

Borderline Resectable Pancreatic Cancer: Definitions and the Importance of Multimodality Therapy

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The exceedingly high rates of distant metastatic recurrence following successful surgical resection of early-stage tumors would suggest that pancreatic adenocarcinoma is a systemic disease at the time of diagnosis in the vast majority of patients, and therefore a compelling case can be made for a neoadjuvant treatment approach in almost all patients. Although the first national trial of neoadjuvant therapy for resectable pancreatic cancer (ACOSOG Z5041) only recently opened, single-institution experiences have supported this form of treatment sequencing for nearly two decades. However, outside of large referral centers with disease-specific investigators committed to clinical and translational research in pancreatic cancer, confusion remains over how to define, on preoperative imaging, what is resectable and what is not (so called locally advanced or borderline resectable pancreatic cancer). In an attempt to clarify the anatomy of resectable, borderline, and locally advanced disease, Varadhachary and colleagues from the University of Texas M. D. Anderson Cancer Center proposed, in this journal in 2006, an objectively defined, computed tomography (CT)-based classification which distinguished borderline resectable from both resectable and locally advanced pancreatic cancer.¹ The Varadhachary definitions considered venous abutment and encasement (without occlusion) to be resectable, in the absence of tumor extension to the celiac or superior mesenteric (SMA) arteries, as this operational definition was developed for the conduct of clinical trials of neoadjuvant treatment sequencing. There was no intent to use this definition outside of such clinical trials, and this definition of “resectable” was not intended to support a surgery-first

strategy for patients who may require vascular resection and reconstruction. The Varadhachary definitions also assumed the technical capability to resect and reconstruct the superior mesenteric-portal vein (SMPV) confluence when necessary and that the major determinant of margin status (R status) was the tumor–artery (celiac, hepatic, SMA) relationship (Table 1). Katz and colleagues in 2008 reported 160 patients with borderline resectable disease (using the Varadhachary definition) treated at M. D. Anderson Cancer Center and introduced three types of borderline resectable disease, now often referred to as Katz type A, B, and C.² Type A patients were those with borderline resectable tumor anatomy as defined in the Varadhachary manuscript. Type B patients were borderline resectable because of a concern for possible extrapancreatic metastatic disease and included those with CT findings suspicious for, but not diagnostic of, metastatic disease as well as those with known local–regional lymph node metastases. It may be reasonable in 2010 to add to this group those patients with very high carbohydrate antigen 19-9 (CA19-9) levels (measured when serum bilirubin is normal). In the future, newer biomarkers (for example, *SMAD4* mutation status) may further refine patient classification in this category. Type C patients were borderline resectable due to marginal performance status or significant pre-existing medical comorbidity thought to require protracted evaluation that precluded immediate surgery. By definition, Type C patients were thought to have reversible causes of their current symptoms such as hyperbilirubinemia-induced anorexia and fatigue. Katz and colleagues provided compelling data in support of induction chemotherapy (followed by chemoradiation) for patients with borderline resectable disease. Of equal importance, they defined borderline resectable disease (with the goal of simplifying stage assignment and treatment) in all three forms which we see clinically: anatomic (local tumor anatomy), oncologic/biologic (possible

TABLE 1 The Varadhachary/Katz CT staging system for adenocarcinoma of the pancreatic head and uncinate process

Clinical stage of disease	AJCC stage	Tumor–vessel relationship on computed tomography			
		SMA	Celiac axis	CHA	SMV-PV
Resectable ^a (all four required to be resectable)	I/II	Normal tissue plane between tumor and vessel	Normal tissue plane between tumor and vessel	Normal tissue plane between tumor and vessel	Patent (may include tumor abutment or encasement)
Borderline resectable (only one of the four required)	III	Abutment	Abutment	Abutment or short segment encasement	May have short segment occlusion if reconstruction possible
Locally advanced (only one of the four required)	III	Encasement	Encasement	Extensive encasement with no technical option for reconstruction	Occluded with no technical option for reconstruction

CHA common hepatic artery, SMV-PV superior mesenteric vein-portal vein confluence

Definitions: abutment, $\leq 180^\circ$ or $\leq 50\%$ of the vessel circumference; encasement, $>180^\circ$ or $>50\%$ of the vessel circumference

^aAssumes the technical ability to resect and reconstruct the SMV, PV, or SMV-PV confluence when necessary

advanced disease not fully apparent on imaging), and physiologic (marginal performance status).

In this issue of the *Annals of Surgical Oncology*, Chun and colleagues from Fox Chase Cancer Center add to the work of Varadhachary and Katz and focus specifically on the relationship of the tumor to the superior mesenteric vein and SMPV confluence using the Ishikawa classification system.³ They conclude that patients with tumor-induced unilateral shift or narrowing of the SMPV confluence should be considered borderline resectable and receive preoperative (neoadjuvant) induction therapy. Their conclusion is supported by detailed analysis of their experience in the care of these complex patients over the past two decades. For those surgeons and medical oncologists who recommend a surgery-first strategy to patients with localized, potentially resectable pancreatic cancer, this manuscript limits the CT definition of what should be considered “resectable” for which immediate surgery may be considered. The Fox Chase definition of resectable (as distinct from borderline resectable) includes only those tumors with no evidence (on CT) of even unilateral shift or narrowing of any aspect of the SMPV confluence as well as no extension to the adjacent mesenteric arteries. This is consistent with the recommendation of the American Hepato-Pancreato-Biliary Association (AHPBA)–Society of Surgical Oncology (SSO)–Society for Surgery of the Alimentary Tract (SSAT) consensus panel which was published in this journal last year by Callery and colleagues.⁴

At present there appears to be growing consensus for the following:

1. Pancreatic cancer (especially in the head, neck, or uncinate process) can be accurately staged

preoperatively and classified as resectable, borderline resectable, and locally advanced.

2. For those who recommend a surgery-first strategy, resectable disease should be narrowly defined as the absence of tumor extension to the adjacent visceral arteries (SMA, celiac, hepatic) and the absence of tumor-induced unilateral shift or narrowing of any aspect of the SMPV confluence.^{3,4}
3. Borderline resectable pancreatic cancer as defined by the Fox Chase group and the AHPBA–SSO–SSAT consensus panel should be treated with induction therapy before surgery. The Chun manuscript provides additional data to suggest that patients with CT evidence of tumor–SMPV abutment resulting in displacement or narrowing of the vein should not go directly to surgery. Of note, their experience also includes routine use of preoperative external-beam radiation therapy. The published experience to date with neoadjuvant treatment sequencing for resectable and borderline resectable pancreatic cancer has largely utilized chemoradiation as a component of the treatment program; experience using chemotherapy alone is relatively untested.

What is not clear at present is how best to treat patients with borderline resectable pancreatic cancer prior to consideration of surgery. The M. D. Anderson experience would argue for a period of induction systemic therapy, especially in those with arterial abutment, to include at least two months of chemotherapy prior to chemoradiation.² Emerging trials, as well as consideration of off-protocol therapy, will likely include what may prove successful in metastatic disease, for example, gemcitabine plus nab-paclitaxel (Abraxane) or FOLFIRINOX [5-fluorouracil (5-FU), leucovorin, irinotecan, and oxaliplatin].^{5,6} The length

of induction systemic therapy, the timing and dose of radiation therapy, and the optimal postoperative systemic therapy remain undefined. In the presence of arterial abutment, few are willing to bypass the use of chemoradiation. The continued refinement of our pretreatment staging systems is resulting in a high level of consensus (for the first time) on stage-specific therapy. There is now general agreement, as discussed in the Chun manuscript, in favor of neoadjuvant treatment sequencing for all pancreatic adenocarcinomas with extension to adjacent mesenteric vasculature, an important step in standardizing our approach to this disease. Future clinical trials will capitalize on the ability to further characterize tumors (beyond CT appearance and serum levels of CA19-9) through molecular analysis of tumor biopsies, opening the door to personalized medicine and what we hope will be more effective therapy.

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