

# Tumor-Node-Metastasis Staging of Pancreatic Adenocarcinoma

Matthew H. G. Katz, MD; Rosa Hwang, MD; Jason B. Fleming, MD; Douglas B. Evans, MD

**ABSTRACT** Accurate disease staging of patients with pancreatic cancer is essential to divide patients into prognostic subgroups, to allow delivery of stage-specific therapies, and to facilitate meaningful discussions between physicians and patients regarding management and expected outcomes. The tumor-node-metastasis staging system of the American Joint Commission on Cancer has undergone significant revisions over the past 2 decades. In its current form, the system places an emphasis on preoperative clinical staging and facilitates division of patients with pancreatic cancer into 4 groups based on a determination of local resectability and the presence or absence of distant disease as determined on high-quality cross-sectional imaging. A modern understanding of local tumor factors that influence technical resectability is incorporated into the algorithm. In this review, we examine the American Joint Commission on Cancer staging system, describe the rationale for its use, and demonstrate how it is a clinically relevant tool for the staging and management of patients with pancreatic cancer. (*CA Cancer J Clin* 2008;58:111–125.) © American Cancer Society, Inc., 2008.



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## INTRODUCTION

The tumor-node-metastasis (TNM) staging system of the American Joint Commission on Cancer (AJCC) facilitates the objective description and classification of the anatomic extent of malignant disease in a simple, reproducible, site-specific algorithm.<sup>1</sup> Fundamental to this staging system is the premise that cancers of the same anatomic site and histology, with a similar extent of disease, share a common natural history. The system provides physicians a language with which to estimate and communicate prognosis, allows for the development and selection of stage-specific treatment strategies, and permits the evaluation of similar groups of patients reported in clinical trials. To these ends, the *Sixth Edition* of the current AJCC staging system separates patients into 4 discrete stage groupings, labeled I to IV, each of which is characterized by a natural history and prognosis that is different from that of the subsequent group; for example, Stage III patients have a more favorable median survival than those with Stage IV disease.

Formally established in 1959, the AJCC updates its staging system every few years in an effort to maintain accuracy and clinical relevance in the face of an ever-increasing body of knowledge and technology. For pancreatic adenocarcinoma, recent advances in diagnostic techniques and strategies have been particularly significant. The definition of a resectable tumor has become more clearly defined anatomically based on the availability of high-quality computed tomography (CT) scans. Such imaging now permits a precise, preoperative, noninvasive assessment of tumor resectability and adds an important level of objectivity to the staging of patients for entry into clinical trials. Importantly, the role of laparotomy is now largely restricted to patients judged “resectable” on preoperative imaging. For the 80% to 90% of patients with pancreatic adenocarcinoma who have unresectable disease, biliary obstruction, when present, can be palliated using minimally invasive endoscopic techniques. Reflecting these advances, the current version of the AJCC staging system for pancreatic adenocarcinoma has been modified to (1) be applied non- or preoperatively using

**Dr. Katz** is Fellow, Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX.

**Dr. Hwang** is Assistant Professor, Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX.

**Dr. Fleming** is Associate Professor, Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX.

**Dr. Evans** is Professor, Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX.

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objective, reproducible radiographic criteria; (2) incorporate our current understanding of tumor anatomy that distinguishes resectable from non-resectable disease; (3) emphasize the prognostic importance of resectability by designating Stages I and II for radiographically resectable disease, Stage III for locally advanced, nonmetastatic disease, and Stage IV for metastatic disease; (4) accurately estimate prognosis with the largest separations in survival duration occurring between stage groups; and (5) provide clinically relevant definitions of disease extent that allow for the development of stage-specific treatment algorithms.

In this review, we will describe the rationale behind the current AJCC staging system for pancreatic adenocarcinoma and will critically evaluate its use as a clinically relevant tool for the management of patients with this disease.

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SIXTH EDITION OF THE AJCC STAGING SYSTEM—  
SUMMARY OF CHANGES FROM THE PREVIOUS  
FIFTH EDITION

Changes to the staging system for pancreatic exocrine tumors have been significant over the past 2 decades.<sup>2</sup> Similar to previous editions, the current *Sixth Edition* of the AJCC staging system evaluates pancreatic exocrine malignancies in terms of the size and anatomic extent of the primary tumor (T), the presence or absence of regional lymph node metastases (N), and the presence or absence of distant metastases (M).<sup>1</sup> While the TNM descriptors have remained constant, their definitions have been revised (Table 1). The T designation has undergone the most significant changes. As in the *Fifth Edition*, the current guidelines use the designations T1 and T2 to describe tumors confined to the pancreas and the designations T3 and T4 to indicate extrapancreatic extension by the primary tumor. In contrast with prior editions, the *Sixth Edition* separates T3 and T4 based on local tumor resectability. T4 tumors are those that are unresectable due to tumor extension to the celiac axis (CA) or superior mesenteric artery (SMA), as defined by direct contact of the low-density tumor as one would see on a CT scan, to either of these arterial structures. In general, tumor extension to these arteries is felt to signify locally advanced, unresectable

disease, as surgical resection and reconstruction of these arteries is technically difficult, is associated with significant risk for mortality and morbidity, and will usually not allow for a gross complete resection. In contrast, extrapancreatic tumor extension that does not involve the CA or SMA does not typically influence the local resectability status of the tumor and, therefore, carries the T3 designation. This classification recognizes the controversial nature of venous resection and reconstruction at the time of pancreatotomy.<sup>3</sup> N-staging has changed only inasmuch as the N1 suffix a or b, previously used to indicate the number of pathologically involved nodes, has been eliminated. M-staging is unchanged, with M1 indicating the presence of distant metastatic disease.

The combination of T, N, and M into stage groupings has been revised in the *Sixth Edition* to more accurately reflect the known differences in survival duration among patients with resectable, locally advanced, and distant metastatic disease. The *Fifth Edition* defined Stages I, II, III, and IV as pancreatic, extrapancreatic, node-positive, and unresectable disease, respectively; the Stage IV category included tumors considered unresectable due to either locally advanced disease (IVA) or distant metastases (IVB). While this system was analogous to that used for other solid tumors, such as breast and colon, in which Stage III described node-positive disease and Stage IV included all patients with metastatic disease, it did not accurately reflect the paramount importance of resectability on prognosis, and, therefore, it was less practical for patients with pancreatic cancer. For example, a patient with a completely resected, node-positive tumor was previously classified as Stage III, a poorer prognostic grouping than a patient with a locally advanced, unresectable tumor without pathologically confirmed lymph node metastasis (due to the absence of surgical staging) who would be classified as Stage II. In the *Sixth Edition*, Stage III is reserved for locally advanced disease; resectable, node-positive disease has been moved into Stage II. In this way, the current AJCC system now divides patients with pancreatic adenocarcinoma into distinct prognostic and clinical groups based on contemporary definitions of resectability (Stage I/II) and unresectability (local-regional, Stage III; metastatic, Stage IV) (Figure 1).

**TABLE 1** Comparison Between the *Fifth* and *Sixth Editions* of the American Joint Commission on Cancer Staging System for Pancreatic Adenocarcinoma

Definitions	<i>Fifth Edition</i>	<i>Sixth Edition</i>	Summary and Significant Changes
Primary tumor (T)			
T0	No evidence of primary	No evidence of primary	
Tis	<i>In situ</i>	<i>In situ</i>	
T1	Limited to pancreas, ≤2 cm	Limited to pancreas, ≤2 cm	
T2	Limited to pancreas, >2 cm	Limited to pancreas, >2 cm	
T3	Extends into duodenum, bile duct, and peripancreatic tissues	Extends beyond pancreas, no involvement of CA or SMA	Emphasis on anatomic factors that determine resectability; extrapancreatic extension to CA or SMA is T4; all other extrapancreatic extension is now T3
T4	Extends into stomach, spleen, colon, CA, SMA, CHA, PV, and SMV	Involves CA or SMA	
Regional lymph nodes (N)			
N0	No nodal metastasis	No nodal metastasis	
N1	Regional lymph node metastasis	Regional lymph node metastasis	No distinction between the number of involved nodes
N1a	Single involved node		
N1b	Multiple involved nodes		
Distant metastasis (M)			
M0	No distant metastasis	No distant metastasis	
M1	Distant metastasis	Distant metastasis	
Stage groupings			
Stage 0	Tis N0 M0	Tis N0 M0	<i>In situ</i> disease
Stage I	T1-2 N0 M0	IA T1 N0 M0 IB T2 N0 M0	Potentially resectable disease that is confined to the pancreas
Stage II	T3 N0 M0	IIA T3 N0 M0 IIB T1-3 N1 M0	Usually potentially resectable; may involve venous structures, adjacent organs, N, or CHA, but not CA or SMA
Stage III	T1-3 N1 M0	T4 N0-1 M0	Locally advanced; unresectable due to CA or SMA involvement
Stage IV	IVA T1-3 N0-1 M1 IVB T4 N0-1 M0-1	T1-4 N0-1 M1	Metastatic; unresectable due to distant metastatic disease

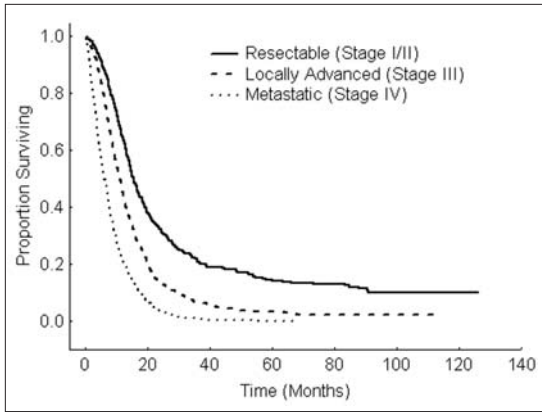
Note that, in general, Stages I and II are reserved for potentially resectable disease, Stage III for locally unresectable disease, and Stage IV for metastatic disease.

Abbreviations: LN, lymph node; CA, celiac axis; SMA, superior mesenteric artery; CHA, hepatic artery; PV, portal vein; SMV, superior mesenteric vein.

#### THE DISTINCTION BETWEEN STAGES I/II (RESECTABLE) AND STAGES III (LOCALLY ADVANCED) AND IV (METASTATIC DISEASE)

At present, it is accepted that surgical resection offers the only chance of cure for patients with pancreatic adenocarcinoma. Whether or not the primary tumor can be removed represents the strongest prognostic factor for patients with this disease and underlies the distinction between Stages I and II (resectable) and Stages III and IV

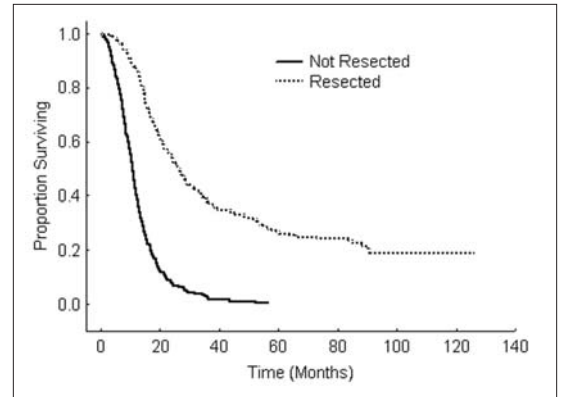
(unresectable due to local-regional factors or metastatic disease). Five-year survival for patients who undergo complete surgical resection of a localized pancreatic cancer now approaches 25%.<sup>4-13</sup> In contrast, patients with potentially resectable disease who do not undergo surgical resection of their primary tumor are assumed to have a natural history marked by continued tumor progression and short survival. In our own experience over the past decade with 662 patients who



**FIGURE 1** The *Sixth Edition* of the American Joint Commission on Cancer Staging System Applied to 2,981 Patients with Pancreatic Adenocarcinoma Evaluated at MD Anderson Cancer Center Between August 1996 and August 2006. The American Joint Commission on Cancer staging system accurately stratified patients into 3 distinct clinical categories: resectable (Stage I/II), locally advanced (Stage III), and metastatic (Stage IV). At MD Anderson Cancer Center, median survival of patients who initially presented with resectable, locally advanced, and metastatic disease was 15 months, 11 months, and 6 months, respectively.

initially presented with resectable Stage I and II pancreatic adenocarcinoma (as objectively defined based on high-quality CT imaging), patients who underwent surgical resection had a median survival of 26 months and a 5-year survival of 27%; patients who were not resected due to early disease progression (after neoadjuvant therapy), medical comorbidities, or other patient-related factors had a median survival of 10.7 months ( $P < .001$ ) (Figure 2). This supports the known powerful impact of performance status on survival duration for patients with pancreatic cancer.

Specific oncologic and anatomic findings distinguish resectable (Stages I and II) from unresectable (Stages III and IV) pancreatic cancer. Surgical resection of the pancreatic tumor is generally considered to be inappropriate in patients with metastatic disease (Stage IV), as the metastases are virtually always multifocal and associated with a survival duration of approximately 6 months. Similarly, there is general consensus that tumor involvement or extension to the CA or SMA indicates locally advanced disease that is unresectable. Because the terms “involvement” and “extension” are vague and difficult to define in an anatomic way, we have introduced the terms “abutment” and “encasement” to describe tumor-vessel relationships seen on cross-sectional



**FIGURE 2** The MD Anderson Cancer Center Experience with Stage I and II Pancreatic Adenocarcinoma over the Past Decade. Patients who underwent surgical resection had a significantly more favorable survival than those who did not undergo resection ( $P < .00001$ ).

imaging.<sup>14</sup> Tumor abutment defines tumor-vessel involvement of 180 degrees or less of the circumference of the vessel. Tumor encasement is defined as tumor involvement of greater than 180 degrees of the vessel. These definitions are consistent with an earlier report by Lu and colleagues<sup>15</sup> and based on the extensive clinical experience at MD Anderson Cancer Center. A low-density tumor mass seen on CT images to encase the SMA or CA is considered to represent locally advanced, surgically unresectable, Stage III disease (Figure 3). Arterial resection and reconstruction in this clinical scenario is technically difficult and is associated with increased risk for perioperative morbidity and mortality. Moreover, resection



**FIGURE 3** Contrast-enhanced Computed Tomography Image of a T4, Stage III, Locally Advanced Pancreatic Adenocarcinoma as Defined by Tumor Encasement of the Superior Mesenteric Artery (Arrow). Tumor encasement of the superior mesenteric vein (arrowhead) is also evident.

of tumors involving the CA or SMA is unlikely to be complete because these vessels are surrounded by a dense perineural plexus through which tumor cells may gain access to the celiac ganglion and the retroperitoneum. Even if a portion of the CA or SMA is resected and reconstructed, complete resection of tumors encasing the CA or SMA is rarely possible due to infiltrative perineural tumor extension. Finally, the majority of patients with such locally advanced disease also have synchronous systemic metastases, even if not apparent on imaging studies.<sup>16-19</sup>

#### **The Controversy of Tumor Involvement of the Superior Mesenteric or Portal Veins**

In contrast with tumor encasement of the CA or SMA, tumor abutment or encasement of the portal vein or superior mesenteric vein (SMV) is not associated with perineural tumor infiltration, as these veins do not have the associated autonomic perineural sheath characteristic of the visceral arteries. In addition, venous resection and reconstruction can be performed safely with no additional morbidity or mortality beyond that associated with standard pancreaticoduodenectomy. Venous resection and reconstruction is, therefore, no longer viewed as a contraindication to pancreaticoduodenectomy at many referral centers, including our own.<sup>3,20-23</sup> We recently reported our experience with 291 patients who underwent pancreaticoduodenectomy for adenocarcinoma of the pancreatic head, of whom 110 required major vascular resection and reconstruction. No association between the need for vascular resection and margin status could be demonstrated on multivariate analysis after adjustment for tumor size and stage. Moreover, there was no difference in survival between the 110 patients who required vascular resection and the 181 patients who underwent standard pancreaticoduodenectomy (median survival 23.4 months versus 26.5 months,  $P = .177$ ).<sup>3</sup> The 23-month median survival for those who required vascular resection was far superior to the 10- to 12-month survival of similar patients historically classified as having locally advanced, unresectable Stage III disease and managed nonoperatively.<sup>24</sup>

Nonetheless, vascular resection and reconstruction at the time of pancreaticoduodenectomy,

even when limited to the SMV or portal vein, remains controversial because of the complexity of the operative procedure combined with the aggressive biologic behavior of pancreatic cancer, which results in modest postoperative survival even in those who undergo potentially curative surgery.<sup>25-34</sup> Further, there are published data that argue against proceeding with pancreaticoduodenectomy in patients who may have tumor involvement of the SMV or portal vein (Table 2). However, in these reports, the assessment of venous resection as a prognostic factor is confounded due to the high number of margin-positive resections or an inability to accurately assess margin status, suggesting the inclusion of patients with grossly incomplete tumor resection. These reports likely contain a substantial number of patients for whom vascular resection was not planned and was performed in a poorly controlled manner without appropriate attention to the completeness of resection. A grossly incomplete (R2) operation will usually result in early tumor recurrence and limited survival, regardless of whether or not vascular resection and reconstruction were performed. This emphasizes the importance of using a standard system for the pathologic analysis of pancreaticoduodenectomy specimens, as suggested in the *Sixth Edition* of the *AJCC Cancer Staging Manual*, to accurately determine R status.

#### **The Category of Borderline Resectable Disease**

Even though CT and magnetic resonance imaging can provide very accurate assessments of the relationship of the pancreatic tumor to adjacent arteries and veins, the Stage III category includes a wide range of tumor-vessel involvement—from minimal tumor abutment of the SMA to complete 360-degree encasement of the SMA often associated with occlusion of the SMV. Tumors that demonstrate arterial abutment (tumor-vessel involvement of 180 degrees or less) may be considered for surgery as part of a multimodality approach to the disease that includes preoperative (neoadjuvant) systemic therapy usually combined with external-beam radiation therapy.<sup>14</sup> In rare situations, even short-segment occlusion of the superior mesenteric/portal vein confluence does not contraindicate

TABLE 2 Published Series of Venous Resection During Pancreaticoduodenectomy

Institution (Year)	No. Patients		Operative Mortality (%)	Median Survival (Months)
	Total	Positive Margin (%)		
MD Anderson Cancer Center (2004) <sup>3</sup>	110	24 (22)	1	23.4
Institute for Research and Cure of Cancer—Italy (2003) <sup>21</sup>	22	5/6 (83)*	0	NR
Indiana U (2003) <sup>22</sup>	13	3 (23)	8	13
Academic Medical Center—The Netherlands (2001) <sup>34</sup>	34	20 (59)	0	14
U Haute-pierre—France (2001) <sup>32</sup>	21	8 (38)	3.2	12
Technische U Munchen—Germany (1996) <sup>28</sup>	22	15 (68)	0	8
Memorial Sloan-Kettering Cancer Center (1996) <sup>33</sup>	42	10 (24)	2	13
Johns Hopkins (1995) <sup>31</sup>	10	NR	NR	NR
Pontchaillou Hospital—France (1993) <sup>26</sup>	9	NR	0	6.1†
Klinikum Mannheim—Germany (1990) <sup>30</sup>	12	NR	0	NR
National Cancer Institute (1989) <sup>29</sup>	20	NR	20	12

\*Retroperitoneal margin assessed in 6 of 22 patients.

†Value given as mean.

Abbreviation: NR, not reported.

Adapted from Tseng JF, Raut CP, Lee JE, et al.<sup>3</sup>

resection, as long as a suitable vein exists both proximal and distal to the obstruction to facilitate venous revascularization, and concomitant arterial encasement is not present.<sup>35</sup> Anatomically, the use of a subcategory of Stage III is helpful in differentiating those patients that may ultimately undergo pancreaticoduodenectomy (borderline category) versus those in whom surgery is likely never going to be possible (locally advanced category). In our practice, patients with borderline resectable pancreatic cancer include those whose tumors exhibit abutment or encasement of a short segment of the hepatic artery, without evidence of tumor extension to the CA, that is amenable to resection and reconstruction (Figure 4); tumor abutment of the SMA involving 180 degrees or less of the circumference of the artery (Figure 5); or short-segment occlusion of the SMV, portal vein, or their confluence, with a suitable option available for vascular reconstruction because the veins are normal above and below the area of tumor involvement.<sup>36</sup> Limited tumor involvement of the common or proper hepatic arteries may occur at the gastroduodenal artery origin and results from cephalad growth of the primary tumor along the gastroduodenal artery; this vessel tethers the tumor to the hepatic artery and may result in limited tumor

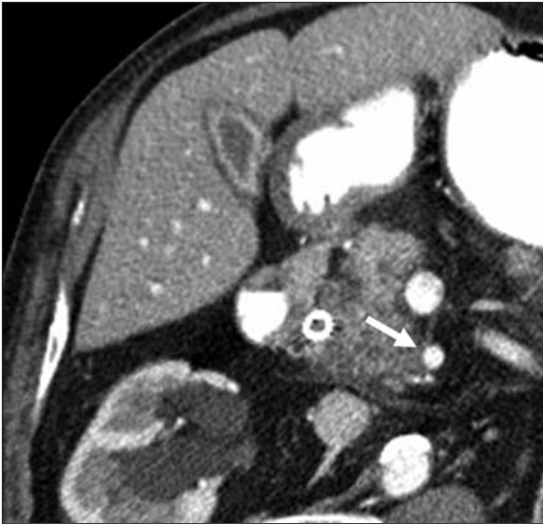
involvement at that level. Vascular reconstruction of the hepatic artery with interposition grafting or segmental resection with primary end-to-end anastomosis can be performed in selected patients when this is the only impediment to a complete resection of all disease.

#### Additional Changes in T Stage in the Sixth Edition

Disease invading the stomach, colon, or spleen, previously designated as T4 in the *Fifth Edition* and therefore staged as IVb disease, is not men-



FIGURE 4 Contrast-enhanced Computed Tomography Image of a Patient with a Borderline Resectable Tumor of the Pancreatic Head that Encases the Hepatic Artery (Arrow).



**FIGURE 5** Contrast-enhanced Computed Tomography Image of a Borderline Resectable Pancreatic Adenocarcinoma with Tumor Abutment of the Superior Mesenteric Artery (Arrow). We have defined abutment as a tumor-vessel interface of 180 degrees or less of the vessel diameter.

tioned in the current AJCC guidelines. Tumor extension to these organs is an uncommon finding in association with an otherwise technically resectable tumor. In the rare case in which adjacent organ involvement is associated with an otherwise resectable tumor, adjacent organ involvement would not preclude a complete resection in the absence of tumor extension to adjacent arteries as described previously.

In summary, the *Sixth Edition* of the *AJCC Cancer Staging Manual* attempts to separate resectable and locally advanced disease into different stage categories with the least amount of controversy. Because tumor abutment or encasement of the SMA or CA would be viewed as unresectable by most physicians and surgeons, this was the definition used for the T4 designation and the Stage III stage grouping. Tumor abutment or encasement of the SMV or portal vein may or may not be considered resectable depending on where the patient is treated; despite emerging data to support venous resection at the time of pancreaticoduodenectomy, this issue remains controversial and, therefore, the presence or absence of venous involvement was not specifically addressed in the T staging. In the *Sixth Edition*, the T3 category includes all forms of nonarterial tumor extension beyond the pancreas, including extension to the SMV and portal vein. With the



**FIGURE 6** Computed Tomography Scan of a Potentially Resectable, T1, Stage I Pancreatic Adenocarcinoma. The low-density tumor is confined to the head of the pancreas, a distinct tissue plane (white arrow) separates it from the superior mesenteric artery (+), and the superior mesenteric vein is patent (\*).

above considerations in mind, resectable (Stage I/II) disease may be distinguished from unresectable (Stage III/IV) disease radiographically by (1) the absence of distant extrapancreatic disease; (2) the absence of tumor extension to the SMA or CA, as defined by the presence of a tissue plane between the tumor and these arterial structures; and (3) the presence of a patent SMV-portal vein confluence (Figure 6).<sup>37</sup>

#### PROGNOSTIC FACTORS IN STAGES I AND II PANCREATIC ADENOCARCINOMA

The pathologic prognostic factors incorporated into the TNM definitions of resectable (Stages I and II) pancreatic cancer include tumor size and extent and lymph node status.

#### Tumor Size

Tumor size (maximal transverse diameter of the tumor as assessed pathologically) has been shown to be a significant independent prognostic factor in several published series of patients who underwent pancreaticoduodenectomy for pancreatic ductal adenocarcinoma.<sup>4,6,7,13,38-40</sup> The size cutoff for statistical significance was between 2 cm and 3 cm in most series. Unfortunately, tumors less than 2 cm in diameter may be found in as few as 2% of all patients who present with pancreatic cancer.<sup>41</sup> Even among resected patients, larger tumors are more frequent and comprise up to 94% of resected

TABLE 3 Tumor Size as a Prognostic Factor After Resection of Pancreatic Adenocarcinoma

Institution (Year)	No. Patients	Tumor Diameter (Inches)	No. Patients (%)	Median Survival (Months)	Five-year Survival (%)	P
Johns Hopkins (2006) <sup>13</sup>	1,175	≥ 3	NR	15	4	< .0001
		< 3	NR	21	23	
University of Amsterdam—The Netherlands (2004) <sup>7</sup>	160	> 2	132 (83)	NR	NR	NR
		< 2	27 (17)	NR	NR	
SEER Database (2003) <sup>39</sup>	396	> 2	239 (77)	15	NR	.002
		≤ 2	70 (23)	38	NR	
Kansai Medical University—Japan (2003) <sup>40</sup>	94	≥ 3	57 (63)	8	7	.006
		< 3	33 (37)	22	26	
Jagiellonian University—Poland (2001) <sup>6</sup>	136	> 2	NR (94)	26	NR	.04
		≤ 2	NR (6)	46	NR	
University of Naples—Italy (2000) <sup>4</sup>	75	> 3	34 (51)	11	9	.006
		< 3	33 (49)	18	33	
Nurnberg—Germany (2000) <sup>38</sup>	113	> 2	80 (78)	13	5	.001
		≤ 2	22 (22)	25	19	
University of Padova—Italy (1996) <sup>10</sup>	113	> 4	27 (24)	9	5	.008
		2–4	66 (58)	16	8	
		≤ 2	20 (18)	27	40	
Mayo Clinic (1995) <sup>9</sup>	174	> 3	97 (56)	NR	1	.001
		≤ 2	42 (24)	NR	20	
Memorial Sloan-Kettering Cancer Center (1993) <sup>5</sup>	146	> 2.5	113 (77)	15	NR	.001
		≤ 2.5	33 (23)	25	NR	

Abbreviation: NR, not reported.

surgical specimens (Table 3). Larger tumors may be associated with higher rates of microscopically positive resection margins and a more frequent need for venous resection to effect complete tumor extirpation due to the retroperitoneal location of the pancreas and associated anatomic constraints.<sup>3</sup> Resection of larger tumors may also be associated with higher rates of technical difficulty as reflected in a larger perioperative blood loss, which has also been identified as an important prognostic factor.<sup>8,42,43</sup> While the survival of patients with small pancreatic cancers is more favorable, as many as 30% to 40% of tumors less than 2 cm in diameter may have associated lymph node metastases. Small tumors, therefore, do not necessarily represent biologically early-stage disease.<sup>38,41</sup>

#### Regional Lymph Node Metastasis

Metastases to regional lymph nodes (N) also are independently related to survival duration in patients who undergo pancreatic resection (Table 4). In published series, microscopically

positive peripancreatic lymph nodes are found in up to 80% of surgical specimens; patients with N1 disease are found to have a median survival approximately 1 year shorter than that of their node-negative counterparts.<sup>4,6,7,13,39,40,43,44</sup> Acknowledging its prognostic significance, the current AJCC staging system designates the presence of lymph node metastases as N1 and classifies node-positive tumors as Stage IIb.

In the absence of pathologic assessment of the pancreaticoduodenectomy specimen, the presence of metastases to regional lymph nodes is difficult to determine radiographically because small, benign-appearing lymph nodes (on imaging studies) frequently harbor radiographically occult metastatic disease, and occasionally, larger nodes may be entirely benign.<sup>45</sup> In a representative study by Diehl<sup>46</sup> of 76 patients in whom helical CT was performed before laparotomy for pancreatic cancer, only 13 of 24 patients with biopsy-proven malignant lymphadenopathy were correctly identified preoperatively. Despite the high incidence of radiographically

TABLE 4 Positive Lymph Nodes as a Prognostic Factor After Resection of Pancreatic Adenocarcinoma

Institution (Year)	No. Patients	Lymph Node Status	No. Patients (%)	Median Survival (Months)	Five-year Survival (%)	P
MD Anderson Cancer Center (2007) <sup>43</sup>	360	Pos	186 (52)	22	NR	.002
		Neg	174 (48)	32	NR	
Johns Hopkins (2006) <sup>13</sup>	1,175	Pos	919 (78)	17	16	.0001
		Neg	256 (22)	23	27	
University of Amsterdam—The Netherlands (2004) <sup>7</sup>	160	Pos	109 (68)	NR	NR	.02
		Neg	51 (32)	NR	NR	
Kansai Medical University—Japan (2003) <sup>40</sup>	94	Pos	42 (48)	9	9	.02
		Neg	46 (52)	20	17	
SEER Database (2003) <sup>39</sup>	396	Pos	193 (49)	16	NR	.05
		Neg	203 (51)	20	NR	
Jagiellonian University—Poland (2001) <sup>6</sup>	136	Pos	86 (63)	15	4	.01
		Neg	50 (37)	38	42	
University of Naples—Italy (2000) <sup>4</sup>	75	Pos	51 (68)	13	8	< .001
		Neg	24 (32)	33	42	
Nurnberg—Germany (2000) <sup>38</sup>	113	Pos	74 (73)	13	5	.008
		Neg	28 (27)	25	27	
Rush-Presbyterian-St. Luke's (1999) <sup>8</sup>	75	Pos	45 (60)	10	NR	.01*
		Neg	30 (40)	26	NR	
University of Kansas (1996) <sup>44</sup>	100	Pos	56 (56)	11.5	6	.0003
		Neg	44 (44)	24	35	
University of Padova—Italy (1996) <sup>10</sup>	113	Pos	50 (44)	8	0	.001
		Neg	63 (56)	22	19	
Mayo Clinic (1995) <sup>9</sup>	174	Pos	98 (56)	NR	1	.001
		Neg	76 (44)	NR	14	
Memorial Sloan-Kettering Cancer Center (1993) <sup>5</sup>	146	Pos	69 (47)	NR	9	.006
		Neg	77 (53)	NR	35	

\*Not significant on multivariate analysis.

Abbreviations: Pos, positive; Neg, negative; NR, not reported.

occult metastases to regional lymph nodes identified in patients with resectable primary tumors, most surgeons do not perform random lymph node sampling for frozen-section analysis at the time of operation. However, in a high-risk patient (advanced age, significant medical comorbidities, high serum level of carbohydrate antigen 19-9, etc.) with suspicious adenopathy, a positive regional lymph node may be viewed as a contraindication to proceeding with pancreaticoduodenectomy. The advent of endoscopic ultrasound-guided fine-needle aspiration biopsy, with associated specificity and accuracy rates approaching 100% and 90%, respectively, has made possible the diagnosis of adenocarcinoma in regional lymph nodes before surgery in selected patients; it may be useful when such knowledge would influence treatment decisions or treatment sequencing.<sup>47,48</sup>

While the *Fifth Edition* of the AJCC staging system used the N1 suffixes a and b to discriminate between single and multiple positive regional lymph nodes, no such distinction is made in the most recent edition. Nonetheless, both the number of metastatic regional lymph nodes and the total number of lymph nodes evaluated in the surgical specimen may have prognostic significance. The ratio of these 2 values (number positive/number total), designated the lymph node ratio (LNR), may improve discrimination between prognostic groupings by taking into account the extent of metastatic disease (number positive nodes), as well as the adequacy of lymphadenectomy and its pathologic analysis (total number of nodes recovered and identified in the surgical specimen). LNR has been found to be a powerful predictor of survival in patients

with colon and gastric cancer, and its use as a discriminatory tool for staging patients with pancreatic adenocarcinoma has recently been investigated. In 2 recent studies, LNR was found to be an independent predictor of poor survival; its incorporation into future staging schemes for patients with pancreatic cancer was suggested.<sup>49,50</sup>

### Surgical Margins

Because it must be applied to both surgical and nonsurgical patients, the AJCC staging system does not incorporate the status of surgical margins (R status) into its classification scheme. However, the AJCC does acknowledge the importance of objectively assessing and recording R status, and a system for pathologic assessment of the pancreaticoduodenectomy specimen is suggested in the *Sixth Edition* of the *AJCC Cancer Staging Manual*. Multiple reports have identified an association between completeness of resection and outcome, and this factor has historically been considered to have the most important prognostic value in patients with resected pancreatic cancers.<sup>4,7-13,30,51-53</sup> Several surgical margins are of importance and should be evaluated and reported at the time of pancreatic resection, including the bile duct, pancreatic, and duodenal or gastric transection margins, as well as the soft tissue margin adjacent to the SMA.<sup>1</sup> The perivascular soft tissue containing autonomic nerves adjacent to the right lateral border of the proximal SMA deserves particular attention. Variably referred to as the SMA, retroperitoneal, mesenteric, or uncinate margin, this margin should be labeled the “SMA margin” due to the greater anatomic precision of this description, which clearly distinguishes this tissue from retroperitoneal tissue anterior to the inferior vena cava or posterior to the pancreatic head.<sup>43</sup> While the pancreatic and bile duct transection margins can be re-resected if intraoperative frozen-section analysis determines that they are positive, the SMA margin cannot be re-excised if the operation was done correctly and included removal of all soft tissue to the right of this vessel. The SMA margin, therefore, represents the margin most commonly positive following pancreaticoduodenectomy.<sup>43,54</sup>

Although the implications for postoperative survival of a grossly positive (R2) margin are

obvious, the prognostic importance of a microscopically positive (R1) surgical resection is not as clear as once assumed. This is because many of the series evaluating margin status as an independent prognostic factor failed to accurately differentiate between microscopically and macroscopically incomplete resections (Table 5). Few authors have had access to margin data obtained prospectively using a standardized system for pathologic analysis of pancreaticoduodenectomy specimens. Moreover, even in studies in which exclusion of R2 resections was intended, it is unclear which margins were reported and how they were analyzed because R status cannot be retrospectively determined by the pathologist unless the surgical margins were inked appropriately and the operative note included a statement on the performance of a gross complete or incomplete resection.

Because of the importance of accurate margin assessment, the *AJCC Cancer Staging Manual* includes a recommended system for the pathologic evaluation and reporting of pancreaticoduodenectomy specimens (Figure 7). This system facilitates prospective evaluation of the status of the SMA margin of resection. The technique for assessment of the SMA margin is the same regardless of whether or not vascular resection is performed. The SMA margin, posterior to the groove of the SMV-portal vein confluence, is inked and submitted in its entirety for microscopic examination on permanent sections by sectioning the specimen perpendicular to the inked margin. The pancreatic transection margin and the common bile/hepatic duct transection margins are evaluated by examining a complete *en face* section of each margin. Final margins are recorded as negative (R0) or positive (R1) for tumor based on the absence or presence of tumor cells present at the inked SMA margin or any of the *en face* sections from the other margins. The closest microscopic approach of the tumor to the margin is recorded in millimeters. We have found that the use of a standardized report template within which all pathology reports are entered enhances the completeness of all reports and prevents inconsistencies between different pathologists.

To analyze the implications of an R1 resection on survival and recurrence using a dataset

TABLE 5 Resection Margin Status as a Prognostic Factor After Resection of Pancreatic Adenocarcinoma

Institution (Year)	No. Patients	Margin Status	No. Patients (%)	Median Survival (Months)	Five-year Survival (%)	P
MD Anderson Cancer Center (2007) <sup>43</sup>	360	R1	60 (17)	22	NR	.03*
		R0	300 (83)	28	NR	
Johns Hopkins (2006) <sup>13</sup>	1,175	R1/2	NR (42)	14	12	< .0001
		R0	NR (58)	20	21	
University of Leeds—UK (2006) <sup>53</sup>	26	R1	22 (85)	11	< 5	.01
		R0	4 (15)	37	50	
University of Amsterdam—The Netherlands (2004) <sup>7</sup>	160	R1/2	80 (50)	NR	NR	.02
		R0	80 (50)	NR	NR	
ESPAC-1 (2001) <sup>51</sup>	541	R1	101 (19)	11	NR	.006
		R0	440 (81)	17	NR	
Humboldt University—Germany (2000) <sup>11</sup>	158	R1/2	NR (37)	NR	NR	.001
		R0	NR (63)	NR	NR	
University of Naples—Italy (2000) <sup>4</sup>	75	R1/2	15 (20)	9	0	.001
		R0	60 (80)	26	23	
Rush-Presbyterian-St. Luke's (1999) <sup>8</sup>	75	R1	22 (29)	8	NR	.01
		R0	53 (71)	17	NR	
Kyoto University—Japan (1997) <sup>52</sup>	157	R1/2	70 (45)	6	NR	.001
		R0	87 (55)	12	NR	
University of Padova—Italy (1996) <sup>10</sup>	113	R1/2	19 (17)	7	0	.01
		R0	94 (83)	14	15	
Mayo Clinic (1995) <sup>9</sup>	174	R2	28 (16)	9†	0	< .05
		R0/1	146 (84)	NR	12	
Massachusetts General Hospital (1993) <sup>12</sup>	72	R1/2	37 (51)	12	0	< .05
		R0	35 (49)	20	22	
Heidelberg University—Germany (1990) <sup>30</sup>	133	R1/2	57 (43)	NR	0	< .05
		R0	76 (57)	NR	36	

\*Not significant on multivariate analysis.

†Mean survival.

Abbreviation: NR, not reported.

in which margin status was assessed and recorded in a standard fashion, Raut<sup>43</sup> studied 360 patients who underwent pancreaticoduodenectomy at our institution. Although the median survival of 300 patients who had an R0 resection was significantly different from 60 patients who had an R1 resection on univariate analysis (27.8 months versus 21.5 months,  $P = .027$ ), an R1 resection did not independently affect overall survival after controlling for other covariates. Resection margin status also was shown to have no effect on the pattern of first recurrence.

of 55%) together account for the overwhelming majority of patients who present with newly diagnosed pancreatic cancer and have a survival that is uniformly poor.<sup>55,56</sup> The patients themselves, however, represent a very diverse group, particularly if assessment is based on performance status. Moreover, while these patients are generally treated with a nonsurgical strategy that employs chemoradiotherapy and/or systemic chemotherapy alone, the cytotoxic agents and dosages, radiotherapy regimens, and sequencing of therapies employed are not standardized, and therefore, the therapeutic strategies employed vary considerably among centers and among individual physicians. For these reasons, it is difficult to identify prognostic factors for patients with advanced pancreatic cancer and to separate patients based on these factors.

#### UNRESECTABLE PANCREATIC CANCER: STAGES III AND IV

Patients with unresectable Stage III (minimum of 13%) and Stage IV disease (minimum

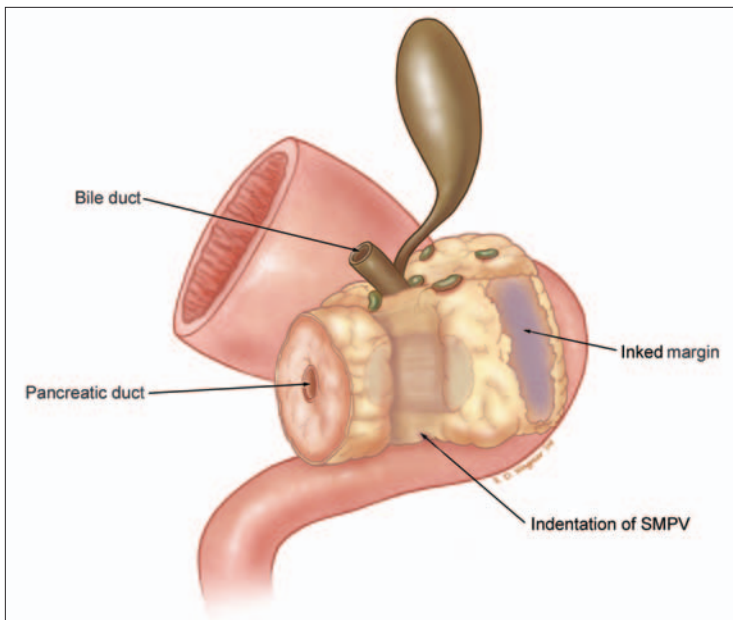


FIGURE 7 Recommended Method for Analysis of the SMA Margin. The soft tissue margin that was adjacent to the proximal SMA is inked at the time of gross evaluation of the specimen.

Abbreviations: SMA, superior mesenteric artery; SMPV, superior mesenteric-portal vein.

Adapted from Greene FL, Page DL, Fleming ID, et al.<sup>1</sup>

However, several groups have studied factors that are associated with survival duration in unresectable patients (Table 6).<sup>57–64</sup> Unfortunately, many of these studies include heterogeneous groups of both Stage III and Stage IV patients, and several studies make conclusions based on an analysis of patients on different therapeutic pathways. Initial patient performance status has been identified consistently as a prognostic factor that influences survival in patients who receive anticancer therapy. This may be due to an increased tumor aggressiveness in patients with poor performance, to an increased disease burden associated with poor performance, to an inability of patients with a poor performance status to receive a complete course of therapy, or to as yet undefined host–tumor interactions that are upset in favor of the tumor and manifested as a declining performance status.<sup>62</sup> Other factors that have been identified to have an effect on survival in advanced-stage pancreatic cancer include anemia, initial serum levels of carbohydrate antigen 19–9, and the absence of distant metastases. Nonetheless, the AJCC does not define subgroups of unresectable patients, except to classify them as locally advanced (Stage III) or

metastatic (Stage IV), as both the prognoses associated with these 2 groups and the treatment strategies afforded them differ significantly.

#### CLINICAL UTILITY OF THE AJCC STAGING SYSTEM

While the AJCC staging system is designed to accurately reflect prognosis, it also facilitates the selection of stage-specific therapies designed to maximize long-term survival while minimizing treatment-related toxicity. Ideally, such therapies should be administered only after precise determination of the stage of disease with high-quality cross-sectional imaging and a subsequent thorough evaluation by a multidisciplinary physician team experienced in the care of patients with pancreatic cancer. While under treatment, periodic restaging is essential, as a change in stage or disease extent (disease progression or response) may change the therapeutic plan.

The cornerstone of treatment for patients with resectable (Stage I/II) disease remains pancreatic resection.<sup>65,66</sup> Surgical resection is associated with prolonged survival in patients of good surgical risk and also may yield durable palliation of symptoms of biliary and gastric outlet obstruction. Although some controversy continues to exist regarding its efficacy, adjuvant therapy (chemoradiation and/or systemic therapy) is usually administered in an attempt to reduce locoregional recurrence and prolong overall survival.<sup>67–70</sup> While adjuvant therapy is traditionally administered postoperatively, several institutions, including our own, favor the use of preoperative or neoadjuvant therapy. Sequencing surgery last in the therapeutic algorithm maximizes the number of patients who receive potentially beneficial systemic therapy (as it is given first), with a reduced overall treatment time (as postoperative recovery does not delay the initiation of systemic therapy or chemoradiation). Moreover, induction therapy may spare patients with rapidly progressive disease the morbidity associated with laparotomy if disease progression is seen after neoadjuvant therapy at the time of a preoperative restaging evaluation.<sup>71,72</sup> Whenever possible, multimodality therapy should be delivered as part of a well-structured clinical trial.

TABLE 6 Prognostic Factors for Patients with Unresectable or Metastatic Pancreatic Cancer

Institution (Year)	No. Patients	Stage	Treatment	Median Survival (Months)	Significant Prognostic Factors
MD Anderson Cancer Center (2006) <sup>62</sup>	247	III	CXRT	8.5	OS: pretreatment Hb, PS DFS: PS
Ege University—Turkey (2005) <sup>63</sup>	67	III/IV	CTX	9	PS
University of Edinburgh—UK (2003) <sup>58</sup>	325	III/IV	Palliative surgery or supportive care	5.7	Absence of therapeutic intervention, CRP, leukocytosis, GGT
National Cancer Center Hospital—Japan (2001) <sup>59</sup>	55	III	CXRT	9.9	PS, CA 19-9, regional lymph node swelling
National Cancer Center Hospital—Japan (2000) <sup>64</sup>	103	IV	CTX	3.2	PS, CRP, CA 19-9
Triple-P Study Group-Multicenter Trial (2000) <sup>57</sup>	1,020	IV	Palliative surgery	NA	Jaundice
National Cancer Center Hospital—Japan (2000) <sup>60</sup>	65	III/IV	CTX	3.9	PS, CEA, absence of distant metastasis
Eastern Cooperative Oncology Group (1985) <sup>61</sup>	91	III	CXRT/CTX	8.3*	PS, anaplasia, reduced appetite

\*8.2 months for patients treated with CTX alone.

Abbreviations: CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CTX, systemic chemotherapy; CXRT, chemoradiotherapy; Hb, hemoglobin; PS, performance status; CRP, C-reactive protein; GGT, gamma-glutamyl transpeptidase; DFS, disease-free survival; OS, overall survival.

Adapted from Krishnan S, Rana V, Janjan NA, et al.<sup>62</sup>

The best treatment for patients with locally advanced, Stage III disease is still unresolved; primary treatment for such patients typically incorporates both chemoradiotherapy and systemic chemotherapy. Although such therapy rarely downstages patients to allow for surgical resection of the primary tumor, it is reasonably effective in palliating pain, and it may prolong survival. Because systemic therapy is generally better tolerated than chemoradiation, patients of good performance status with Stage III disease usually receive systemic therapy first, and chemoradiation is reserved for those with responding or stable disease, thereby limiting chemoradiation-related toxicities to those patients most likely to experience its benefits. In those patients for whom tumor-related pain is an issue, chemoradiation may be delivered early in the treatment program due to its effective palliation of pain caused by the primary tumor.

As could be expected, there is a limited role for surgery or chemoradiation in most patients with Stage IV disease. At present, good performance status patients should be treated with systemic chemotherapy and as part of a clinical trial whenever possible.<sup>24</sup>

#### CONCLUSION

Accurate staging using the *Sixth Edition* of the AJCC staging system is essential to divide patients with pancreatic adenocarcinoma into prognostic subgroups predictive of survival duration and to allow the delivery of stage-specific therapies, which ideally are protocol-based. The current AJCC staging classification emphasizes the use of clinical staging based on high-quality imaging studies and is applicable to patients with both resectable and unresectable disease. In the future, we may identify novel prognostic factors that may more accurately separate patient subsets by survival duration. At present, however, the current TNM staging system is simple to apply, has high prognostic accuracy, and facilitates the delivery of stage-specific therapy both on- and off-protocol.

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