

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

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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 that 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 with standard resections but appears to be better compared with 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.

Conclusion. 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 that are crucial for comparison of results of future trials across different practices and countries, in particular for those using neoadjuvant therapy. (*Surgery* 2014;156:1-14.)

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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 United States, with overall 5-year survival rates of 5–6%.^{1,2} Complete operative 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 Because of 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 that 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 performed on February 28, 2013.

All relevant literature and a summary of the extracted data were reviewed by the study group (W.H., C.M.V., A.F., C.J.Y., J.P.N., M.W.B.) of the 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 23–24, 2013 and attended by members of the ISGPS, the first draft was discussed. A final consensus statement on the definition and role of extended pancreatectomy in pancreatic surgery was formulated and agreed by all cosignatories using the Grading of Recommendations Assessment, Development, and Evaluation 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 I 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. In several studies authors have assessed the role of additional colonic resection, either by including only patients with pancreatectomy and additional colectomy¹⁸ 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 nonresectable disease and is staged as American Joint Committee on Cancer/Union for International Cancer Control stage III (7th edition).^{28,29} Several studies and one meta-analysis³⁰ 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 portomesenteric vein resection negatively affects short- and long-term prognosis of pancreatectomies is inhomogenous,³¹⁻³⁵ some studies excluded portomesenteric 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 et al,^{14,24,26} 28–38% 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^{20,27} included the left adrenal gland in their posterior, radical, antegrade modular pancreatosplenectomy procedure to achieve R0 resection regardless of whether the gland is involved grossly with tumor infiltration. Although 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. On the basis of four randomized controlled trials³⁶⁻³⁹ and two meta-analyses,^{40,41} no survival advantage has been demonstrated for any extended lymphadenectomy. Currently, a form of standard radical lymphadenectomy is recommended by the ISGPS in pancreatectomy,⁴² although extended lymphadenectomy may be warranted in patients with obviously enlarged intra-aortic or para-aortic 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. On the basis of 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;

Table I. Literature on extended pancreatectomy with a focus on additional organ resection in pancreatic cancer

<i>First author (year)</i>	<i>N (all/extended)</i>	<i>Tumor</i>	<i>Procedure</i>	<i>Additional organ resection/specific issues in analysis</i>	<i>Perioperative morbidity/mortality (extended vs standard, when available)</i>	<i>Median/5-year survival (extended vs standard, when available)</i>	<i>Conclusions/subgroup analysis/remarks</i>
Klempnauer et al, 1996 ¹⁴	189/75	Ductal pancreatic carcinoma	Any kind of pancreatectomy: PD <i>N</i> = 131, subtotal PD <i>n</i> = 7, DP <i>n</i> = 24, TP <i>n</i> = 27	In 75 patients extended resections: portomesenteric vein <i>n</i> = 37, hepatic artery <i>n</i> = 10, SMA <i>n</i> = 7, stomach <i>n</i> = 23, colon <i>n</i> = 17, liver <i>n</i> = 14, adrenal gland <i>n</i> = 8, kidney <i>n</i> = 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 et al, 2002 ¹⁵	116/37	Adenocarcinoma of pancreas	Any kind of pancreatectomy; of extended resections: PD <i>n</i> = 26, DP <i>n</i> = 5, TP <i>n</i> = 5, central <i>n</i> = 1	In 37 patients extended resections: portomesenteric vein <i>n</i> = 16, hepatic artery/celiac trunk <i>n</i> = 9, mesocolon <i>n</i> = 3, colon <i>n</i> = 13, adrenal <i>n</i> = 3, liver or stomach <i>n</i> = 1	Morbidity: 35% vs 39%; In-hospital or 30-d mortality: 2.7% vs 1.7%	Median: 26 mo vs 16 mo 5-year: 16% vs 9.5%	Similar survival compared with standard resection; Operative time greater
Shoup et al, 2003 ¹⁶	57/22	Adenocarcinoma of body and tail	DP	In 22 patients extended resections: portal vein <i>n</i> = 8, contiguous organ <i>n</i> = 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 with standard resections; blood loss, blood transfused, and hospital stay greater in extended resections

(continued)

Table I. (continued)

<i>First author (year)</i>	<i>N (all/extended)</i>	<i>Tumor</i>	<i>Procedure</i>	<i>Additional organ resection/specific issues in analysis</i>	<i>Perioperative morbidity/mortality (extended vs standard, when available)</i>	<i>Median/5-year survival (extended vs standard, when available)</i>	<i>Conclusions/subgroup analysis/remarks</i>
Adam et al, 2004 ¹⁷	301/41	Pancreatic or periampullary cancer <i>n</i> = 103, chronic pancreatitis <i>n</i> = 175, other malignant tumors <i>n</i> = 9, other benign or indetermined lesions <i>n</i> = 14	Pancreatic head resections	In 41 patients additional organ resection, of those 13 with malignant disease: spleen <i>n</i> = 2, colon <i>n</i> = 8, liver <i>n</i> = 3, kidney <i>n</i> = 2, stomach <i>n</i> = 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 et al, 2004 ¹⁸	95/12	Pancreatic head and periampullary tumors; of extended resections: pancreatic/periampullary cancer <i>n</i> = 10, other <i>n</i> = 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 with patients with standard PD, operating time greater in extended resections
Muscari et al, 2005 ¹⁹	300/11	Pancreatic or periampullary cancer <i>n</i> = 225, chronic pancreatitis <i>n</i> = 30, benign tumors <i>n</i> = 31, other <i>n</i> = 14	PD	In 11 patients extended resections: colon <i>n</i> = 2, hepatic metastasis <i>n</i> = 2, small intestine <i>n</i> = 1, portomesenteric vein <i>n</i> = 4, hepatic artery/SMA <i>n</i> = 2	Intra-abdominal complications: 64% vs 29% Mortality: 27% vs 9%	n/a	Extended resection as a risk factor for intra-abdominal 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 <i>n</i> = 5, stomach <i>n</i> = 7, colon <i>n</i> = 10, small bowel <i>n</i> = 7 kidney <i>n</i> = 3, diaphragm <i>n</i> = 1	Mortality: 13.3% for pancreatectomies; Morbidity: 80% for pancreatectomies	n/a for pancreatic malignancies	Very inhomogeneous patient cohort; incomplete data presentation

(continued)

Table I. (continued)

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
Kleeff et al, 2007 ²²	302/109	Benign and malignant pancreatic tumors <i>n</i> = 186, metastasis or extrapancreatic tumors <i>n</i> = 70, chronic pancreatitis <i>n</i> = 36, other <i>n</i> = 10	DP	In 109 patients multivisceral resections: stomach <i>n</i> = 53, colon <i>n</i> = 41, kidney <i>n</i> = 19, liver <i>n</i> = 16, adrenal gland <i>n</i> = 15, small intestine <i>n</i> = 7, esophagus <i>n</i> = 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 <i>n</i> = 7, duodenal cancer <i>n</i> = 1, IPMN <i>n</i> = 2, neuroendocrine <i>n</i> = 1, GIST/sarcoma/metastases <i>n</i> = 7, others <i>n</i> = 1	PD	In 19 patients extended resections: right colectomy <i>n</i> = 12, right nephrectomy <i>n</i> = 2, liver resection <i>n</i> = 2, other <i>n</i> = 3	Morbidity: 68% vs 58%; Operative mortality: 0%	n/a	No significant differences in complication rate; operating time and surgical ICU stay greater
Hartwig et al, 2009 ²⁴	101/101	Primary pancreatic malignancies: ductal adenocarcinoma / undifferentiated <i>n</i> = 71, malignant IPMN <i>n</i> = 7, periampullary <i>n</i> = 5, malignant endocrine <i>n</i> = 10, other <i>n</i> = 8	Any kind of pancreatotomy: PD <i>n</i> = 21, DP <i>n</i> = 60, TP <i>n</i> = 20; PV/SMV resection not defined as multivisceral resection	All patients with multivisceral resections: colon <i>n</i> = 38, stomach <i>n</i> = 34, adrenal gland <i>n</i> = 28, liver <i>n</i> = 19, hepatic artery/celiac trunk <i>n</i> = 17, kidney <i>n</i> = 12, small intestine <i>n</i> = 7; Additional portomesenteric 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% (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 with standard resections

(continued)

Table I. (continued)

<i>First author (year)</i>	<i>N (all/extended)</i>	<i>Tumor</i>	<i>Procedure</i>	<i>Additional organ resection/specific issues in analysis</i>	<i>Perioperative morbidity/mortality (extended vs standard, when available)</i>	<i>Median/5-year survival (extended vs standard, when available)</i>	<i>Conclusions/subgroup analysis/remarks</i>
Seeliger et al, 2010 ²⁵	110/47	Malignant (65%) and benign (35%) disease; ductal adenocarcinoma <i>n</i> = 24, neuroendocrine <i>n</i> = 18, extrapancreatic malignancy or pancreatic metastasis <i>n</i> = 31, chronic pancreatitis <i>n</i> = 7; benign tumors and others <i>n</i> = 30	DP	47 patients with additional organ resection: stomach <i>n</i> = 28, colon <i>n</i> = 24, adrenal gland <i>n</i> = 19, other <i>n</i> = 18	Incomplete data on extended resections	n/a	Multivisceral resection not a risk factor for morbidity in uni- and multivariate analysis
Burdelski et al, 2011 ²⁶	55/55	Ductal pancreatic cancer	Any kind of pancreatectomy: classic PD <i>n</i> = 30, subtotal PD <i>n</i> = 14, TP <i>n</i> = 11, PV resection not defined as additional organ resection	All patients with multivisceral resections: stomach <i>n</i> = 32, liver <i>n</i> = 24, colon <i>n</i> = 22, kidney <i>n</i> = 17, diaphragm <i>n</i> = 11, small intestine <i>n</i> = 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

(continued)

Table I. (continued)

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
Mitchem et al, 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 pancreatotomy with additional vascular resection, those studies are not included in Table II (see list of systematic reviews in Table II). Periapillary tumors include tumors of the ampulla, distal bile duct, and duodenum. Studies with cohorts of fewer than 10 patients are not included. Patients reported in Strasberg et al²⁰ are included in Mitchem et al.²⁷ DP: Distal pancreatotomy, ICU: intensive care unit; n/a , not available or reported; PD, pancreaticoduodenectomy; PV, portal vein; RAMPS, radical antegrade modular pancreatosplenectomy; SMA, superior mesenteric artery; SMV, superior mesenteric vein; TP, total pancreatoduodenectomy.

- lymphadenectomy;
- sometimes pylorus and/or antrum of stomach; and
- sometimes elements of the transverse mesocolon exclusive of relevant vasculature (eg, limited soft tissue contiguous to the tumor but not including the colon itself).

Standard distal pancreatotomy:

- body and/or tail of the pancreas;
- spleen, including splenic vessels;
- lymphadenectomy;
- sometimes fascia of Gerota; and
- sometimes elements of the transverse mesocolon exclusive of relevant vasculature (eg, limited soft tissue contiguous to the tumor, but not including the colon itself).

Standard total pancreatotomy:

- head, neck, body, and tail of the pancreas;
- duodenum and first segment of jejunum;
- common bile duct and gallbladder;
- spleen including splenic vessels;
- lymphadenectomy;
- sometimes pylorus and/or antrum of stomach;
- sometimes fascia of Gerota; and
- sometimes elements of the transverse mesocolon exclusive of relevant vasculature (eg, limited soft tissue contiguous to the tumor but not including the colon itself).

Extended pancreatoduodenectomy: Standard pancreatoduodenectomy as defined previously 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 segment of jejunum;
- portal, superior mesenteric, and/or inferior mesenteric vein;
- hepatic artery, celiac trunk, and/or superior mesenteric artery;
- inferior vena cava;
- right adrenal gland;
- right kidney and/or its vasculature;
- liver; and
- diaphragmatic crura

Extended distal pancreatotomy: Standard distal pancreatotomy as defined previously 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);

Table II. Systematic reviews on extended pancreatectomy with a focus on vascular resections in pancreatic cancer

<i>First author (year)</i>	<i>N (vascular resection)</i>	<i>Procedure</i>	<i>Perioperative morbidity/mortality (vascular vs standard resection, when available)</i>	<i>Median/1-, 3-, and 5-year survival (extended vs standard, when available)</i>	<i>Authors' conclusions</i>
Siriwardana and Siriwardana, 2006 ³¹	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 and Saxena, 2010 ³²	1,458	Extended pancreatoduodenectomy with vascular resection	Mortality: 4%	<i>Vein resection:</i> Median survival: 13 mo; 1-, 3-, and 5-year survival: 56%, 18%, and 12% (respectively) <i>Vein and artery resection:</i> Median survival: 18 mo; 1-, 3-, and 5-year survival: 65%, 13%, and 0% (respectively)	Acceptable morbidity, mortality, and survival outcome after undertaking extended pancreatoduodenectomy with vascular resection for pancreatic cancer with venous involvement and/or limited arterial involvement
Tang et al, 2011 ³³	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 et al, 2011 ³⁰	366	Pancreatectomy with arterial resection	Mortality: OR, 5.04; 95% CI, 2.69-9.45; <i>P</i> < .0001	1-year: OR, 0.49; 95% CI, 0.31-0.78; <i>P</i> = .002; 3-year: OR, 0.39; 95% CI 0.17-0.86; <i>P</i> = .02	Significantly increased risk for perioperative mortality and lesser survival compared with patients without arterial resection and compared with patients with venous resections
Zhou et al, 2012 ³⁴	661	Pancreatectomy with portomesenteric vein resection	Morbidity: OR, 0.95; 95% CI, 0.74-1.21; <i>P</i> = .67; Mortality: OR, 1.19; 95% CI, 0.73-1.96; <i>P</i> = .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; <i>P</i> = .062 3-year: OR, 0.71; 95% CI, 0.47-1.06; <i>P</i> = .062 5-year: OR, 0.57; 95% CI, 0.32-1.02; <i>P</i> = .06;	Perioperative outcome and long-term survival comparable with that of standard resections

CI, Confidence interval; *OR*, odds ratio.

- small bowel;
- portal, superior mesenteric, and/or inferior mesenteric vein;
- 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; and
- liver

Extended total pancreatectomy: Standard total pancreatectomy as defined previously 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 segment of jejunum;
- portal, superior mesenteric, and/or inferior mesenteric vein;
- 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; and
- liver.

For all types of extended pancreatectomy: To facilitate the comparability of studies, a partial pancreatectomy that 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 (eg, 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 (eg, 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 42–81%, in 9–39%, and in 8–14% of patients, respectively,^{14,15,24,26,27} Given the various definitions of a R0 and R1 resection margin (eg, R1 being tumor cells within 1 mm of the margin versus tumor cells at the margin),⁴³⁻⁴⁵ 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.⁴⁶⁻⁴⁸ 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 in which investigators compare 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. In several studies, however, authors 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 intensive care unit and hospital stays (Table I).^{15,16,18,23,24,26} 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 one¹⁹ study. Importantly, of all of these, only the study by Hartwig et al²⁴ used a group of patients with standard resection for comparison that was matched for the type of pancreatic resection, age, sex, and histology.

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,^{32-34,47} whereas a recent large, population-based analysis on 10,206 patients identified increased perioperative morbidity and mortality rates (Table II).³⁵ 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 (Table II).³⁰ 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 nephrectomy²⁶ 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} whereas 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 duration 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 with 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 with that of locally advanced disease treated nonoperatively. Data from a randomized, controlled, multicenter trial on chemo- or radiochemotherapy suggest a median survival between 8.6 and 13 months in locally advanced, “unresectable” ductal adenocarcinoma, depending on the type of therapy.⁴⁹ The best survival data from randomized trials on palliative chemotherapy of metastatic pancreatic adenocarcinoma have been described with FOLFIRINOX (ie, FOL [leucovorin calcium] F [fluorouracil], IRIN [irinotecan hydrochloride], and OX [oxaliplatin]), with a median overall survival of 11.1 months.⁵⁰ Importantly, 5-year survival was not reported in these two palliative trials but supposedly was very low according to Kaplan-Meier curves that 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 I. 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 one²⁶ of these studies reported survival rates of extended resections similar to that of standard resections.^{14-16,18,24} Although not truly comparable with data from randomized trials with palliative therapy, survival of patients with extended pancreatectomy seems superior. However, 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 combination 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.
- 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 an evidence level of 3 to 4. Available data come exclusively from retrospective, nonrandomized, 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 portomesenteric³¹⁻³⁴ or arterial resections³⁰ 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 with 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

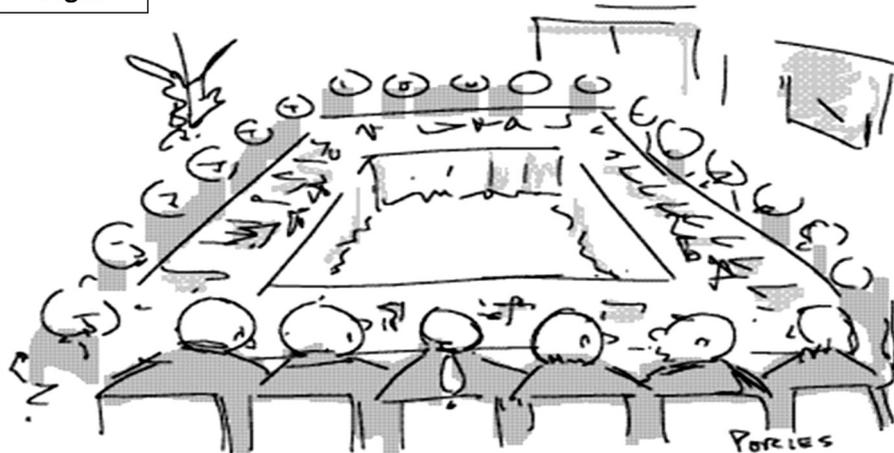
include not only morbidity and mortality but also quality of life.

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IV League

“Ok, here’s the plan. Talk fast, very softly and go on a long time. They’ll all vote for it. Works every time.”