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BORDERLINE RESECTABLE PANCREATIC CANCER: Need for Standardization and Methods for Optimal Clinical Trial Design

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Abstract

Methodological limitations of prior studies have prevented progress in the treatment of patients with borderline resectable pancreatic adenocarcinoma. Shortcomings have included the absence of staging and treatment standards and pre-existing biases with regard to the use of neoadjuvant therapy and the role of vascular resection at pancreatectomy. In this manuscript, we will review limitations of studies of borderline resectable PDAC reported to date, highlight important controversies related to this disease stage, emphasize the research infrastructure necessary for its future study, and present a recently-approved Intergroup pilot study (Alliance A0201101) that will provide a foundation upon which subsequent well-designed clinical trials can be performed.

INTRODUCTION

Defining borderline resectable pancreatic ductal adenocarcinoma (PDAC) as a unique entity worthy of investigation is rational based on five clinical observations: 1) complete resection

of the primary tumor and regional lymph nodes is mandatory for long-term survival¹, 2) the incidence of margin-negative resection following surgery *de novo* decreases with increasing involvement of the superior mesenteric vein-portal vein (SMV-PV) and superior mesenteric artery (SMA)²⁻⁴, 3) resection of the SMV-PV and hepatic artery—but not the SMA—at pancreatectomy is associated with acceptable outcomes⁵⁻⁷, 4) “downstaging” of locally advanced cancers is rare following the administration of conventional cytotoxic agents⁸, and 5) chemotherapy and chemoradiation may be used to select patients with favorable physiology and tumor biology who may benefit from aggressive operations. Within this context, borderline resectable tumors are best conceptualized as those that involve the mesenteric vasculature to a limited extent, and for which resection, while possible, would likely be compromised by positive surgical margins in the absence of preoperative therapy.

Recognition of borderline resectable PDAC as a unique clinical entity is critical, both for optimal patient care, as well as for the proper evaluation of novel treatment regimens in clinical trials. Unfortunately, methodological limitations and biases associated with prior studies have impeded progress and have contributed to confusion. In this manuscript, we review limitations of studies of borderline resectable PDAC reported to date, emphasize the research infrastructure necessary for its future study, and present a recently approved Intergroup pilot study that will provide a foundation upon which subsequent well-designed clinical trials can be performed.

HISTORICAL CONTEXT

A collection of radiographic criteria characterizing a subset of non-metastatic PDAC tumors with anatomic features intermediate between resectable and unresectable was first described in 2001⁹. This evolved from the recognition that a margin-negative resection was critical to long-term survival and that venous resection at pancreatectomy could be performed safely and could enhance the ability to achieve a margin-negative resection in cases where this had previously been considered impossible¹⁰. Simultaneously, the potential benefits of neoadjuvant therapy with regard to both patient selection and margin sterilization were emerging¹¹. These advances reduced the clinical gap between resectable cancers, for which R0 resection as primary therapy was considered potentially curative, and unresectable cancers, for which palliative nonsurgical therapies were historically favored. By 2006, the National Comprehensive Cancer Network (NCCN) adopted the term “borderline resectable” to describe localized cancers thought to be at high risk for margin-positive resection and treatment failure when treated primarily with surgery, and for which the administration of neoadjuvant therapy was logical.

To our knowledge, 23 studies that report outcomes of patients with tumors labeled as borderline resectable and who were treated with chemotherapy and/or chemoradiation prior to surgery have been published (TABLE 1). These studies primarily represent retrospective, single-institution series or small prospective studies of patients with locally advanced disease in which patients with borderline resectable cancers were included as a subset. Only two prospective trials of neoadjuvant therapy for borderline resectable PDAC have previously been reported^{9, 12}. Just one of these was a multi-institutional trial and it closed prematurely almost a decade ago for reasons including the absence of a well-defined study

population and the absence of standardized therapeutic algorithms¹². Since then, a universally accepted radiographic definition of borderline resectable PDAC has not been established. Likewise, preoperative assessment, disease staging, surgical decision-making and technique, and integration of chemotherapy and chemoradiation into the care of these patients have not been standardized¹³.

INTERGROUP TRIAL

Within this historical context, multi-institutional study of borderline resectable PDAC is justified given the following considerations. First, no standard therapeutic approach has been established for patients with this disease stage. Second, although a significant number of patients with borderline resectable PDAC exist nationwide, the number treated at most institutions is small. Third, the application of both neoadjuvant therapy and vascular resection for patients with localized PDAC has increased, indicating a growing acceptance of these two historically controversial treatment modalities; the recent publication of national “consensus statements” suggests interest in this unique patient population^{14, 15}.

The Alliance for Clinical Trials in Oncology (Alliance), in cooperation with the Southwest Oncology Group, Eastern Cooperative Oncology Group and Radiation Therapy Oncology Group, recently obtained NCI approval to conduct a multi-institutional treatment trial for patients with borderline resectable PDAC (Alliance A021101). Opening in early 2013, this single-arm pilot study will evaluate the survival outcomes and toxicity rates associated with four cycles of mFOLFIRINOX (oxaliplatin 85 mg/m², irinotecan 180 mg/m², leucovorin 400 mg/m², 5-fluorouracil 2,400 mg/m²) followed by external beam radiation therapy to 50.4 Gy with capecitabine (825 mg/m²) administered prior to surgery (FIGURE 1). More importantly, however, it will evaluate the feasibility of conducting future multi-institutional trials of borderline resectable PDAC and will establish a research infrastructure upon which those future trials can be based. This will include standardization and quality control of the following elements.

Definition

A uniformly accepted set of criteria that define patients with borderline resectable PDAC does not exist. The two most commonly cited definitions are those proposed by the MD Anderson group and the Americas Hepatopancreatobiliary Association (AHPBA)/Society for Surgery of the Alimentary Tract (SSAT)/Society of Surgical Oncology (SSO, and modified by the NCCN) (TABLE 2)¹⁵⁻¹⁷. Both criteria differentiate borderline resectable from unresectable cancers on the basis of radiographic evidence for limited SMA involvement (predicted radiographically by a tumor-SMA interface less than 180 degrees³) that would allow resection of the tumor without resection of the artery because pancreatectomy with concomitant resection and reconstruction of the SMA has generally been found to be futile^{6, 7}.

The two classifications differ primarily in the extent to which radiographic evidence of tumor involvement of the superior mesenteric vein-portal vein (SMV-PV) discriminates borderline resectable primary tumors from resectable ones. The MD Anderson group, which favors the use of neoadjuvant chemoradiation for both resectable and borderline resectable

cancers, considers venous occlusion to represent the cutoff; tumors that radiographically abut (< 180 degree tumor-vessel interface) or encase (≥ 180 degree interface) the SMV-PV are considered resectable. In contrast, the AHPBA/SSAT/SSO considers venous abutment the cutoff; all tumors with any degree of abutment or encasement of the SMV-PV are considered borderline resectable⁴.

Increasing evidence suggests that the radiographic indicator of venous involvement that best describes tumors at high risk of margin-positive resection among those which are not clearly unresectable lies somewhere between venous abutment and outright occlusion. Tumors that approach the right lateral aspect of the SMV-PV can typically be resected with negative margins, while tumors that infiltrate to the left lateral aspect of the vein have a higher likelihood of margin-positive resection whether or not concomitant venous resection is performed. In an early study of patients who all underwent venous resection at pancreatectomy, Ishikawa found that patients with bilateral narrowing or long-segment abutment of the SMV-PV on preoperative angiograms had a poorer prognosis than patients with radiographically normal, shifted, or unilaterally (right) narrowed veins, suggesting that these patients had more aggressive disease biology and/or a higher rate of positive margins². More recently, Nakao confirmed these findings and investigators from the Central Pancreas Consortium showed that margin-negative resection of tumors with minimal radiographic evidence for SMV-PV involvement could be performed without the need for neoadjuvant therapy⁴.

The differences between the AHPBA/SSAT/SSO and MD Anderson classifications notwithstanding, over half of prior studies that included patients with borderline resectable disease did not use either definition. Indeed, the radiographic criteria used to define a group of tumors labeled “borderline resectable” often vary between or even within institutions, and reflect preconceptions about the results of surgery for patients with PDAC, as well as deep biases with regard to the performance of vascular resection at pancreatectomy and the role of neoadjuvant therapy rather than objective data.

The ideal definition for borderline resectable PDAC should be free of subjective terminology (e.g. impingement, abutment), could be applied using routine, axial pancreatic protocol CT images, and should be reproducible. Based on the data available, and within the context of a cooperative group setting, we have defined borderline resectable PDAC radiographically as localized cancers *with one or more of the following* (Figure 2):

- a. An interface between the primary tumor and SMV-PV measuring 180° or greater of the circumference of the vein wall, *and/or*
- b. Short-segment occlusion of the SMV-PV with normal vein above and below the level of obstruction that is amenable to resection and venous reconstruction, *and/or*
- c. Short-segment interface (of any degree) between tumor and hepatic artery with normal artery proximal and distal to the interface that is amenable to resection and arterial reconstruction, *and/or*

- d. An interface between the tumor and SMA or celiac trunk measuring less than 180° of the circumference of the artery wall.

Study Populations

Conversion of unresectable cancers with significant involvement of the SMA or aorta to resectable ones is a distinctly uncommon event. In a study of 87 patients with well-staged, unresectable tumors, Kim identified only one patient who was able to undergo curative resection following preoperative therapy⁸. Thus, trials evaluating the effects of novel preoperative regimens for borderline resectable PDAC would be negatively biased by the enrollment of patients with unresectable cancers whose tumors are unlikely to ever be resectable despite preoperative therapy. Borderline resectable cancers should be studied independently. In over half of prior trials, however, patients with borderline resectable cancers were studied together with patients considered to have locally advanced disease.

The Intergroup trial incorporates a pre-registration phase during which a real-time, centralized review of the staging CT images of all patients will be performed by a dedicated gastrointestinal radiologist prior to final enrollment. This mechanism will ensure enrollment of similarly staged patients who each meet well-defined radiographic criteria.

Metrics of Therapeutic Response

Recent consensus has established that patients with borderline resectable cancers should be treated with neoadjuvant chemotherapy and chemoradiation either on- or off-protocol¹⁸, but the true effects of these therapies are unknown. Theoretically, preoperative therapy can improve patient selection for surgery, downstage the primary tumor to allow margin-negative resection of advanced disease, and yield longer durations of survival.

A complete understanding of the role of preoperative therapy has remained elusive, however, because the outcome metrics reported in prior studies are biased by variability in the regimens used, response criteria applied, and indications and surgical techniques for resection following treatment. Resection rate, for example, has been routinely reported as a primary outcome measure of studies of borderline resectable PDAC, and has been used as a principal metric of comparison of the effects of different preoperative regimens^{19, 20}. This metric, however, is a subjective one that reflects biases not only in pre- and post-treatment staging, but also in preoperative and intraoperative decision-making. Comparatively few studies have reported unbiased measures of treatment response such as Response Evaluation Criteria in Solid Tumors (RECIST); change in primary tumor diameter or radiographic stage following treatment; or even durations of survival.

The conclusions of an oft-cited meta-analysis of neoadjuvant therapy illustrate the pitfalls of using resection rate as a meaningful comparator¹⁹. The authors found that 33% of patients with unresectable PDAC in the analysis were resected following neoadjuvant therapy, and concluded that one-third of unresectable tumors can be converted to resectable ones with neoadjuvant therapy. However, 53% of the studies included in the meta-analysis did not state the criteria used to stage disease, only 40% reported the criteria used to measure treatment response, and most did not report the indications for surgery. The high resection rate reported likely reflected less “downstaging” by neoadjuvant therapy than an artifact of

variability in staging and criteria used to indicate operative intervention. Indeed, in a recent analysis of patients treated at MD Anderson that used objective radiographic response criteria, only 12% of 129 patients with borderline resectable cancers had a reduction in size sufficient to meet the definition of a RECIST response following neoadjuvant therapy, and the tumor of only one patient was downstaged to meet a radiographic definition of potentially resectable²¹. Nonetheless, R0 resection was performed in 66% of patients. Vascular resection was required at 60% of all resections.

Objective outcome metrics must be defined and reported to allow meaningful comparisons of the effects of future novel preoperative treatment regimens. In the Intergroup trial, the diameter and radiographic stage of each patient's primary tumor will be documented prior to therapy, between chemotherapy and chemoradiation, and prior to surgery. Response will be characterized by RECIST and a change in radiographic stage. Survival of the entire group and the resected group will be reported independently.

Indications for Surgery and Technical Considerations

The criteria used to select patients for surgery and the use of vascular resection at pancreatectomy may both effect outcomes of patients with borderline resectable PDAC. However, these critical elements of surgery—the only therapeutic component proven to be potentially curative—have been among the least standardized in previous trials of any stage of disease²². Indeed, no consensus yet exists with regard to the indications for surgical resection following neoadjuvant therapy, and controversy continues to surround the use of vascular resection at pancreatectomy. This variability may explain the wide range in both rates of resection (24 – 100%) and vascular resection (31 – 73%) reported in prior studies.

In the Intergroup trial, attempted resection is mandatory for all patients with preserved performance status in the absence of radiographic evidence for cancer progression. Venous resection and hepatic arterial resection is advocated, when necessary, to obtain negative margins, but SMA resection is prohibited because survival is poor when SMA resection is performed⁶. This protocol requirement is based upon an assumption that enrolling multidisciplinary groups will include surgeons skilled and willing to perform vascular reconstructions when indicated. In this context, using the anatomic criteria discussed above, margin-negative resection may be expected in a significant proportion of patients without SMA resection, even when abutment of the SMA is observed radiographically^{3, 23, 24}. This reflects the concept that the tumor-SMA interface can be 'sterilized' in the absence of radiographic changes.

Other Clinical Areas

Attention to these methodological issues that are particularly germane to the study of borderline resectable disease does not minimize the need for standardization and quality control of all other trial components as should be required in the multi-institutional study of any stage of PDAC. For example, specific guidelines for chemotherapy drug and dose adjustments should be in place, and radiation therapy plans should be centrally reviewed prior to initiation of treatment²⁵. Similarly, uniform histopathologic review of the surgical specimen at each participating center is essential to accurately determine the influence of

preoperative therapy upon tumor response^{22, 26}. Mechanisms to standardize these components are incorporated into the Intergroup trial.

CONCLUSION

Variability in patients studied, therapeutic algorithms employed, and metrics reported may introduce heterogeneity in the reported outcomes of patients with borderline resectable PDAC treated with preoperative therapy. Rigorous standards of clinical trial design incorporated into trials of other disease stages must therefore be adopted in all future studies of borderline resectable PDAC. The Intergroup trial should serve as a paradigm for such investigations.

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Synopsis

No multiinstitutional trial of preoperative therapy for patients with borderline resectable pancreatic cancer has yet been completed. Herein we highlight the research infrastructure necessary to conduct such a trial and present a recently-approved Intergroup pilot study (Alliance Trial A0201101).

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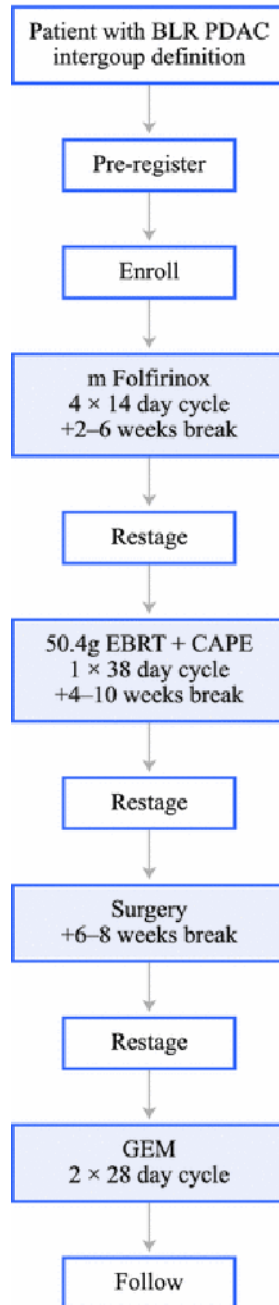


Figure 1. Study schema from intergroup trial (Alliance Trial #A021101). BLR PDAC, borderline resectable pancreatic adenocarcinoma; mFOLFIRINOX, modified FOLFIRINOX; EBRT, external beam radiation therapy; CAPE, capecitabine; GEM, gemcitabine.

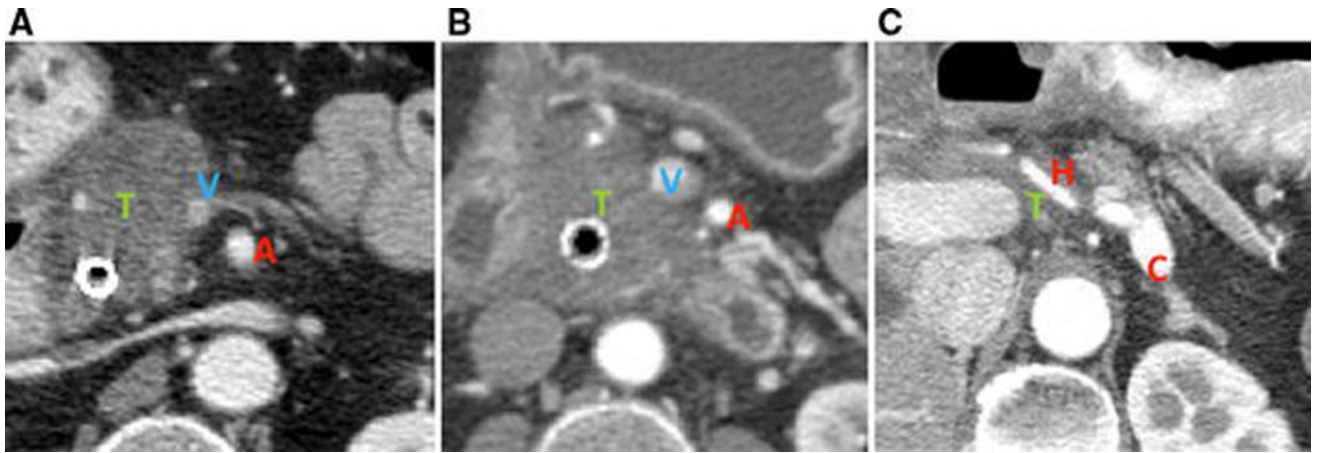


Figure 2.

Radiographic findings consistent with borderline resectable PDAC. A) An interface between the primary tumor and the superior mesenteric vein measuring at least 180° of the circumference of the vessel wall; B) An interface between the tumor and superior mesenteric artery measuring less than 180° of the circumference of the vessel wall; C) Circumferential interface between the tumor and the common hepatic artery. T, tumor; A, superior mesenteric artery; V, superior mesenteric vein; H, common hepatic artery; C, celiac trunk.

Table 1

Prior studies of borderline resectable pancreatic cancer

Author ^{Ref}	Year	Study Centers/ Type	Staging Definitions Used	Stages Studied	Neoadjuvant Regimen	Indication for Surgery	Response Criteria Reported	Resection Rate Reported	Vascular Resection Rate Reported	Survival Reported
Leone ²⁷	2012	S/1	Other	LA BLR	CTX-CXRT	No progression	RECIST	Yes	No	Yes
Lee ²⁸	2012	S/1	NCCN * 2008	LA BLR	CTX	No progression	RECIST	Yes	Yes	No
Hosein ²⁹	2012	S/2	AHPBA	LA BLR PR	CTX	Radiographically resectable	NR	Yes	No	No
Katz ²¹	2012	S/2	AHPBA MDACC	BLR	Various	No progression	RECIST Stage	Yes	Yes	Yes
Barugola ³⁰	2012	S/3	Other	LA BLR	Various	No progression	RECIST	N/A	No	No
Kang ³¹	2012	S/3	AHPBA	BLR	CXRT	No progression	NR	N/A	Yes	No
Chuong ³²	2011	S/3	Other	BLR	CTX-CXRT	Significant radiographic response	WHO RECIST	N/A	No	No
Stokes ³³	2011	S/2	MDACC	BLR	CXRT	No progression	NR	Yes	Yes	No
Arvold ³⁴	2011	S/2	Other	LA BLR	Various	NR	NR	Yes	No	No
Sahora ³⁵	2011	S/1	AHPBA	LA BLR	CTX	Partial response and at least stable disease	RECIST	Yes	No	No
Sahora ³⁶	2011	S/1	AHPBA	LA BLR	CTX	Borderline resectable or unresectable with improved PS or CA 19-9	RECIST	No	No	No
Takahashi ³⁷	2011	S/3	NCCN * 2010	LA BLR	Various	NR	NR	No	No	No
Chun ³⁸	2010	S/3	Other	BLR	Various	NR	NR	N/A	Yes	Yes
McClaine ²⁴	2010	S/2	Other	BLR	Various	Response	NR	Yes	Yes	No
Landry ¹²	2010	S/4	Other	BLR	Various	NR	RECIST	Yes	No	Yes
Turrini ³⁹	2009	S/2	MDACC	BLR	CXRT	NR	RECIST	No	No	No
Satoi ⁴⁰	2009	S/2	NCCN * 2005	PR BLR	CXRT	NR	NR	Yes	No	No
Brown ⁴¹	2008	S/3	NR	BLR	CXRT-CTX	No progression	NR	N/A	Yes	Yes
Small ⁴²	2008	S/1	NCCN	BLR LA	CXRT	Resectable	RECIST	Yes	No	Yes
Massucco ⁴³	2006	S/2	Other	BLR LA	Various	Downstaging or stable disease with normal CA 19-9	RECIST	Yes	No	No
Pipas ⁴⁴	2005	S/1	Other	PR BLR LA	CTX-CXRT	Resectable or borderline resectable	RECIST	Yes	No	No
Zimmermann ⁴⁵	2004	S/1	Other	BLR LA	CXRT	No progression	NR	Yes	No	Yes

Author ^{Ref}	Year	Study Centers/ Type	Staging Definitions Used	Stages Studied	Neoadjuvant Regimen	Indication for Surgery	Response Criteria Reported	Resection Rate Reported	Vascular Resection Rate Reported	Survival Reported
Mehta⁹	2001	S/1	Other	BLR	CXRT	No progression	RECIST	Yes	No	Yes

Studies included are those published in English that included patients treated with neoadjuvant therapy for borderline resectable PDAC (using any definition) and specifically provided data for borderline resectable patients independently.

Study Centers/Type: S, single-center; M, multi-center; 1, prospective, single-arm; 2, retrospective, observational; 3, retrospective, only resected patients; 4, prospective, randomized

Stages Studied: PR, potentially resectable; BLR, borderline resectable; LA, locally advanced

Staging Definitions Used: NCCN, National Comprehensive Cancer Network; MDACC, MD Anderson Cancer Center; AHPBA, Americas Hepatopancreatobiliary Association/Society for Surgery of the

Gastrointestinal Tract/Society of Surgical Oncology

Neoadjuvant Regimen: CTX, chemotherapy; CXRT, chemoradiation

NR, not reported

N/A, not applicable because only resected patients were included in the study

*The NCCN criteria have changed over the years. The date of publication of the NCCN criteria used is included, when reported

Table 2

Comparison of Americas Hepatopancreaticobiliary Association/Society for Surgery of the Alimentary Tract/ Society of Surgical Oncology (AHPBA/SSO/SSAT), MD Anderson, National Comprehensive Cancer Network (NCCN) and Intergroup radiographic definitions of borderline resectable pancreatic cancer.

	AHPBA/SSAT/SSO ¹²	MD Anderson ^{5,8}	NCCN 2012 ^{17*}	Intergroup Trial
SMV-PV	Abutment ^a , encasement ^b or occlusion	Occlusion	Abutment with impingement or narrowing	Interface between tumor and vessel measuring 180° or greater of the circumference of the vessel wall, and/or reconstructable [‡] occlusion
SMA	Abutment	Abutment	Abutment	Interface between tumor and vessel measuring less than 180° of the circumference of the vessel wall
CHA	Abutment or short-segment encasement	Abutment or short-segment encasement	Abutment or short-segment encasement	Reconstructable [‡] , short-segment interface between tumor and vessel of any degree
Celiac Trunk	No abutment or encasement	Abutment	No abutment or encasement	Interface between tumor and vessel measuring less than 180° of the circumference of the vessel wall

Abbreviations: SMV, superior mesenteric vein; PV, portal vein; SMA, superior mesenteric artery; CHA, common hepatic artery.

*The NCCN criteria have changed over the years. The most recent criteria (2.2012) are included.

^aDefined as tumor-vessel interface less than 180 degrees of vascular circumference.

^bDefined as tumor-vessel interface at least 180 degrees of vascular circumference.

[‡]Normal vein or artery proximal and distal to the site of suggested tumor-vessel involvement suitable for vascular reconstruction

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