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ORIGINAL ARTICLE – PANCREATIC TUMORS

Duodenal Involvement is an Independent Prognostic Factor for Patients with Surgically Resected Pancreatic Ductal Adenocarcinoma

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ABSTRACT

Background. The current staging system for pancreatic ductal adenocarcinoma (PDAC) includes information about size and local extension of the primary tumor (T stage). The value of incorporating any local tumor extension into pancreatic staging systems has been questioned because it often is difficult to evaluate tumor extension to the peri-pancreatic soft tissues and because most carcinomas of the head of the pancreas infiltrate the intra-pancreatic common bile duct. This study sought to evaluate the prognostic implications of having PDAC with local tumor extension.

Methods. A single-institution, prospectively collected database of 1128 patients who underwent surgical resection for PDAC was queried to examine the prognostic significance of extra-pancreatic tumor involvement ("no involvement," "duodenal involvement," and "extensive involvement"; e.g., gastric, colon or major vein involvement).

Results. The median overall survival for the patients without extra-pancreatic involvement was 26 months versus 19 months for the patients with duodenal involvement and 16 months for the patients with extensive involvement ($p < 0.001$). In the multivariable analysis, duodenal and extensive involvement independently predicted increased risk of death compared with no involvement (hazard ratio [HR] 1.30; 95% confidence interval [CI] 1.08–1.57 and 1.78; 95% CI 1.25–2.55, respectively). A multivariable model combining duodenal and extensive extra-pancreatic involvement, tumor grade, lymph node ratio, and other prognostic features had the highest *c*-index (0.67).

Conclusions. Inclusion of duodenal involvement in the staging of PDAC adds independent prognostic information.

The staging system for pancreatic ductal adenocarcinoma (PDAC) is determined by the American Joint Committee on Cancer (AJCC 7th edition) and includes information about tumor size and extension beyond the pancreas (T-stage), nodal involvement (N stage), and distant metastases (M stage).[1]

Although stage is one of the most important prognostic factors for patients with PDAC,[2] limitations of the current staging system have been identified.[3–5] Most surgical resections are performed for cancers with nodal metastases (stage 2B).[6,7] However, stage 2B cases encompass a wide spectrum of tumor burden including small cancers confined to the pancreas and cancers extending to surrounding organs but still technically resectable. In addition, all

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surgically resected node-positive PDACs are currently included in the stage 2B group regardless of the number of nodes involved. Several studies have found that incorporating the number and ratio of involved lymph nodes provides additional prognostic information.[8–12]

Another limitation to the AJCC staging system for PDACs in its current form is that T-staging requires evaluating whether the primary cancer has extended beyond the pancreas. However, unlike the thyroid and other well-encapsulated organs, the pancreas lacks an appreciable external capsule, so it often is difficult to define precisely what constitutes extension beyond the gland (T3). In addition, Saka et al.[3] recently reported a series of 223 carefully sampled Whipple specimens using a meticulous grossing protocol and demonstrated that more than 95% of the specimens presented some degree of infiltration of the distal common bile duct (CBD) and peri-pancreatic soft tissue, arguing that such a high prevalence invalidates the prognostic significance of this parameter.

Because of the challenges in defining "extra-pancreatic," a proposal has been made to disregard local tumor extension completely and instead use a tumor size-based staging system in which T stage is composed of incremental size classes as follows T1 (<2 cm), T2 (2–4 cm), and T3 (>4 cm).[3] This most recent AJCC staging system for PDAC (AJCC 8th edition) [3] was recently evaluated in a multi-institutional study of more than 2000 patients.[13] The study confirmed good reproducibility of the 8th-edition T-staging system across institutions and validated the size cutoffs proposed.

Although a size-based system is likely to facilitate reproducibility of staging, a size-based system may overlook some potentially relevant pathologic features not necessarily associated with tumor size such as duodenal invasion and more extensive direct extra-pancreatic involvement that involves the major nearby veins or adjacent organs (stomach, intestine). In this regard, a recent meta-analysis confirmed that patients who required portal vein/superior mesenteric vein resection had poorer outcomes than those who did not.[14]

In the current study, we evaluated the prognostic significance of tumor pathologic characteristics of a large single-institution series of patients who underwent surgical resection for PDAC to evaluate whether including duodenal invasion and extra-pancreatic involvement in T-staging improves the ability to predict outcome.

MATERIALS AND METHODS

The study was approved by the Johns Hopkins University Institutional Review Board. All consecutive patients who underwent pancreatic resection for PDAC at the Johns Hopkins hospital between 1994 and 2014 were examined. Clinical and demographic data, follow-up data, survival data, and available information about adjuvant therapy were retrieved from patient clinical records and from a prospectively collected surgical database. Patients with distinct pathologic subtypes of PDAC with different natural histories such as those arising from mucinous cystic neoplasm or intraductal papillary mucinous neoplasm were excluded from the study. To remove confounding effects of preoperative therapies on staging, all patients who had undergone neoadjuvant therapy also were excluded.

Pathologic Assessment

Tumor pathology information was obtained from surgical pathology reports retrieved from the Johns Hopkins surgical pathology prospective database. The AJCC 7th edition (AJCC7) staging system was used to define T, N, and M stages. Dissection of surgical resection specimens was performed in a standard fashion.[15] Tumor size was defined as the largest diameter documented in the surgical pathology report. In cases that had cancer infiltrating most of the gland, the maximum tumor diameter was greater than the average tumor diameter. Margin status was considered negative if the cancer was more than 1 mm distant from the resection margin. The pattern of extra-pancreatic tumor extension was documented (T3 by AJCC7).

To assess the prognostic implications of extra-pancreatic involvement, the patients were divided into three groups as follows: 1 (no involvement of extra-pancreatic structures), 2 (duodenal and/or ampullary involvement, hereafter referred to as "duodenal"), and 3 (extensive involvement). Duodenal involvement was defined as invasion of the muscularis propria of the duodenum.

Extensive extra-pancreatic involvement was defined as local extension to the stomach, colon, jejunum, portal vein, or superior mesenteric vein irrespective of duodenal involvement. Extension to the intra-pancreatic portion of the CBD, the peri-pancreatic soft tissue, or both was not considered in this classification. Because 16 patients (1.4%) with T3 cancers lacked documentation regarding extra-pancreatic invasion, they were excluded from further analyses. Locally advanced cancers (T4) were not included in the study.

The patients were divided into four groups based on their lymph node ratio (LNR), calculated as the number of nodes with metastatic carcinoma divided by the number of nodes examined). The four groups comprised the node-negative group (LNR = 0) and three N1 groups subclassified using the cutoff values of 0.2 and 0.4 (e.g., LNR > 0–0.2, LNR > 0.2–0.4, LNR > 0.4), as previously reported.[8] Nodal status also was classified according to

Balci et al.[16] as follows: N0 (node-negative), N1 (1–2 nodes with metastases), and N2 (3 or more nodes with metastases). Cancers also were T-staged using tumor size-based staging.[3] In this analysis, primary cancers were reclassified according to the following definitions: pT1 (<2 cm), T2 (2–4 cm), and T3 (>4 cm). A side-by-side comparison of the AJCC7 and proposed 8th edition (AJCC8) is provided (electronic Table S1).

Statistical Analyses

Patient and tumor characteristics are presented as mean ± standard deviation, and continuous variables as median and range, and compared using Wilcoxon rank-sum tests. Categorical variables are presented as frequency and percentage and compared using Fisher's exact test or the Chi square test, when appropriate.

Overall survival was defined as the time from the date of surgery to the date of death. Patients who had experienced mortality within 30 days after surgical resection were removed from survival analysis. Survival times were estimated using the Kaplan–Meier method and compared using the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) and median survival were estimated using the multivariable Cox proportional hazards model adjusted for competing factors. The Cox models also were used to test for interactions between pattern of local involvement and effect of nodal status on overall survival. The predictive ability of each survival model was measured using the Concordance Index. All statistical analyses were performed using R (R Core Team-2014; R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org).

RESULTS

Patient Clinicopathologic Characteristics

Prognostic analysis was performed for the entire study cohort (1128 cases) (electronic Table S2) and for cases involving the pancreatic head (925 cases) (Table 1). Demographic profiles were similar across T stages. The clinical and pathologic features of the patients stratified by their extra-pancreatic tumor status are presented in electronic Table S3 (presenting all patients) and Table S4 (presenting head-only cancers). Duodenal involvement was present in 510 patients (45.2%) and extensive extra-pancreatic involvement in 79 patients (7%). Of the 1128 cases, 523 (46%) had no evidence of duodenal or extensive extra-pancreatic invasion. Duodenal involvement was detected only in cases that had pancreatic head involvement.

Prognostic Significance of Local Extra-pancreatic Tumor Spread

According to univariate log-rank analysis, the median overall survival of the entire cohort was 23 months (Table 2). The patients without any extra-pancreatic involvement had a median overall survival of 26 months versus 19 months for the patients with duodenal involvement and 16 months for the patients with extensive extra-pancreatic involvement ($p < 0.001$). Among the patients with nodal involvement (N1), those without any extra-pancreatic involvement had better survival than those with duodenal-only or extensive extra-pancreatic involvement (24 vs 18 and 15 months; $p = 0.0068$). The patients who had N0 cancers without duodenal involvement tended to have better overall survival than those with duodenal involvement or extensive extra-pancreatic involvement, although the difference was not statistically significant with our sample size (42 vs 29 and 27.5 months; $p = 0.44$).

Median overall survival was compared according to the AJCC7 and the proposed AJCC8 T-staging system (Table 2). The median overall survival among the patients whose cancers were staged as T1, T2, and T3 (AJCC7) was 64, 30, and 20 months, respectively ($p < 0.001$). In contrast, the median overall survival using AJCC8 was 27, 24, and 15 months for T1, T2, and T3 cancers, respectively ($p < 0.001$).

The pattern of extra-pancreatic cancer spread then was incorporated into the current tumor-node-metastasis (TNM) staging to evaluate whether a partition of T stage would highlight survival differences among subgroups (electronic Table S5). Among the patients without extra-pancreatic involvement, those with AJCC7 T1 and T2 stage cancers had better median overall survival than the patients with T3 cancers (64 vs 30 vs 23 months, respectively) ($p < 0.0001$). The patients who had AJCC7 T3 cancers with duodenal involvement or extensive extra-pancreatic involvement showed worse median overall survival than those without these features (19 and 16 months, respectively) ($p < 0.0001$; electronic Table S5; Fig. 1).

A multivariable model was developed to assess whether extra-pancreatic spread would remain a predictor of overall survival after adjustment for other clinical and pathologic variables associated with outcome including tumor size, nodal status, margin status, use of adjuvant therapy, treatment period (1994–2004 vs 2005–2014), and other factors (model 1, Table 3). The patients whose cancer had duodenal or extensive extra-pancreatic involvement experienced significantly poorer survival than the patients without any extra-pancreatic involvement (duodenal involvement vs no involvement: HR 1.33; 95% CI 1.10–1.60; $p = 0.003$; extensive extra-pancreatic involvement vs no involvement: HR 1.73; 95% CI 1.25–2.55; $p = 0.003$). In

TABLE 1 Patient and tumor characteristics for the head of pancreas PDACs

	All patients ($n = 925$) n (%)	T1 ($n = 39$) n (%)	T2 ($n = 86$) n (%)	T3 ($n = 800$) n (%)	p value
Mean age (years)	66.37 ± 10.76	66.97 ± 9.26	67.36 ± 9.73	66.23 ± 10.93	0.611
Gender					
Female	437 (47.2)	19 (48.7)	47 (54.7)	371 (46.4)	0.363
Male	488 (52.8)	20 (51.3)	39 (45.3)	429 (53.6)	
Type of surgery					
Whipple	910 (98.4)	39 (100)	84 (97.7)	787 (98.4)	0.817
Total	15 (1.6)	0 (0)	2 (2.3)	13 (1.6)	
Median tumor size (range)	2.8 (1–8.5)	1.7 (1.2–2)	3 (2.1–6)	3 (1–8.5)	<0.001
Pathology grade					
1	28 (3)	3 (7.7)	4 (4.7)	21 (2.6)	0.005
2	503 (54.6)	29 (74.4)	47 (55.3)	427 (53.5)	
3–4	391 (42.4)	7 (17.9)	34 (40)	350 (43.9)	
Unknown	3	0	1	2	
N stage					
N0	173 (18.7)	21 (53.8)	33 (38.4)	119 (14.9)	<0.001
N1	752 (81.3)	18 (46.2)	53 (61.6)	681 (85.1)	
Median positive nodes (range)	3 (0–20)	0 (0–15)	2 (0–18)	3 (0–20)	<0.001
Median total nodes (range)	19 (0–74)	17 (6–38)	21 (3–53)	19 (0–74)	0.02
Nodal ratio					
Node-negative (0)	173 (18.7)	21 (53.8)	33 (38.4)	119 (14.9)	<0.001
0–0.2	407 (44)	14 (35.9)	34 (39.5)	359 (44.9)	
0.2–0.4	218 (23.6)	3 (7.7)	16 (18.6)	199 (24.9)	
>0.4	127 (13.7)	1 (2.6)	3 (3.5)	123 (15.4)	
Stage					
1A	21 (2.3)	21 (53.8)	0 (0)	0 (0)	<0.001
1B	33 (3.6)	0 (0)	33 (38.4)	0 (0)	
2A	119 (12.9)	0 (0)	0 (0)	119 (14.9)	
2B	752 (81.3)	18 (46.2)	53 (61.6)	681 (85.1)	
AJCC T stage, 8th ed					
T1	137 (14.8)	24 (61.5)	0 (0)	113 (14.1)	<0.001
T2	664 (71.8)	15 (38.5)	79 (91.9)	570 (71.2)	
T3	124 (13.4)	0 (0)	7 (8.1)	117 (14.6)	
AJCC N stage, 8th ed					
N0	173 (18.7)	21 (53.8)	33 (38.4)	119 (14.9)	<0.001
N1	388 (41.9)	14 (35.9)	30 (34.9)	344 (43)	
N2	364 (39.4)	4 (10.3)	23 (26.7)	337 (42.1)	
Margin status					
R0	642 (69.4)	33 (84.6)	64 (74.4)	545 (68.1)	0.047
R1	283 (30.6)	6 (15.4)	22 (25.6)	255 (31.9)	
Vascular invasion	496 (53.6)	15 (38.5)	42 (48.8)	439 (54.9)	0.075
Perineural invasion	820 (88.6)	36 (92.3)	78 (90.7)	706 (88.2)	0.718

PDAC pancreatic ductal adenocarcinoma, *AJCC* American Joint Committee on Cancer

addition, nodal status, patient age at surgery, resection margin status, year of surgery, and treatment period (survival has improved in the last decade) also were independent prognostic factors. The *c*-index for this model (model 1 incorporating duodenal involvement, extra-pancreatic involvement, nodal status, patient age, resection

TABLE 2 Overall survival for the entire cohort, and by American Joint Committee on Cancer (AJCC) 7th ed, and involvement type

	n	Median (95% CI)	6-month OS (95% CI)	1-year OS (95% CI)	2-year OS (95% CI)	*p* value (log rank)
All patients[a]	1103	23 (21–25)	89 (87–91)	72 (69–75)	47 (45–51)	
Involvement						
None	517	26 (24–32)	91 (88–93)	77 (73–81)	53 (49–58)	<0.0001
Duodenal	507	19 (18–23)	88 (85–91)	69 (65–73)	43 (39–47)	
Extensive	79	16 (14–25)	86 (79–94)	63 (54–75)	39 (29–51)	
Involvement, N0						
None	165	42 (30–59)	95 (91–98)	83 (77–89)	63 (56–70)	0.4376
Duodenal	60	29 (23–39)	93 (87–100)	83 (74–93)	54 (43–69)	
Extensive	16	27.5 (15–199+)	94 (83–100)	75 (57–100)	56 (37–87)	
Involvement, N1						
None	352	24 (21–29)	89 (85–92)	74 (69–79)	49 (44–55)	0.0068
Duodenal	447	18 (17–20)	87 (84–90)	67 (62–71)	41 (37–46)	
Extensive	63	15 (12–23)	84 (76–94)	60 (49–74)	34 (24–49)	
AJCC 8th ed T stage						
T1	151	27 (23–42)	95 (92–99)	80 (74–87)	54 (47–63)	<0.0001
T2	778	24 (22–26)	89 (87–92)	74 (71–77)	50 (46–53)	
T3	190	15 (13–18)	81 (76–87)	57 (51–65)	33 (27–41)	
AJCC 8th ed T stage, N0						
T1	43	41 (25–85)	95 (89–100)	84 (73–96)	65 (52–81)	0.1539
T2	176	37 (29–49)	95 (92–99)	84 (78–89)	61 (54–69)	
T3	24	20 (15–199+)	83 (70–100)	71 (55–92)	45 (28–70)	
AJCC 8th ed T stage, N1						
T1	108	24 (21–39)	95 (91–99)	79 (71–87)	50 (41–60)	6.00E−04
T2	602	22 (19–25)	88 (85–90)	71 (68–75)	46 (42–50)	
T3	166	14 (12–18)	81 (75–87)	55 (48–64)	32 (25–40)	
AJCC 7th ed T stage						
T1	53	64 (50–231+)	96 (91–100)	92 (86–100)	79 (69–91)	<0.0001
T2	175	30 (24–63)	91 (87–95)	78 (72–85)	56 (49–64)	
T3	891	20 (19–23)	88 (86–90)	69 (67–73)	44 (41–47)	
AJCC 7th ed T stage, N0						
T1	30	52 (26–199+)	93 (85–100)	87 (75–100)	77 (63–93)	0.0065
T2	68	69 (41–199+)	99 (96–100)	88 (81–96)	69 (58–81)	
T3	145	26 (23–35)	92 (88–97)	79 (72–86)	53 (45–62)	
AJCC 7th ed T stage, N1						
T1	23	NR	100 (100–100)	100 (100–100)	82 (67–100)	<0.0001
T2	107	23 (18–35)	86 (80–93)	72 (64–81)	49 (40–59)	
T3	746	19 (18–22)	87 (85–90)	68 (64–71)	42 (39–46)	

Estimates for median survival are in months. Other values are survival probability and 95% confidence intervals

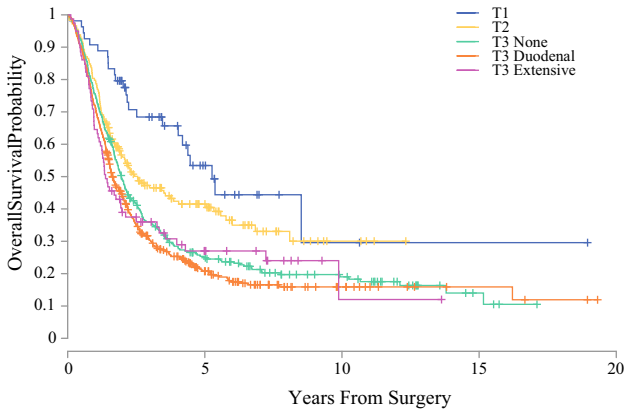
OS overall survival, *CI* confidence interval

[a] Does not include patients who experienced postoperative mortality within 30 days after surgery

margin status, and year of surgery) was 0.6546. We also stratified cases by tumor size (0–2, 2–4, and >4 cm) and compared survival by Kaplan-Meir analysis (electronic Fig. S1; Table S6).

In addition, we analyzed two multivariable models for overall survival, stratified by nodal status (electronic Table S7). No interaction was observed, suggesting that the effect of involvement on overall survival was independent of nodal status.

Two additional models were developed to evaluate the prognostic utility of duodenal and extensive extra-pancreatic involvement together with LNR (model 2) rather than an N0/N1 classification and T-staging by size using the proposed AJCC8 staging system (model 3) (electronic



	N	Events	N	Events	N	Events	N	Events
T1	54	21	14	3	2	0	1	0
T2	178	97	40	7	4	0	0	0
T3 None	291	213	61	12	27	4	4	1
T3 Duodenal	510	383	63	12	14	0	4	1
T3 Extensive	79	55	13	2	1	0	0	0

FIG. 1 Overall survival by American Joint Commission on Cancer (AJCC) 7th edition T stage of 1103 patients who underwent resection for pancreatic ductal adenocarcinoma. Type of extra-pancreatic cancer involvement was incorporated into the T3-stage group

Table S8). The inclusion of LNR resulted in only a slightly improved c-index (0.6681), compared with model 1, despite the strong association of LNR with prognosis (HR 2.46; 95% CI 1.77–3.42; $p < 0.001$ for patients with LNR >0.4 vs LNR of 0). Including the AJCC8 T-staging-by-size system together with duodenal involvement and extra-pancreatic involvement in the model yielded a *c*-index (0.66) similar to that in models 1 and 2.

Predictive Ability of the Current and Revised Staging Systems

The predictive performance of the AJCC7 and AJCC8 editions was evaluated with the entire cohort of patients and compared with a staging system in which extra-pancreatic cancer invasion (either duodenal or extensive extra-pancreatic) was incorporated into the 7th edition system to stratify patients with T3 stage (electronic Table S9). The N-staging also was modified using the definitions proposed in the 8th-edition system.

The AJCC7 T3N0 pancreatic cancers with duodenal only or extensive extra-pancreatic involvement had survival similar to that of AJCC7 stage 2B cancers (Table 2). The patients who had T3N1 pancreatic cancers with duodenal only and/or extensive extra-pancreatic involvement had worse average survival than those without such involvement and thus could potentially be upgraded to a new stage category (stage 2C). The patients with N2 cancers had average survival similar to that of AJCC7 stage 3 cancers regardless whether they had duodenal or extra-pancreatic involvement or not. Additional results are provided in supplemental materials.

The hazard ratios for overall survival obtained from each staging system are presented in Table 4. The c-indices for the AJCC7, AJCC8, and our alternative staging system that includes duodenal and extensive involvement and three tier nodal staging were 0.56, 0.59, and 0.60 respectively.

DISCUSSION

Recent evidence indicates that the 7th AJCC staging system has imperfect prognostic ability and needs improvements.[3] Ambiguity in the T-staging definitions is one of the main limitations of the current staging system (AJCC7). The two parameters used to determine T-staging are primary tumor size and extra-pancreatic tumor spread. However, the determination of some components of extra-

TABLE 3 Hazard ratios and concordance index from a single multivariable model for overall survival (model 1)

	HR	95% CI	*p* value	*c*-index
Duodenal vs no involvement	1.33	(1.08–1.57)	0.003	0.6546
Extensive vs no involvement	1.73	(1.25–2.55)	0.003	
Node-positive vs node-negative	1.41	(1.14–1.84)	0.005	
Tumor size	1.17	(1.07–1.24)	<0.001	
Age	1.02	(1.01–1.02)	<0.001	
Male vs female	1.02	(0.88–1.25)	0.84	
R1 vs R0 margin	1.44	(1.19–1.73)	<0.001	
Adjuvant therapy: yes vs no	0.83	(0.66–1.11)	0.16	
Perineural invasion: yes vs no	1.51	(1.13–2.06)	0.007	
Vascular invasion: yes vs no	1.07	(0.86–1.25)	0.48	
Grade: 3/4 vs 1/2	1.36	(1.12–1.6)	0.001	
Year of surgery: 2005–2014 vs 1994–2004	0.75	(0.63–0.9)	0.002	

HR hazard ratio, *CI* confidence interval

TABLE 4 Hazard ratios from multivariable models for overall survival determined by different American Joint Committee on Cancer (AJCC) classifications systems

	HR	95% CI	*p* value	*c*-index
AJCC 7th ed				
1B (ref = 1A)	1	(0.55–1.81)	0.84	0.5576
2A	1.53	(0.9–2.6)	0.08	
2B	1.97	(1.2–3.23)	0.008	
Year of surgery: 2005–2014 vs 1994–2004	0.74	(0.64–0.85)	<0.001	
AJCC 8th ed				
1B (ref = 1A)	0.95	(0.63–1.43)	0.95	0.5936
2A	1.51	(0.83–2.74)	0.17	
2B	1.27	(0.87–1.84)	0.21	
3	1.91	(1.31–2.79)	<0.001	
Year of surgery: 2005–2014 vs 1994–2004	0.72	(0.62–0.82)	<0.001	
Revised AJCC				
1B (ref = 1A)	0.96	(0.64–1.44)	0.83	0.6024
2A	1.48	(0.68–3.23)	0.33	
2B	1.21	(0.83–1.76)	0.32	
2C	2.32	(1.44–3.79)	<0.001	
3	1.92	(1.32–2.8)	<0.001	
Year of surgery: 2005–2014 vs 1994–2004	0.71	(0.61–0.82)	<0.001	

HR hazard ratio, *CI* confidence interval

pancreatic spread is either not very reproducible (infiltration beyond the pancreas into extra-pancreatic tissues) or of limited value (CBD involvement). Removing these factors from the T-staging system and relying on tumor size alone creates a more reproducible system but may not account for other prognostic aspects of T stage that are quite reproducible.

We find that including duodenal invasion and extensive extra-pancreatic involvement in T-staging would improve prognostication. Unlike the evaluation of spread into peripancreatic soft tissue, diagnosing carcinomatous infiltration of the duodenum or ampulla is straightforward and should be highly reproducible among pathologists. Although larger cancers are more likely to invade extra-pancreatic structures, small cancers often have duodenal or extensive extra-pancreatic involvement. Approximately 42% of the PDACs in our series classified as T1 and 52% of all T2 PDACs using the AJCC8 had duodenal or extensive extra-pancreatic involvement.

The value of using duodenal/ampullary involvement in a future staging system would be particularly helpful for patients with a diagnosis of stage 2B disease, who represent the vast majority of all surgically resected patients.[7] In our analysis, the patients who had AJCC7 T3 PDAC without duodenal or extensive extra-pancreatic invasion experienced a median overall survival of 23 months, significantly longer than those with T3 duodenal involvement (19 months) or T3 extensive extra-pancreatic involvement (16 months). Although previous findings show that patients with PDACs extensively involving extra-pancreatic organs have reduced survival.[17–19] the independent prognostic significance of duodenal involvement has not been determined.

Interestingly, the 7th and the 8th AJCC staging systems had concordance indices of 0.55 and 0.59, respectively, similar to those reported by Allen et al.[13] Adding duodenal involvement and extra-pancreatic involvement to a revised 8th-edition staging system did modestly improve prognostic accuracy (*c*-index, 0.60). Generally, TNM staging classifications of cancer use only reproducible T, N, and M variables without any additional prognostic pathologic variables, but there may be a role for expanding the prognostic parameters used to stage PDAC such as margin status, LNR, and perineural invasion. We found the prognostic model with the highest concordance index included these parameters as well as patient age (*c*-index, 0.67). It is not surprising that a TNM-based PDAC staging system would not be sufficient to predict prognosis optimally. Staging systems based on TNM do not include well-known factors that influence patient prognosis such as patient comorbidities and overall performance status,[20] the presence of micrometastases, certain molecular alterations (e.g., *SMAD4* mutations),[21,22] and tumor response to therapy (because certain mutational profiles predict response to therapy even for PDAC).[23,24]

It is important that the independent prognostic significance of duodenal invasion and extensive extra-pancreatic involvement be confirmed in other cohorts before it is incorporated into any revised TNM staging system of PDAC.

In conclusion, we find that inclusion of duodenal invasion and extensive extra-pancreatic involvement adds additional prognostic information to the proposed AJCC staging system for patients with resected PDAC.

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