" whenever possible as opposed to violating tumor planes.

The consensus group prefers not to use the term "multivisceral pancreatectomy" because standard pancreatectomy itself is multivisceral in nature. The term "extended pancreatectomy" should not be applied for standard pancreatectomies combined with the concomitant resection of distant organs (e.g. liver) because of synchronous distant metastases or a second primary tumor. For these types of resections, the ISGPS recommends to use the terminology "non-contiguous organ resection in the setting of pancreatectomy".

Resectability

Only a few studies have provided the resection margin status for extended pancreatectomy. R0, R1, and R2 resections were described in 42% to 81%, in 9% to 39%, and in 8% to 14% of patients, respectively [14,15,24,26,27]. Given the various definitions of a R0 and R1 resection margin (e.g. R1 being tumor cells within 1mm of the margin vs. tumor cells at the margin) [40-42], caution is warranted in the comparison between results of studies using different definitions.

Consensus:

- Macroscopic complete tumor resection can be achieved in the majority of extended pancreatectomies. A locally advanced tumor is "resectable" when margins are macroscopically negative and if no distant metastases are present, and if remaining or reconstructed visceral vasculature provides adequate perfusion of preserved organs.

Perioperative morbidity and mortality

Despite improvements in surgical techniques and perioperative patient care, pancreatoduodenectomies as well as distal pancreatectomies are still associated with substantial perioperative morbidity. Moreover, in-hospital mortality rate is not negligible, but has been shown to be determined in part by hospital and surgeon volume [43-45]. One of the most relevant issues concerning extended pancreatectomy is whether resections can be achieved with acceptably low morbidity and mortality rates to justify such extensive interventions.

At present, no randomized trials are available comparing standard pancreatectomy to extended pancreatectomy. Moreover it is unlikely that such a trial will ever be undertaken, because this might mean comparing complete versus incomplete tumor resections in locally advanced tumors that invade adjacent organs. Several studies, however, have compared the perioperative outcome of patients who underwent standard pancreatectomies with those who had extended pancreatectomies. Not-surprisingly, extended resections are associated with greater operating times, blood loss, blood transfusion, and ICU and hospital stays [15,16,18,23,24,26]. (**Table 1**) The majority of these studies reported increased morbidity rates with extended resections [14,17,19,22,24,26], whereas only two studies reported comparable morbidity [23,25]. Similar findings were described for postoperative mortality. No significant differences in operative mortality between standard and extended resections were found in all [14-16,18,22-24,26] but one [19] study. Importantly, of all of these, only the study by Hartwig et al. used a group of patients with standard resection for comparison that was matched for the type of pancreatic resection, age, sex, and histology [24].

Only a few studies have assessed the differences in morbidity and mortality specifically for the type of additionally resected organs. The outcome of pancreatectomies with and without porto-mesenteric vein resection is fairly well documented. Large systematic reviews and meta-analyses demonstrated comparable perioperative morbidity and mortality as well as survival [31,32,46], whereas a recent large, population-based analysis on 10,206 patients identified increased perioperative morbidity and mortality rates [33] (**Table 2**). In contrast, one systematic review indicated that morbidity and mortality rates were greater if one of the main arteries (celiac axis, hepatic artery, and/or

superior mesenteric artery) was resected [30] (**Table 2**). The effects of the resection of other adjacent organs are inconsistently and less well documented. Increased morbidity and/or mortality rates in the case of additional colectomy [14,17] or nephrectomy [26] were identified by univariate analysis in some studies, whereas congruous liver resections were associated with less morbidity [24]. Two studies found that the morbidity rate increased with the number of additionally resected organs [24,26].

Of importance, the interpretation of studies on extended pancreatectomy is difficult because of the variations regarding the type of pancreatectomy performed. Several studies have focused on pancreatoduodenectomies [17-19,23] or distal pancreatectomies only [16,22,25,27], while others included any type of pancreatectomy [14,15,24,26]. It is not possible to present more specific conclusions on outcomes according to the type of pancreatectomy performed, because the number of patients in most of these studies was moderate to low, and the majority of studies which included a mix of types of pancreatectomy did not present outcomes according to the type of pancreatectomy.

Consensus:

- Operating time, blood loss, need for blood transfusions, and duraion of intensive care unit and hospital stay may be increased in extended pancreatectomy.
- Data suggest that surgical morbidity is increased in extended pancreatectomy.
- Overall perioperative mortality seems to be similar compared to standard pancreatectomies. There is an inhomogeneous identification of specific organ-attributable morbidity and mortality. Morbidity and mortality is increased if one of the named arteries (celiac axis, common hepatic artery, and/or superior mesenteric artery) is resected.

Prognosis

Notwithstanding the increased perioperative morbidity and possibly also mortality rates, the justification for extended pancreatectomy must be to provide benefits in long-term survival rates. Survival has to be seen in comparison to that of locally advanced disease treated non-operatively.

Data from a randomized, controlled, multicenter trial on chemo- or radiochemotherapy suggests a median survival between 8.6 and 13 months in locally advanced, "unresectable" ductal adenocarcinoma, depending on the type of therapy [47]. The best survival data from randomized trials on palliative chemotherapy of metastatic pancreatic adenocarcinoma have been described with FOLFIRINOX, with a median overall survival of 11.1 months [48]. Importantly, 5-year survival was not reported in these two palliative trials but supposedly was very low according to Kaplan-Meier curves which were presented in the publications.

Median and 5-year survival rates from published reports on extended pancreatectomy for pancreatic cancer are summarized in the **Table 1**. For pancreatic adenocarcinoma, median survival varied between 8.4 months and 25.9 months, with 5 year survival rates between 13% and 36%. All but one [26] of these studies reported survival rates of extended resections similar to that of standard resections [14] [15,16,18,24]. Although not truly comparable to data from randomized trials with palliative therapy, survival of patients with extended pancreatectomy seems superior. But as with the analysis of postoperative morbidity, patient numbers were too small to allow a survival analysis according to the type of extended resection. Although potential downstaging therapy by combinational chemotherapy or radiochemotherapy is being used increasingly in locally advanced pancreatic cancer at most pancreatic centers and may be relevant for the proper selection of patients ultimately for pancreatectomy and for achieving long-term survival, insufficient data on multimodal therapy are available in the current literature on extended pancreatectomy. Likewise, valid data on quality of life after extended pancreatectomy are also not available. These issues need to be addressed in future studies.

Consensus:

- Long-term survival after extended pancreatectomy appears to be similar to that after standard pancreatectomy.

- When compared with the best available data from randomized, controlled studies on palliative chemo- or radiochemotherapy in locally advanced disease (accepting that a true statistical comparison is flawed), median survival and notably 5-year survival rates for extended pancreatectomy are superior.
- Insufficient data are available to assess the effects on long-term survival of the individual types of extended pancreatectomy and specific organ resections.
- The potential of neoadjuvant therapy combined with extended pancreatectomy for pancreatic cancer appears to be very encouraging and needs to be investigated systematically in future randomized studies.

Grade of evidence

The level of evidence regarding the value of extended pancreatectomy in ductal adenocarcinoma of the pancreas is moderate to poor with evidence level of 3 to 4. Available data come exclusively from retrospective, non-randomized, cohort studies, and in all but one study [24], the control arm was not well-matched for the main patient and tumor characteristics. All relevant studies come from specialized, high-volume pancreas centers. Likewise, available systematic reviews and meta-analyses on porto-mesenteric [31,32,46,49] or arterial resections [30] include only retrospective cohort studies. The comparability of the studies is hampered by inhomogeneous inclusion criteria and variations in the definition of extended pancreatectomy. A publication bias cannot be excluded.

SUMMARY:

Within the present ISGPS consensus statement, a definition of extended pancreatectomy is provided to allow valid comparisons of various future treatments across centers and countries. Presently, it appears from the available literature that extended pancreatectomies with complete tumor resection are feasible in selected patients with locally advanced tumors within specialized, high volume pancreas centers and surgeons with focused experience in these complicated

resections. Whereas perioperative morbidity and possibly also mortality increased, long-term results are favorable compared to palliative bypass procedures or chemo- and/or radiotherapy. It is important to emphasize that currently, extended pancreatectomy can only be recommended in carefully selected patients within specialized centers. All extended pancreatectomies should be performed according to strict protocols: follow-up and assessment of outcome should include not only morbidity and mortality but also quality of life.

REFERENCES

1. Malvezzi M, Bertuccio P, Levi F, La Vecchia C, Negri E. European cancer mortality predictions for the year 2012. Ann Oncol 2012; 23:1044-1052.

2. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012; 62:10-29.

3. Shaib Y, Davila J, Naumann C, El Serag H. The impact of curative intent surgery on the survival of pancreatic cancer patients: a U.S. Population-based study. Am J Gastroenterol 2007; 102:1377-1382.

4. Hartwig W, Hackert T, Hinz U, Gluth A, Bergmann F, Strobel O, Büchler MW, Werner J. Pancreatic cancer surgery in the new millennium: better prediction of outcome. Ann Surg 2011; 254:311-319.

5. Mayo SC, Nathan H, Cameron JL, Olino K, Edil BH, Herman JM, Hirose K, Schulick RD, Choti MA, Wolfgang CL, Pawlik TM. Conditional survival in patients with pancreatic ductal adenocarcinoma resected with curative intent. Cancer 2012; 118:2674-2681.

6. Konstantinidis IT, Warshaw AL, Allen JN, Blaszkowsky LS, Fernandez-del Castillo C, Deshpande V, Hong TS, Kwak EL, Lauwers GY, Ryan DP, Wargo JA, Lillemoe KD, Ferrone CR. Pancreatic Ductal Adenocarcinoma: Is There a Survival Difference for R1 Resections Versus Locally Advanced Unresectable Tumors? What Is a "True" R0 Resection? Ann Surg 2013; 257:731-736.

7. Baxter NN, Whitson BA, Tuttle TM. Trends in the treatment and outcome of pancreatic cancer in the United States. Ann Surg Oncol 2007; 14:1320-1326.

8. Butturini G, Stocken DD, Wente MN, Jeekel H, Klinkenbijl JH, Bakkevold KE, Takada T, Amano H, Dervenis C, Bassi C, Büchler MW, Neoptolemos JP. Influence of resection margins and treatment on survival in patients with pancreatic cancer: meta-analysis of randomized controlled trials. Arch Surg 2008; 143:75-83.

9. Gillen S, Schuster T, Meyer Zum BC, Friess H, Kleeff J. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. PLoS Med 2010; 7:e1000267.

10. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, Neoptolemos J, Sarr M, Traverso W, Buchler M. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005; 138:8-13.

11. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, Neoptolemos JP, Padbury RT, Sarr MG, Traverso LW, Yeo CJ, Büchler MW. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery 2007; 142:761-768.

12. Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, Neoptolemos JP, Padbury RT, Sarr MG, Yeo CJ, Büchler MW. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery 2007; 142:20-25.

13. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, Nasser M, Meerpohl J, Post PN, Kunz R, Brozek J, Vist G, Rind D, Akl EA, Schunemann HJ. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol 2013.

14. Klempnauer J, Ridder GJ, Bektas H, Pichlmayr R. Extended resections of ductal pancreatic cancer--impact on operative risk and prognosis. Oncology 1996; 53:47-53.

15. Sasson AR, Hoffman JP, Ross EA, Kagan SA, Pingpank JF, Eisenberg BL. En bloc resection for locally advanced cancer of the pancreas: is it worthwhile? J Gastrointest Surg 2002; 6:147-157.

16. Shoup M, Conlon KC, Klimstra D, Brennan MF. Is extended resection for adenocarcinoma of the body or tail of the pancreas justified? J Gastrointest Surg 2003; 7:946-952.

17. Adam U, Makowiec F, Riediger H, Schareck WD, Benz S, Hopt UT. Risk factors for complications after pancreatic head resection. Am J Surg 2004; 187:201-208.

18. Suzuki Y, Fujino Y, Tanioka Y, Sakai T, Ajiki T, Ueda T, Tominaga M, Kuroda Y. Resection of the colon simultaneously with pancreaticoduodenectomy for tumors of the pancreas and periampullary region: short-term and long-term results. World J Surg 2004; 28:1007-1010.

19. Muscari F, Suc B, Kirzin S, Hay JM, Fourtanier G, Fingerhut A, Sastre B, Chipponi J, Fagniez PL, Radovanovic A. Risk factors for mortality and intra-abdominal complications after pancreatoduodenectomy: multivariate analysis in 300 patients. Surgery 2006; 139:591-598.

20. Strasberg SM, Linehan DC, Hawkins WG. Radical antegrade modular pancreatosplenectomy procedure for adenocarcinoma of the body and tail of the pancreas: ability to obtain negative tangential margins. J Am Coll Surg 2007; 204:244-249.

21. McKay A, Sutherland FR, Bathe OF, Dixon E. Morbidity and mortality following multivisceral resections in complex hepatic and pancreatic surgery. J Gastrointest Surg 2008; 12:86-90.

22. Kleeff J, Diener MK, Z'graggen K, Hinz U, Wagner M, Bachmann J, Zehetner J, Müller MW, Friess H, Büchler MW. Distal pancreatectomy: risk factors for surgical failure in 302 consecutive cases. Ann Surg 2007; 245:573-582.

23. Nikfarjam M, Sehmbey M, Kimchi ET, Gusani NJ, Shereef S, Avella DM, Staveley-O'Carroll KF. Additional organ resection combined with pancreaticoduodenectomy does not increase postoperative morbidity and mortality. J Gastrointest Surg 2009; 13:915-921.

24. Hartwig W, Hackert T, Hinz U, Hassenpflug M, Strobel O, Büchler MW, Werner J. Multivisceral resection for pancreatic malignancies: risk-analysis and long-term outcome. Ann Surg 2009; 250:81-87.

25. Seeliger H, Christians S, Angele MK, Kleespies A, Eichhorn ME, Ischenko I, Boeck S, Heinemann V, Jauch KW, Bruns CJ. Risk factors for surgical complications in distal pancreatectomy. Am J Surg 2010; 200:311-317.

26. Burdelski CM, Reeh M, Bogoevski D, Gebauer F, Tachezy M, Vashist YK, Cataldegirmen G, Yekebas E, Izbicki JR, Bockhorn M. Multivisceral resections in pancreatic cancer: identification of risk factors. World J Surg 2011; 35:2756-2763.

27. Mitchem JB, Hamilton N, Gao F, Hawkins WG, Linehan DC, Strasberg SM. Long-term results of resection of adenocarcinoma of the body and tail of the pancreas using radical antegrade modular pancreatosplenectomy procedure. J Am Coll Surg 2012; 214:46-52.

28. TNM classification of malignant tumours. Wiley-Blackwell; 2009.

29. AJCC Cancer Staging Manual. New York: NY:Springer; 2010.

30. Mollberg N, Rahbari NN, Koch M, Hartwig W, Hoeger Y, Büchler MW, Weitz J. Arterial resection during pancreatectomy for pancreatic cancer: a systematic review and meta-analysis. Ann Surg 2011; 254:882-893.

31. Chua TC, Saxena A. Extended pancreaticoduodenectomy with vascular resection for pancreatic cancer: a systematic review. J Gastrointest Surg 2010; 14:1442-1452.

32. Zhou Y, Zhang Z, Liu Y, Li B, Xu D. Pancreatectomy combined with superior mesenteric vein-portal vein resection for pancreatic cancer: a meta-analysis. World J Surg 2012; 36:884-891.

33. Worni M, Castleberry AW, Clary BM, Gloor B, Carvalho E, Jacobs DO, Pietrobon R, Scarborough JE, White RR. Concomitant Vascular Reconstruction During Pancreatectomy for Malignant Disease: A Propensity Score-Adjusted, Population-Based Trend Analysis Involving 10 206 Patients. Arch Surg 2012;1-8.

34. Pedrazzoli S, DiCarlo V, Dionigi R, Mosca F, Pederzoli P, Pasquali C, Kloppel G, Dhaene K, Michelassi F. 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.

35. Yeo CJ, Cameron JL, Lillemoe KD, Sohn TA, Campbell KA, Sauter PK, Coleman J, Abrams RA, Hruban RH. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma, part 2: randomized controlled trial evaluating survival, morbidity, and mortality. Ann Surg 2002; 236:355-366.

36. Farnell MB, Pearson RK, Sarr MG, DiMagno EP, Burgart LJ, Dahl TR, Foster N, Sargent DJ. A prospective randomized trial comparing standard pancreatoduodenectomy with pancreatoduodenectomy with extended lymphadenectomy in resectable pancreatic head adenocarcinoma. Surgery 2005; 138:618-628.

37. Riall TS, Cameron JL, Lillemoe KD, Campbell KA, Sauter PK, Coleman J, Abrams RA, Laheru D, Hruban RH, Yeo CJ. 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.

38. Michalski CW, Kleeff J, Wente MN, Diener MK, Büchler MW, Friess H. Systematic review and meta-analysis of standard and extended lymphadenectomy in pancreaticoduodenectomy for pancreatic cancer. Br J Surg 2007; 94:265-273.

39. Iqbal N, Lovegrove RE, Tilney HS, Abraham AT, Bhattacharya S, Tekkis PP, Kocher HM. A comparison of pancreaticoduodenectomy with extended pancreaticoduodenectomy: a meta-analysis of 1909 patients. Eur J Surg Oncol 2009; 35:79-86.

40. Verbeke CS, Leitch D, Menon KV, McMahon MJ, Guillou PJ, Anthoney A. Redefining the R1 resection in pancreatic cancer. Br J Surg 2006; 93:1232-1237.

41. Esposito I, Kleeff J, Bergmann F, Reiser C, Herpel E, Friess H, Schirmacher P, Büchler MW. Most pancreatic cancer resections are R1 resections. Ann Surg Oncol 2008; 15:1651-1660.

42. Campbell F, Foulis AK, Verbeke CS. Dataset for the histopathologic reporting of carcinomas of the pancreas, ampulla of Vater and common bile duct. http://www.rcpath.org [May 2010]. 2010. Royal College of Pathologists.

43. Birkmeyer JD, Siewers AE, Finlayson EV, Stukel TA, Lucas FL, Batista I, Welch HG, Wennberg DE. Hospital volume and surgical mortality in the United States. N Engl J Med 2002; 346:1128-1137.

44. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. N Engl J Med 2003; 349:2117-2127.

45. Gooiker GA, van Gijn W, Wouters MW, Post PN, van de Velde CJ, Tollenaar RA. Systematic review and meta-analysis of the volume-outcome relationship in pancreatic surgery. Br J Surg 2011; 98:485-494.

46. Tang D, Zhang JQ, Wang DR. Long term results of pancreatectomy with portal-superior mesenteric vein resection for pancreatic carcinoma: a systematic review. Hepatogastroenterology 2011; 58:623-631.

47. Chauffert B, Mornex F, Bonnetain F, Rougier P, Mariette C, Bouche O, Bosset JF, Aparicio T, Mineur L, Azzedine A, Hammel P, Butel J, Stremsdoerfer N, Maingon P, Bedenne L. 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 FFCD/SFRO study. Ann Oncol 2008; 19:1592-1599.

48. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la FC, Bennouna J, Bachet JB, Khemissa-Akouz F, Pere-Verge D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011; 364:1817-1825.

49. Siriwardana HP, Siriwardena AK. Systematic review of outcome of synchronous portal-superior mesenteric vein resection during pancreatectomy for cancer. Br J Surg 2006; 93:662-673.

Table 1: Literature on extended pancreatectomy with a focus on additional organ resection in pancreatic cancer

First Author (Year)	**N** (all/ extended)	**Tumor**	**Procedure**	**Additional organ resection / specific issues in analysis**	**Perioperative morbidity / mortality** (extended vs. standard, when available)	**Median / 5-year survival** (extended vs. standard, when available)	**Conclusions / subgroup analysis / remarks**
Klempnauer 1996 [14]	189 / 75	Ductal pancreatic carcinoma	Any kind of pancreatectomy: PD N=131, subtotal PD n=7, DP n=24, TP n=27	In 75 patients extended resections: porto-mesenteric vein n=37, hepatic artery n=10, SMA n=7, stomach n=23, colon n=17, liver n=14, adrenal gland n=8, kidney n=5; Of those 21 with distant metastasis	Morbidity: Relaparotomy 32% vs. 19% Mortality: 13.3% vs. 6.1%	Median: 8.4 vs. 12.2 mo 5-Year: 13.3 vs. 13.8	Increased relaparotomy rate in extended resections; no significant difference in mortality (mortality increased with additional colectomies, but not with other organs); long-term prognosis not different (subgroup analysis: impaired after additional organ resections but not after vascular resection).
Sasson 2002 [15]	116 / 37	Adenocarcinoma of pancreas	Any kind of pancreatectomy; of extended resections: PD n=26, DP n=5, TP n=5, central n=1	In 37 patients extended resections: porto-mesenteric vein n=16, hepatic artery/celiac trunk n=9, mesocolon n=3, colon n=13, adrenal n=3, liver or stomach n=1)	Morbidity: 35% vs. 39%; In-hospital or 30d mortality: 2.7% vs. 1.7%	Median: 26 mo vs. 16 mo 5-year: 16% vs. 9.5%	Similar survival compared to standard resection; Operative time greater
Shoup 2003 [16]	57 / 22	Adenocarcinoma of body and tail	DP	In 22 patients extended resections: portal vein n=8, contiguous organ N=14	Morbidity: relaparotomy: 9% vs. 0%; Postoperative mortality: 0%	Disease-specific: median: 9 mo vs. 16 mo, 5-year: 22% vs. 8%	Similar long-term survival compared to standard resections; blood loss, blood transfused and hospital stay greater in extended resections
Adam 2004 [17]	301 / 41	Pancreatic or periampullary cancer n=103, chronic pancreatitis n=175, other malignant tumors n=9, other benign or indetermined lesions n=14	Pancreatic head resections	In 41 patients additional organ resection, of those 13 with malignant disease: spleen n=2, colon n=8, liver n=3, kidney n=2, stomach n=1	Morbidity: 65.9% vs. 36.9%; Mortality: n/a for extended resections	n/a for multivisceral resections	Extended resection as an independent risk factor for complications (multivariate analysis); In subgroup of patients with extended resection, colectomy as a significant risk factor for complications
Suzuki 2004 [18]	95 / 12	Pancreatic head and periampullary tumors; of extended resections: pancreatic/periampullary cancer n=10, other n=2	PD +/- right colectomy	In 12 patients extended resections: right hemicolectomy	Surgical morbidity: 50% vs. 44.6%; In-hospital mortality: 0%	Median: 14 mo vs. 12 mo for malignant tumors	No survival difference compared to patients with standard PD, operating time greater in extended resections

Muscari 2005 [19]	300 / 11	Pancreatic or periampullary cancer n=225, chronic pancreatitis n=30, benign tumors n=31, other n=14	PD	In 11 patients extended resections: colon n=2, hepatic metastasis n=2, small intestine n=1, porto-mesenteric vein n=4, hepatic artery/SMA n=2	Intraabdominal complications: 64% vs. 29% Mortality: 27% vs. 9%	n/a	Extended resection as a risk factor for intraabdominal complications and mortality in multivariate analysis
McKay 2008 [21]	27 / 15	Various, 3 patients with pancreatic adenocarcinoma	Any kind of multivisceral pancreatectomy or hepatectomy	In 15 patients multivisceral pancreatic resections: liver n=5, stomach n=7, colon n=10, small bowel n=7 kidney n=3, diaphragm n=1	Mortality: 13.3% for pancreatectomies; Morbidity: 80% for pancreatectomies	n/a for pancreatic malignancies	Very inhomogeneous patient cohort; incomplete data presentation
Kleeff 2007 [22]	302 / 109	Benign and malignant pancreatic tumors n=186, metastasis or extrapancreatic tumors n=70, chronic pancreatitis n=36, other n=10	DP	In 109 patients multivisceral resections: stomach n=53, colon n=41, kidney n=19, liver n=16, adrenal gland n=15, small intestine n=7, esophagus n=2	Overall and surgical morbidity: 42% and 34% vs. 32% and 23%; Mortality: 5.5% vs. 0%	n/a	Multivisceral resection as an independent risk factor for morbidity in multivariate analysis
Nikfarjam 2009 [23]	105 / 19	Various, malignant and benign. Of extended resections: pancreatic cancer n=7, duodenal cancer n=1, IPMN n=2, neuroendocrine n=1, GIST/ sarcoma/metastases n=7, others n=1	PD	In 19 patients extended resections: right colectomy n=12, right nephrectomy n=2, liver resection n=2, other n= 3	Morbidity: 68% vs. 58%; Operative mortality: 0%	n/a	No significant differences in complication rate; operating time and surgical ICU stay greater
Hartwig 2009 [24]	101 / 101	Primary pancreatic malignancies: ductal adenocarcinoma / undifferentiated n=71, malignant IPMN n=7, periampullary n=5, malignant endocrine n=10, other n=8	Any kind of pancreatectomy : PD n=21, DP n=60, TP n=20; PV/SMV resection not defined as multivisceral resection	All patients with multivisceral resections: colon n=38, stomach n=34, adrenal gland n=28, liver n=19, hepatic artery/celiac trunk n=17, kidney n=12, small intestine n=7; Additional porto-mesenteric vein resection in 20.8% of patients; Matched pair analysis with 202 standard pancreatic resections	Overall morbidity: 55.5% vs. 42.8%; Surgical morbidity: 36.6% vs. 25.3%; In-hospital and 30-d mortality: 6.9% and 3.0% vs. 3.5% and 1.5% (respectively)	Median: 19.8 mo vs. 23.1 mo; 3-year: 37.2% ; 5-year: n/a	Morbidity but not mortality increased in multivisceral resections, operative time, blood loss, relaparotomy rate, ICU and hospital stay greater in multivisceral resections; long operative time or resection of more than 2 addition organs as a risk factor for surgical morbidity; Long-term survival comparable to standard resections
Seeliger 2010 [25]	110 / 47	Malignant (65%) and benign (35%) disease; ductal adenocarcinoma n=24, neuroendocrine n=18, extrapancreatic malignancy or pancreatic metastasis n=31, chronic pancreatitis n=7; benign tumors and others n=30	DP	47 patients with additional organ resection: stomach n=28, colon n=24, adrenal gland n=19, other n=18	Incomplete data on extended resections	n/a	Multivisceral resection not a risk factor for morbidity in uni- and multivariate analysis

Burdelski 2011 [26]	55 / 55	Ductal pancreatic cancer	Any kind of pancreatectomy : classic PD n=30, subtotal PD n=14, TP n=11 , PV resection not defined as additional organ resection	All patients with multivisceral resections: stomach n=32, liver n=24, colon n=22, kidney n=17, diaphragm N=11, small intestine n=5; Comparison (not matched) with 303 standard PD in pancreatic adenocarcinoma and 154 palliative bypass patients with locally unresectable tumors	Major complications: 69% vs. 37%; In-hospital mortality: 7% vs. 4%	Median: 16 mo vs. 18 mo; 5-year: n/a	Morbidity but not mortality increased in multivisceral resections; Increased need for intraoperative transfusions; Increased morbidity with kidney resections and with intraoperative transfusion; Survival of multivisceral resections inferior to standard resections, but significantly better than in palliative bypass group
Mitchem 2012 [27]	47 / 24	Adenocarcinoma of the body and tail of the pancreas	RAMPS; adrenalectomy not defined as additional organ resection	In 24 patients extended resections: stomach n=11, kidney n=4, omentum/mesocolon n=4, colon n=4, diaphragm n=3, porto-mesenteric vein n=5, small bowel or duodenum n=2	In-hospital or 30d mortality: 0%	Median: 25.9 mo; 5-year: 35.5% (all patients)	No comparison of patients with additional organ resection vs. no additional organ resection

Because of the large amount of studies that focus on extended pancreatectomy with additional vascular resection, those studies are not included in table 1 (see list of systematic reviews in table 2)

PD: Pancreaticoduodenectomy, DP: distal pancreatectomy, TP: total pancreatoduodenectomy, RAMPS: radical antegrade modular pancreatosplenectomy

PV: portal vein, SMV: superior mesenteric vein, SMA: superior mesenteric artery

n/a: not available or reported

Periampullary tumors include tumors of the ampulla, distal bile duct, and duodenum

Studies with cohorts of less than 10 patients are not included. Patients reported in Strasberg et al. (2007) [20] are included in Mitchem et al. (2012) [27]

Table 2: Systematic reviews on extended pancreatectomy with a focus on vascular resections in pancreatic cancer

First Author (Year)	**N** (vascular resection)	**Procedure**	**Perioperative morbidity / mortality** (vascular vs. standard resection, when available)	**Median / 1-, 3-, and 5-year survival** (extended vs. standard, when available)	**Authors' conclusions**
Siriwardana 2006 [49]	1,646	Pancreatectomy with porto-mesenteric vein resection	Morbidity: 42% Mortality: 5.9%	Median survival: 13 mo; 1-, 3-, and 5-year survival: 50%, 16%, and 7% (respectively)	The high rate of nodal metastases and low 5-year survival rates suggest that by the time of tumour involvement of the portal vein cure is unlikely, even with radical resection
Chua 2010 [31]	1,458	Extended pancreatoduodenectomy with vascular resection	Mortality: 4%	*Vein resection:* Median survival: 13 mo; 1-, 3-, and 5-year survival: 56%, 18%, and 12% (respectively) *Vein and artery resection:* Median survival: 18 mo; 1-, 3-, and 5-year survival: 65%, 13%, and 0% (respectively)	Acceptable morbidity, mortality, and survival outcome after undertaking extended pancreaticoduodenectomy with vascular resection for pancreatic cancer with venous involvement and/or limited arterial involvement
Tang 2011 [46]	1,983	Pancreatectomy with porto-mesenteric vein resection	Morbidity: 33% Mortality: 3.5%	Median survival: 15 mo; 1-, 3-, and 5-year survival: 57%, 17%, and 12% (respectively)	Pancreatectomy combined with portal vein/superior mesenteric resection is a feasible surgical procedure with a survival benefit for pancreatic carcinoma
Mollberg 2011 [30]	366	Pancreatectomy with arterial resection	Mortality: OR, 5.04; 95% CI, 2.69-9.45; P < 0.0001	1-year: OR, 0.49; 95% CI, 0.31-0.78; P=0.002; 3-year: OR, 0.39; 95% CI, 0.17-0.86; P=0.02	Significantly increased risk for perioperative mortality and lesser survival compared to patients without arterial resection and compared to patients with venous resections
Zhou 2012 [32]	661	Pancreatectomy with porto-mesenteric vein resection	Morbidity: OR, 0.95; 95% CI, 0.74-1.21; P = 0.67; Mortality: OR, 1.19; 95% CI, 0.73-1.96; P = 0.48	1-, 3-, and 5-year survival: 61.3%, 19.4%, and 12.3% (respectively) 1-year: OR, 0.92; 95% CI, 0.66-1.28; P=0.062 3-year: OR, 0.71; 95% CI, 0.47-1.06; P=0.062 5-year: OR, 0.57; 95% CI, 0.32-1.02; P=0.06;	Perioperative outcome and long-term survival comparable to that of standard resections

OR: Odds ratio; CI: confidence interval