

Borderline resectable pancreatic cancer: A consensus statement by the International Study Group of Pancreatic Surgery (ISGPS)

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Background. This position statement was developed to expedite a consensus on definition and treatment for borderline resectable pancreatic ductal adenocarcinoma (BRPC) that would have worldwide acceptability.

Methods. An international panel of pancreatic surgeons from well-established, high-volume centers collaborated on a literature review and development of consensus on issues related to borderline resectable pancreatic cancer.

Results. The International Study Group of Pancreatic Surgery (ISGPS) supports the National Comprehensive Cancer Network criteria for the definition of BRPC. Current evidence supports operative exploration and resection in the case of involvement of the mesentericoportal venous axis; in addition, a new classification of extrahepatic mesentericoportal venous resections is proposed by the ISGPS. Suspicion of arterial involvement should lead to exploration to confirm the imaging-based findings. Formal arterial resections are not recommended; however, in exceptional circumstances, individual therapeutic approaches may be evaluated under experimental protocols. The ISGPS endorses the recommendations for specimen examination and the definition of an R1 resection (tumor within 1 mm from the margin) used by the British Royal College of Pathologists. Standard preoperative diagnostics for BRPC may include: (1) serum levels of CA19-9, because CA19-9 levels predict survival in large retrospective series; and also (2) the modified Glasgow Prognostic Score and the neutrophil/lymphocyte ratio because of the prognostic relevance of the systemic inflammatory response. Various regimens of neoadjuvant therapy are recommended only in the setting of prospective trials at high-volume centers.

Conclusion. Current evidence justifies portomesenteric venous resection in patients with BRPC. Basic definitions were identified, that are currently lacking but that are needed to obtain further evidence and improvement for this important patient subgroup. A consensus for each topic is given. (Surgery 2014;155:977-88.)

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THE 2012 EUROPEAN HEALTH REPORT has again identified pancreatic cancer as a leading cause of cancer-related death within the region (>100,000 deaths). Furthermore, pancreatic cancer is one of the few types of cancer with an increasing mortality (8.1% in 1981 vs 9.7% in 2009), in contrast to overall cancer mortality, which has decreased by 15% since the mid-1990s.¹ The Cancer Statistics Review (2002–2008) from the US Surveillance Epidemiology and End Results showed that 53% of all patients with pancreatic cancer had concomitant distant metastases at the time of diagnosis²; only 15–20% of the remaining patients were eligible for potentially curative resection, and up to 25% were staged as having locally advanced disease and thus were potentially “inoperable” because of involvement of surrounding major vessels.

In recent decades, this exceptionally low rate of “resectability” has increased because of technical advances in operative techniques and the establishment of experienced high-volume centers. Two early successful pancreatoduodenectomies with portal vein resection reported by Asada et al³ in 1963. The next evolution of extended resections, the en bloc resection including the portal vein and/or combined arterial resection, was described by Fortner in 1973,⁴ but enthusiasm for this “regional resection” decreased rapidly because the morbidity and mortality rates were prohibitive. In the following 40 years, operative techniques have improved and evolved and the term “borderline resectable pancreatic cancer” (BRPC) is now used commonly to describe pancreatic cancer involving the mesentericoportal or arterial axis, that is, an intermediate stage between straightforwardly resectable and technically unresectable disease. This subgroup of patients, however, is not yet considered in the latest pancreatic cancer staging system by the American Joint

Committee on Cancer (AJCC) because any venous occlusion (of the superior mesenteric vein [SMV], portal vein [PV], or their confluence) or arterial encasement (of the celiac axis, superior mesenteric artery [SMA], or common hepatic artery) is defined currently as local unresectability.⁵ Patients with BRPC may thus have a high risk of being classified falsely as having unresectable disease. Moreover, the concept of BRPC is currently not well-defined, and there is broad variation internationally in how it is applied, even though BRPC serves as the basis of the decision to either attempt downstaging by neoadjuvant therapy or to proceed directly to operative exploration for potential resection.

The current absence of adequate staging tools that can differentiate accurately between non-neoplastic inflammatory “infiltration” and true malignant infiltration leads to nonvalidated, “personalized” treatment regimens. Our position statement by the International Study Group for Pancreatic Surgery (ISGPS) is intended to expedite an internationally agreed definition and treatment consensus for this subgroup of patients with pancreatic ductal adenocarcinoma and to allow for the recognition of patients with BRPC to be offered the option of a curative attempt at resection for suitable patients with an expected favorable outcome.

The ISGPS believes that advances in treatment, especially for patients with BRPC, require progress on the following issues:

1. Which objective criteria should be used to preoperatively identify patients with borderline resectable pancreatic cancer?
2. Is there enough evidence for operative exploration and resection in the presence of mesenteric-portal axis or arterial involvement?

3. Is there enough evidence for neoadjuvant treatment regimes in this subgroup of patients?
4. How should the pathologic specimen be examined, and which definition of tumor-free resection margins should be used?
5. Should the site of residual tumor be reported and should the depth of vessel invasion be assessed if present?
6. Which prognostic markers should be considered regarding patient selection?

These areas are crucial for improving patient selection and treatment pathways in BRPC. To this end, major publications and meta-analyses focusing on right-sided pancreatic resections with mesentericoportal and arterial resections are reviewed. Limitations of the data arising from non-uniformity of definitions are discussed. Each issue is followed by a consensus statement from the ISGPS for each query.

METHODS

A computerized search of the PubMed and Embase databases was done in February 2013, using the following terms: “pancreatic cancer,” “borderline resectable,” “extended resection,” “superior mesenteric vein,” “portal vein,” “celiac axis,” “superior mesenteric artery,” “common hepatic artery,” “irresectability,” “morbidity,” “mortality,” and “survival.” All levels of evidence were included and rated, according to the evidence level of individual studies defined by the recommendations of the Centre for Evidence-Based Medicine, Oxford, UK (<http://www.cebm.net/>), in descending order: 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. Only studies published in English were included. Case studies were excluded. References of the included articles were checked to ensure no relevant studies had been missed.

All relevant literature and a summary of the extracted data were reviewed by the ISGPS study subgroup (M.B., F.G.U., Y.V., M.A., A.A.S., C.I., M.M., and J.R.I.), who then provided a first draft of the consensus definitions and statement. This first draft was discussed by members of the ISGPS at a Consensus Meeting held in Garda/Verona, Italy, on April 23–24, 2013. A final consensus statement on BRPC was formulated and agreed by all cosignatories, following the Grading of Recommendations Assessment, Development, and Evaluation (ie, GRADE) guidelines.⁶

RESULTS AND DISCUSSION

Which patients have borderline resectable disease? Several study groups have proposed a

preoperative classification to identify patients with BRPC. Their goal was to optimize perioperative treatment and to minimize the risk of falsely categorizing a tumor as locally advanced.

The ISGPS suggests that preoperative evaluation of resectability be based on computed tomography (CT). The use of a pancreatic protocol is mandatory to assess clinical resectability. Such a protocol should achieve an optimal balance between visualization/resolution of normal pancreatic and malignant parenchyma as well as of liver parenchyma and arterial and venous vessel enhancement/visibility and is mandatory to assess the attributes of surgical resectability.⁷⁻¹⁰

The most well-established, CT-based classification was developed at the M. D. Anderson Cancer Center (MDACC) and uses key parameters based on preoperative, multidetector CT imaging.¹¹ This classification has reached broad acceptance within the United States. It was confirmed at the consensus conference of the American Hepato-Pancreato-Biliary Association, the Society of Surgical Oncology, and the Society of the Alimentary Tract in 2009. Thereafter, this classification was adopted by the National Comprehensive Cancer Network (NCCN) in their current guidelines.¹²⁻¹⁵ According to the NCCN guidelines, given absence of distant metastases, tumors with borderline resectability include the following (see also [Table 1](#)):

- CT findings of venous distortion of the SMV/portal venous axis even including short-segment venous occlusion with proximal and distal sufficient vessel length allowing safe reconstruction;
- encasement of the gastroduodenal artery up to the hepatic artery, with either short-segment encasement or direct abutment of the hepatic artery without extension to the celiac axis; and
- tumor abutment of the SMA but with no greater than 180° of the vessel wall circumference.

Whereas 180° encasement of the gastroduodenal artery is still considered borderline resectable, the encasement of the SMA must be no greater than 180° for borderline resectability, regardless of whether the tumor is in the head, body, or tail of the pancreas. Regarding the celiac axis and tumor location, a tumor is considered to be unresectable if there is any celiac abutment from a tumor in the pancreatic head and also unresectable if there is celiac encasement of greater than 180° from a tumor in the body or tail. The ISGPS supports these imaging-based criteria of the NCCN for borderline resectability.

Table I. NCCN guidelines, version 1.2013, defining resectability status

<i>Localized and resectable</i>	<i>Borderline resectable</i>	<i>Unresectable*</i>
No distant metastasis	No distant metastasis	Distant metastasis
No radiographic evidence of SMV or PV distortion	Venous involvement of the SMV or PV with distortion or narrowing of the vein or occlusion of the vein with suitable vessel proximal and distal, allowing for safe resection and replacement.	Greater than 180° SMA encasement, any celiac abutment, IVC
Clear fat planes around CA, HA, and SMA	GA encasement up to the hepatic artery with either short segment encasement or direct abutment of the HA without extension to the CA	Unreconstructible SMV/portal occlusion
	Tumor abutment of the SMA not to exceed 180° of the circumference of the vessel wall.	Aortic invasion or encasement

*Criteria are given only for carcinomas of the head.

Adopted from: NCCN guidelines, version 1.2013, pancreatic adenocarcinoma.

CA, Celiac axis; GA, gastroduodenal artery; HA, hepatic artery; IVC, inferior vena cava; NCCN, National Comprehensive Cancer Network; PV, portal vein; SMA, superior mesenteric artery; SMV, superior mesenteric vein.

Consensus statement.

- Criteria for borderline resectability should be applied using a specialized pancreatic protocol CT performed in the previous 4 weeks that includes all of the abdomen and pelvis. Multidetector CT with high-resolution, multiplanar reconstructions facilitates accurate stratification (strong recommendation).
- All cases should be discussed and managed by a multidisciplinary team or board in high-volume centers (strong recommendation).
- The ISGPS supports the imaging-based NCCN criteria for borderline resectability in the case of venous mesentericoportal axis involvement (including encasement of the SMV/PV confluence and even short-segment occlusions) and arterial involvement (strong recommendation).

Is there an indication for operative exploration and resection in the presence of mesentericoportal axis involvement?

One of the largest systematic reviews on this topic published by Siriwardana et al¹⁶ in 2006 included 1646 patients from 52 studies with portal vein and/or superior mesenteric vein resections because of pancreatic cancer. Median postoperative morbidity was 42%, and mortality was 5.9%. Survival analyses indicated that portal vein resections did not improve survival rates over nonresective treatments. Reservations, however, were raised about this large study relating to the duration of the period analyzed from 1966 to 2005 and the lack of uniformity in the study cohorts. Moreover by 2006, results contradicting the findings of Siriwardana and colleagues had been published by high-volume centers in Europe, Japan, and the United States; morbidity, mortality,

and disease-free and overall survival were reported to be no different from those of patients who underwent standard resection and were better than in patients without operative treatment because of venous involvement.¹⁷⁻²¹

Zhou et al²² published the most recent meta-analysis in 2012, involving 19 studies (from 1994 to 2010) of pancreatectomies for pancreatic cancer, and including 661 patients with and 2,247 patients without portomesenteric venous resections. In contrast to the study by Siriwardana et al, Zhou and colleagues found no difference in overall survival between the cohorts with and without vascular resections, and a 5-year survival rate of 12.3% in the latter group. These findings are in line with more recent study results from high-volume, single center reviews, and consensus statements published by experts around the world.^{12-14,23-28}

On the basis of these data, the limiting factor for resectability in the case of venous involvement is, therefore, the possibility of venous reconstruction. Venous resections range from partial venous excisions with direct suture closure (venorrhaphy) to segmental resections with vein-vein anastomoses or interposed venous conduits. To date, the type of venous resection has not been included routinely in the analyses of postoperative morbidity and mortality; The ISGPS suggests that such a more specific categorization of the types of venous reconstruction should be incorporated in analyses for more detailed and evidence-based evaluation in patients classified as having borderline resectable tumors because of venous involvement.

The ISGPS does, however, acknowledge that there may be a possibility of publication bias,

with underreporting of rates for major morbidity. Some studies do question the current leading opinion that portomesenteric involvement is not a contraindication for resection. Ouaiissi et al²⁹ indicate that the procedure is safe but does not improve either patient survival or “cure rate” as shown by 10-year disease-free survival (pancreatoduodenectomy, 0% in groups with vascular resection versus 20% in group without vascular resection). In line with this, the findings of Muller et al³⁰ suggested that vascular resections are not associated with a favorable long-term survival because of frequent distant metastases and local recurrence. Despite long-term observations, the results of postoperative morbidity are still debated. In contrast to the results of published, single-center studies and associated meta-analyses, in 10,206 patients from a US inpatient administrative database (Nationwide Inpatient Sample) who underwent pancreatectomy for malignant disease, analysis revealed an increase in intraoperative and postoperative morbidity but no increase in operative mortality in patients undergoing concomitant vascular resections.³¹ Apart from the limitations of this study using an administrative database where outcomes are based on hospital charges, there were other limitations in that nearly 10% of the 412 vascular resections analyzed were arterial resections, which might have caused an increased overall morbidity rate. In addition, the lack of significant difference with regard to the operative re-intervention rate may imply equal rates of major complications.

Neoadjuvant treatment in patients with BRPC continues to be debated. A recently published study based on a multi-institutional database reviewed a total of 492 patients, including 70 (14%) with venous resection and 422 (86%) without venous resection.²⁸ None of these patients received neoadjuvant therapy. No difference was found in survival after an R0 resection, nor was vein involvement shown to be a prognostic marker for survival. In consequence, the authors questioned the indication for neoadjuvant treatment in the presence of resectable/reconstructable assumed major visceral venous involvement.²⁸ In line with these results, the ISGPS does not support neoadjuvant therapy regimes in BRPC patients with isolated venous involvement provided, if technical options of resections are possible.

Consensus statement.

- On the basis of the currently available evidence suggesting similar survival rates to those reported for patients undergoing a standard resection, there is clear

evidence supporting straightforward operative exploration and resection in the presence of reconstructable mesentericoportal axis involvement (strong recommendation).

- There is currently no evidence for neoadjuvant treatment protocols in BRPC patients with isolated venous involvement, provided technical options of reconstruction are given (strong recommendation).
- After intraoperative evaluation of tumor extent, venous resection is indicated if complete tumor excision (R0) is possible, although this may lead to greater overall rates of intraoperative and postoperative morbidity rates (strong recommendation).
- The type of venous resections performed should be reported (see below) to help with more detailed, evidence-based future recommendations. Surgical misadventures that lead to vascular resections should be documented and labeled as such (strong recommendation).
 - Proposed ISGPS classification of venous resections:
 - Type 1: partial venous excision with direct closure (venorrhaphy) by suture closure;
 - Type 2: partial venous excision using a patch;
 - Type 3: segmental resection with primary venovenous anastomosis; and
 - Type 4: segmental resection with interposed venous conduit and at least two anastomoses.
- The ISGPS strongly suggests that these vascular resections should be limited to high-volume centers with experienced surgical and multidisciplinary teams (strong recommendation).

Is there an indication for operative exploration and arterial resection in the presence of arterial involvement? The perioperative and long-term outcomes of patients with arterial resection during pancreatectomy for pancreatic cancer were evaluated by Mollberg et al³² in a meta-analysis that included 26 studies (published from 1977 to 2010) with 366 patients undergoing arterial resection and 2,243 patients without arterial resection. This meta-analysis showed significantly greater perioperative morbidity (median 53.6%) and mortality (median 11.8%) in patients undergoing arterial resection. In addition to these drawbacks, the survival analysis did not show a benefit compared with patients who underwent only venous resection, however, compared with patients who did not undergo resection, the 1-year survival was favorable being threefold greater for patients with arterial resection. The authors concluded that arterial resection is only justified in highly selected patients. This conclusion agrees with similar conclusions in previous studies from high-volume centers,^{29,33-35} although a case-matched

controlled study by Bachellier et al reported a similar 3-year survival rate of patients with and without arterial resection.^{29,33-35}

The meta-analysis of Mollberg et al³² included primarily pancreatoduodenectomies and a general review of arterial resections should take some account of distal pancreatectomies. In 2000 Kondo et al³⁶ reported of two patients who underwent a distal pancreatectomy with en bloc celiac axis resection after preoperative embolization of the common hepatic artery; arterial reconstruction was not needed because of the immediate development of collateral arterial pathways from the superior mesenteric artery via the pancreatoduodenal arcades. Subsequent reports, based on small cohorts, describe morbidity rates of nearly 50%, but with encouraging mortality rates of 0%, and median survivals of more than 20 months. Because early hepatic recurrence still persists, the Japanese study groups conclude that distal pancreatectomy with en bloc celiac axis resection has proven its merit only when development of hepatic metastases is unlikely.^{37,38}

Although the ISGPS supports the imaging-based, NCCN criteria for borderline resectability with regard to arterial involvement, based on current available data, we do not recommend arterial resections on a routine basis. Thus, the accuracy of CT-based diagnosis of arterial infiltration needs to be evaluated critically. Specific criteria for arterial invasion proposed to date are based mainly on the extent of circumferential vessel involvement and accord with the basis of the MDACC classification. Although a diagnostic sensitivity of up to 97% has been reported, the specificity ranges from 67% of up to 91% due to the inadequate differentiation between fibrous, tumor-mimicking adhesion and true cancerous invasion.^{9,23,39,40} We believe that patients categorized as having disease that is only borderline resectable because of the suspicion of arterial infiltration on the basis of imaging criteria should undergo surgical exploration. The risk of the potential inaccuracy of surgical exploration itself should be respected before reaching the “point of no return.”

Especially in the presence of arterial involvement, advocates of neoadjuvant therapy point out the potential for improvement of resectability and the rate of clear tumor resection margins.⁴¹ In a systematic review and meta-analysis involving 19 studies and 2,148 patients, the authors concluded that neoadjuvant chemoradiotherapy was associated with improved tumor clearance⁴²; however, the study included patients with resectable cancer and BRPC. In general, studies analyzing only

patients with BRPC are rare. Katz et al⁴³ analyzed retrospectively a well-characterized patient cohort ($n = 122$) with borderline resectable pancreatic cancer and neoadjuvant chemoradiation. They found that downstaging after neoadjuvant therapy was rare (0.8%); nevertheless, 66% ($n = 84$) of the study cohort underwent exploration with an R0 resection (AJCC definition) was achieved in 80% (81 of 101 patients). The authors concluded that the Response Evaluation Criteria in Solid Tumors are not applicable in restaging of pancreatic cancer. It is likely that inflammatory lesions mimicking tumor without real vessel infiltration contributed to the R0 rate of 80% that was found despite the lack of downstaging success. In conclusion, there is currently no evidence for improved tumor clearance after neoadjuvant treatment protocols in BRPC patients. Ongoing phase 2 trials may contribute new evidence for or against neoadjuvant treatment (NCT01359007, NCT00557492).

In terms of survival, Papalezova et al⁴⁴ reviewed 236 patients with resectable pancreatic cancer with and without neoadjuvant treatment. They reported a survival benefit of an additional 10 months (median) in patients, who underwent neoadjuvant treatment followed by resection in contrast to patients with upfront surgery. The authors conclude that neoadjuvant therapy should be considered even in patients with resectable cancer with the primary goal of adequate patient selection before attempted resection. In addition, Laurence et al reported that neoadjuvant chemoradiotherapy in patients with initially unresectable pancreatic cancer was associated with a 1-year survival rate similar to that in patients with resectable disease, even though only 40% of the former patients ultimately underwent resection.⁴² Advocates of neoadjuvant treatment suggest that these retrospective findings may arise from the effect of neoadjuvant treatment on occult microscopic metastases, which have been shown to occur prior to the formation of the primary tumor in mouse models.^{45,46}

Future randomized studies may provide evidence-based clarification. In the United States, Katz et al⁴⁷ have initiated a multi-institutional feasibility trial with FOLFIRINOX, followed by a capecitabine-based chemoradiotherapy protocol (Alliance trial A0201102). A comparable study has been initiated by high-volume German centers (NEOPA-Trial; 1.8 Gy in 28 fractions with concurrent gemcitabine 300 mg/m²; registered at EudraCT [European Union Drug Regulating Authorities Clinical Trials] www.eudract.ema.europa.eu), Reg-No. 2012-003669-17) with the start of recruitment in January 2014.

Consensus statement.

- There is no good evidence that arterial resections during right-sided pancreatic resections are of benefit. Such resections may be harmful with increased morbidity and mortality and should not be recommended on a routine basis (strong recommendation).
- Patients categorized as borderline resectable on the basis of features of arterial involvement seen at imaging, should undergo surgical exploration in order to obtain further verification of any arterial infiltration (strong recommendation).
- In case of verification of arterial involvement, palliative treatment is the standard of care (strong recommendation).
 - Respecting patients' age, grade of comorbidities, tumor biology, and performance status, two options may be evaluated in addition to the standard of care:
 1. There is no level I evidence to recommend neoadjuvant therapy regimens in patients with arterial infiltration (strong recommendation); therefore, evaluation of neoadjuvant therapeutic options is only recommended in the setting of prospective trials (qualified recommendation). If neoadjuvant therapy regimes are applied, an exploratory laparotomy and attempt at resection should be considered in the absence of disease progression after neoadjuvant treatment (distant metastasis) and if patients' performance status is adequate (strong recommendation).
 2. Straightforward, noncurative resections have a role only in clinical trial settings (strong recommendation).

Pathology protocol and reporting methods.

There are now several established, high-volume centers for pancreatic surgery worldwide, and the operative techniques for the mobilization and transection steps have become standardized. The reported rates for microscopic tumor involvement of the resection margin (R1) still range from 0 to 83%, because of differing definitions of tumor involvement.^{48,49}

This variability arises from the pathologic criteria used. A worldwide-standardized pathology protocol is indispensable for coordinated and substantial improvements in the field of borderline resectable pancreatic tumors.⁵⁰ In the United States, the Union for International Cancer Control/AJCC criteria is used to define positive resection margins, whereas in Europe the criteria of the British Royal College of Pathologists (RCPATH) and the Leeds Pathology Protocol are adopted by leading high-volume centers.⁵¹⁻⁵³ Because the protocols for specimen examination with multicolor

staining, axial slicing, and tissue sampling are largely similar, the important difference is solely in the definition of "positive microscopic margins."

The Union for International Cancer Control/AJCC criteria define positive resection margins only when tumor cells are present at the edges of the operative specimen (tumor clearance 0 mm); in contrast, the European criteria define positive resection margins if tumor cells are ≤ 1 mm from the margin. In addition, the former AJCC recommendations did not consider the anterior surface of specimens; this may also have influenced the variability of reported rates of R1 resections. However, pathologic criteria have begun to converge. In 2009, Wittekind et al⁵⁴ proposed an expanded R classification that included the minimal distance between tumor and resection margin. In addition, the current NCCN guidelines include a new pathologic analysis section which advises that the tumor clearance of all margins should be reported.¹⁵

The aforementioned advice takes into account, to some extent, the results of several studies showing that when the European R1 definition is applied, the rate for positive resection margins is usually $>70\%$, with an impact on survival analysis in retrospective and prospective studies.^{55,56} Most of the currently available data indicate that a microscopic positive resection margin within 1 mm is an independent negative prognostic marker after curative-intent surgery, having a corresponding impact on decisions about adjuvant therapy. Other studies,⁵⁷⁻⁶⁰ however, including an earlier one by Neoptolemos et al, could not show a prognostic impact of using the AJCC definition of R0 tumor clearance. Furthermore, a greater margin of clearance of at least 1.5 mm as a definition of R1 resection has been shown to further strengthen the predictive value for survival of the residual margin status.^{61,62}

The findings on R1 classification raised the question which of the seven specimen margins is of prognostic relevance if positive. In a recent study from the United Kingdom, authors investigated the relevance for survival of the location of microscopically positive resection margins.⁵⁸ No survival difference was found between patients with R1 status at the anterior or posterior margins and patients with R0 resection. These results supported the previous US guidelines because these had not included assessment of the anterior margin. In contrast, patients with microscopic tumor residue within 1 mm of the medial, pancreatic, distal bile duct, or gastric resection margin had significantly worse survival compared with R0

patients or those with R1 status at the anterior or posterior margin.

These results indicate that the term “circumferential margin positive” (analogous to rectal cancer “R” classification), is insufficiently detailed for R-status in pathology reports, and that a specific margin nomenclature is needed. The expert consensus statement published by the American Hepato-Pancreato-Biliary Association, the Society of Surgical Oncology, and the Society of the Alimentary Tract in 2009 notes that the status of the superior mesenteric artery margin (termed the “SMA margin”) is the most important driver of survival, because it is the most frequently involved positive margin (in up to 85%), having no buffer of fat and areolar tissue between the uncinate process and the SMA.^{14,63} This approach is similar to the nomenclature established in European high-volume centers. The margins created by simple mobilization are termed the anterior and posterior surface (covering the vena cava and the right renal vein). The medial resection margin refers to the pancreatic head that lies inferior to the pancreatic transection margin (at the neck), including the SMV groove, and the SMA margin is located to the patient’s left of the medial resection margin.

Portal venous tumor invasion has been shown to be a negative prognostic factor,^{20,64} and Fukuda et al²⁵ indicated in 2007 that the depth of tumor invasion is an even more accurate determinant for survival. The authors analyzed 121 patients with complete microscopic (R0) resections, including 37 patients with portal venous resections. The latter patients were subclassified into three groups (no PV wall invasion, superficial invasion up to the tunica adventitia, and deeper invasion into the tunica media or intima). Deeper PV invasion was found to be an independent prognostic marker for poorer disease-free and overall survival, with median survival being similar to that in patients with non-curative resections. No difference in terms of survival was seen between patients with superficial invasion, without portovenous invasion or even without portovenous resection.^{20,25,64} These results were confirmed recently by Han et al.⁶⁵ These data support the overall surgical approach in patients with BRPC, especially given that between 20 and 43% of all patients with suspected portomesenteric invasion turn out to have fibrous adhesions without true cancer invasion.^{22,23,30} Further studies are needed to evaluate the depth of portomesenteric invasion as a possible contraindication to resection, because the study cohorts are small, and reliable preoperative estimation of the depth of vessel invasion is currently a major concern.

Corresponding data on depth of arterial vessel invasion were not available.

Consensus statement.

- The definition of R1 resection that has been applied must be clearly detailed in future study reports, and the ISGPS endorses the RCPATH recommendations for specimen examination and the R1 definition (strong recommendation).
- Tumor clearance according to the RCPATH definition should be given for all seven margins (strong recommendation), and these margins should be designated as:
 - anterior;
 - posterior;
 - medial or superior mesenteric vein groove;
 - superior mesenteric artery;
 - pancreatic transection;
 - bile duct; and
 - enteric.
- In the case of vessel resections, accurate assessment of vessel invasion is mandatory (strong recommendation). The following classification of depth of venous vessel invasion is advised:
 - superficial invasion up to the tunica adventitia;
 - deep invasion, defined as invasion of the tunica media and further; and
 - true tumor at the intima, in contact with the vessel lumen.

Preoperative clinicopathologic characteristics: prognostic relevance. At present, patient selection for exploration for resection in the presence of BRPC is based on anatomic characteristics. The MDACC study group considered patient characteristics as well as anatomic parameters of the patients.⁶⁶ Patients with BRPC were categorized into three distinct groups: group A patients had BRPC with no suspicion of extrapancreatic metastatic disease; group B had suspicion of metastatic disease and known nodal positive disease (N1); and group C had marginal but reversible performance status and severe comorbidities, precluding immediate surgery. When patients underwent neoadjuvant radiochemotherapy, followed by restaging before potential exploration, to exclude disease progression, all three groups profited from surgery in terms of survival (total study cohort $n = 160$, resection rate 41%, treatment effect in 56%). Even more notably, 50% of group B and 38% of group C patients underwent operation after neoadjuvant and multidisciplinary supportive treatment, resulting in a median survival that was up to three times greater than with patients who did not undergo resection. Although the proposed

classification has shown the importance of reevaluation after neoadjuvant treatment for a subset of patients, this classification was not identified as a preoperative prognostic factor for survival.

There are promising results from prognostic scores related to systemic inflammation. Both Jamieson et al⁵⁷ and La Torre et al⁶⁷ have validated the modified Glasgow Prognostic Score (mGPS) in potentially resectable pancreatic ductal adenocarcinoma (Table II). The 135 patients from Glasgow and 101 from Rome were scored preoperatively for systemic inflammatory response (score 0, C-reactive protein [CRP] <10 mg/L; score 1, CRP ≥10 mg/L; score 2, CRP ≥10 mg/L, and albumin <35 g/L). The groups with score 0 had median survivals after pancreatoduodenectomy of 26.7 months (Glasgow study, 55% of patients) and 37.2 months (Rome study, 45% of patients). Corresponding values for patients with a score of 1 were poorer at 16.5 and 11.5 months, respectively, and even poorer for those with a score of 2, at 13.1 and 7.3 months, respectively. The mGPS showed independent prognostic value. The GPS, described originally in 2003, has now been validated in more than 60 studies of different organ-specific cancers, involving more than 30,000 patients from 13 different countries.⁶⁸

Wang et al⁶⁹ attempted to compare the mGPS score with the CRP-based prognostic index score and scoring systems based on circulating white cells (neutrophil/lymphocyte ratio, platelet/lymphocyte ratio), or in combination with albumin (prognostic nutritional index) in patients with pancreatic cancer. On the basis of 177 patients, they found that only a neutrophil/lymphocyte ratio >5 predicted poorer overall survival, and this was superior to the mGPS score. These results were afterwards confirmed by Stotz et al⁷⁰ based on a study cohort of 371 pancreatic cancer patients (neutrophil/lymphocyte ratio >5: hazard ratio 1.6, $P = .039$ in surgically treated patients). Results for both scoring systems indicate that systemic inflammatory response may have an important prognostic role in pancreatic cancer patients.

Serum levels of carbohydrate antigen 19-9 (CA19-9) were proposed as a preoperative marker by Hartwig et al.⁷¹ In the largest cohort of patients discussed so far ($n = 1,543$), the authors indicated that CA19-9 levels predict resectability, stage of disease, and survival. Patients with Serum CA19-9 levels ≥4,000 U/mL had a resectability rate of 38% and a 5-year survival rate of 0%, compared with 80% and 27%, respectively, in patients with CA19-9 <37 U/mL. Furthermore, the R0 resection rate was only 15.4% in patients with CA19-9 ≥1,000 U/mL.

Table II. Systemic inflammation-based prognostic scores: mGPS

	<i>mGPS 0</i>	<i>mGPS 1</i>	<i>mGPS 2</i>
CRP	<10 mg/L	CRP <10 mg/L or	≥10 mg/L
Albumin	≤35 g/L	albumin >35 g/L	<35 g/L

CRP, C-reactive protein; mGPS, modified Glasgow Prognostic Score.

In recent years, an increasing number of studies have reported on genetic markers as predictors for survival or for response to neoadjuvant/adjvant therapy, and a complete overview would go beyond the scope of this article. However to take one example, Reid-Lombardo et al⁷² examined inflammation-related genes and their polymorphisms in 1,308 patients and identified single-nucleotide polymorphisms within the MAPK8IP1 and SOCS3 genes to be associated with overall survival in pancreatic cancer. Other studies indicate a predictive value of angiogenesis-related gene polymorphisms in pancreatic cancer patients, and Varadhachary et al reviewed studies highlighting genetic variations, that have potential impact on intratumoral drug levels as predictive markers for neoadjuvant and adjuvant chemotherapy.^{73,74}

In summary, especially in patients with BRPC, the preoperative prognostic evaluation of survival may be an important tool to identify patients who are most likely to profit from surgery, independently of the CT-based anatomic results, which indicate technical feasibility and probability of complete tumor clearance. The reported prognostic markers, however, must be evaluated with caution, because they are based on retrospective cohort analyses. Prospective evidence is awaited.

Consensus statement.

- Patients with BRPC with suspected but not proven distant metastasis and patients ineligible for surgery because of comorbidity should be reevaluated for operative intervention after multidisciplinary supportive treatment (eg, nutritional supplementation) and/or neoadjuvant treatment; these patients should be offered exploration for potential resection only in the absence of disease progression (strong recommendation).
- Serum levels of CA19-9 may be included in standard preoperative diagnostics for patients with BRPC to assess potential benefits in survival with surgery but not for prediction of resectability (qualified recommendation).
- The modified mGPS score or the platelet/lymphocyte ratio may be included in standard preoperative diagnostics for patients with BRPC, to obtain further validation on the prognostic relevance of systemic inflammatory response (qualified recommendation)

- Current data on genetic markers predictive of resection or survival are not sufficient to justify an impact on decision-making at present (strong recommendation).

SUMMARY

Current evidence supports portomesenteric resection in patients with BRPC. There is no good evidence that arterial resections during right-sided, proximal pancreatic resections are of benefit and should not be recommended. Basic definitions were suggested and are needed for obtaining further evidence and improvements in this important subgroup of patients with vessel involvement. A consensus for each topic is given that is supported by all members of the ISGPS. Multimodal therapy comprising neoadjuvant chemotherapy, radiation, and surgery may in the future provide the most favorable outcome in patients with BRPC. Given the paucity of multi-institutional and multinational studies, prospective trials related to the proposed basic consensus are mandatory.

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