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Validation of the American Joint Committee on Cancer 8th edition staging system for the pancreatic ductal adenocarcinoma

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ABSTRACT

Background & aims: The American Joint Commission on Cancer (AJCC) 8th edition staging system for pancreatic ductal adenocarcinoma (PDA) contains several significant changes. This study aimed to validate the AJCC 8th edition staging system of PDA.
Methods: We analyzed patients with resected PDA between 2001 and 2017 using the Korean Pancreatic Cancer (K-PaC) registry. Overall survival (OS) was estimated using the Kaplan-Meier survival curves and compared via the log-rank test.
Results: In total, 701 resected PDA patients were identified. During a median follow-up of 24.5 months, the median OS was 21.7 months. Meanwhile, the median OS of each stage according to the AJCC 8th edition was 73.5 months (stage IA), 41.9 months (stage IB), 24.2 months (stage IIA), 18.3 months (stage IIB), and 16.8 months (stage III). However, the new N-category (pN1 vs. pN2) did not subdivide prognosis, although the lymph node ratio (i.e., the ratio of the number of LN involved to the number of examined LN) did. Although pT3 and pN2 belong under stage III, pN2 has a significantly longer median OS than pT3 (16.9 months vs 11.2 months; $p < 0.01$).
Conclusion: The AJCC 8th edition staging system appropriately stratifies the prognosis of PDA patients. However, the cutoff of the N-category is not statistically valid, and the new stage III includes a heterogeneous category (pN2 and pT4). Therefore, we propose that stage III be divided into stage IIIA (Tany N2 M0) and stage IIIB (T4 Nany M0).

Introduction

In 2018, 55,440 new cases of pancreatic ductal adenocarcinoma (PDA) were diagnosed in the United States. PDA is the fourth leading cause of cancer-related death, accounting for 7% of the cancer mortality rates; approximately 23,020 men and 21,310 women died from PDA in the United States in 2018 [1]. Despite numerous clinical studies, PDA remains to have dismal prognosis, with a 5-year survival rate of less than 10% in all stages [1,2]. Moreover, accurately predicting prognosis is more crucial in the management of PDA.

The American Joint Commission on Cancer (AJCC) developed an internationally applicable TNM staging system comprising three factors: tumor size (T), whether or not the cancer cell is present in adjacent lymph nodes (LNs) (N), and whether or not the metastasis has spread to distant area (M) [3]. This staging system is currently used to determine the appropriate treatment modality (surgery or chemotherapy) and predict prognosis. The system has been

Abbreviations: AJCC, American Joint Commission on Cancer; HR, hazard ratio; K-PaC registry, Korean Pancreatic Cancer Registry; LN, lymph node; LNR, lymph node ratio; NCC, National Cancer Center; OS, overall survival; PDA, pancreatic ductal adenocarcinoma; SD, standard deviation; SNUBH, Seoul National University Bundang Hospital; TNM, tumor-node-metastasis; 95% CI, 95% confidence interval.

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continually revised, and the AJCC 8th edition TNM staging system, which includes significant changes compared to the 7th edition, was published in October 2016 [4,5]. The two most important changes in PDA staging in the AJCC 8th edition are the new definitions of the T- and N-category (Table 1). (1) The T-category of the 7th edition was controversial because the patient's prognosis could not be adequately stratified. In particular, pT3, defined as "a tumor that extends beyond the pancreas," was difficult to assess, and there were many inconsistencies among pathologists [6]. In the AJCC 8th edition, the guideline for the new T-category classifies PDA strictly by size only, regardless of the extrapancreatic invasion, except in the case of large vascular infiltrates classified as pT4 tumors. These changes are aimed at improving the reproducibility of the T-category by reducing the number of tumors classified as pT3. (2) The previous node-positive pN1 category has been subdivided into pN1 (1-3 metastatic LNs) and N2 (4 or more metastatic LNs).

The purpose of this study was to investigate whether the AJCC 8th edition staging system is clinically relevant and to validate the newly developed N-category, particularly if pN2 versus pT4 PDA can be categorized as stage III, using a Korean Pancreatic Cancer (K-PaC) registry.

Methods

Patient and data collection

We recently launched a multicenter, web-based registry called the Korean Pancreatic Cancer (K-PaC) registry. This database contains information on demographic, radiologic, and pathologic characteristics; blood test results; treatment modality (surgery, chemotherapy, and radiotherapy); recurrence; and death of 1,609 PDA patients (2003-2017) from Seoul National University Bundang Hospital (SNUBH) and 2,139 PDA patients (2001-2017) from the National Cancer Center (NCC). The registry was a retrospectively collected database initially. After completing the analysis of retrospective data in 2017 using the electronic case report form, we are prospectively following up with patients and collecting newly-diagnosed patients' data. The K-PaC registry was approved by the Institutional Review Boards (IRB) of the two institutions (IRB number of SNUBH Medical Ethics: B-1804/463-104; IRB number of the NCC Ethics Committee: NCC2018-0054).

In this study, we retrieved the clinical data of PDA patients who underwent curative-intent pancreatectomy from the K-PaC registry. The inclusion criteria were: (a) pathologically proven PDA; (b) underwent curative-intent pancreatectomy; and (c) without neo-adjuvant treatment.

Pathologic review based on the modified AJCC staging system

We reviewed the pathologic record of surgical specimens including the tumor size, the number of resected LNs, the number of metastatic LNs, and the extent of invasion. The size of the tumor was defined as the maximum length measured via pathological gross examination. The LN ratio (LNR) was calculated by dividing the number of metastatic nodes by the total number of resected nodes. The "margin positive" was defined as the presence of cancer cells within 1 mm of the resection margin. The patients with PDA were categorized into the following three groups according to the resection margin status: R0, no cancer cells at the resection margin (at least a 1 mm tumor-free margin); R1, cancer cells are visible microscopically within 1 mm of the resection margin; and R2, cancer cells present on gross examination [7]. Based on this information, the pathological stage of each PDA patient was determined according to the AJCC 7th and 8th edition staging systems (Table 1). The new T-category (AJCC 8th edition) is defined as follows: pT1, $\leq$ 2 cm in maximal diameter; pT2, $>$ 2 cm but $\leq$ 4 cm; pT3, $>$ 4 cm; pT4, locally unresectable due to involvement of major arteries (the celiac axis or the superior mesenteric artery). Extrapancreatic extension was excluded from this new T-category. Meanwhile, the new N-category is defined as follows: pN0, no LN involvement; pN1, 1-3 involved regional LNs; and pN2, 4 or more involved regional LNs. In addition, pN2 patients are classified to have stage III disease regardless of tumor size (Table 1).

Statistical analyses

Continuous variables are presented as mean $\pm$ standard deviation (SD) and categorical variables as frequency and proportion. Continuous variables with normal distributions were analyzed using Student's t-test. Overall survival (OS) was calculated from the date of pathologic diagnosis to death or the last follow-up date. Survival time was estimated using Kaplan-Meier survival curves and compared using the log-rank test. Correlations between clinicopathological factors and patient survival were assessed using

Table 1
Comparison of American Joint Committee on Cancer (AJCC) 7th and 8th edition staging system for PDA.

	Primary tumor (T-category)	Regional lymph node (N-category)	Distant metastasis (M-category)	Stage
AJCC 8th edition	T1, Maximum tumor diameter $\leq$ 2 cm	N0, No regional LN metastasis	M0, No distant metastasis	Stage IA, T1 N0 M0
	T2, Maximum tumor diameter $>$ 2 cm, but $\leq$ 4 cm	N1, Metastasis in 1–3 regional LNs	M1, Distant metastasis	Stage IB, T2 N0 M0
	T3, Maximum tumor diameter $>$ 4 cm	N2, Metastasis in $\geq$4 regional LNs		Stage IIA, T3 N0 M0
	T4, Tumor involves the CA or the SMA (unresectable primary tumor)			Stage IIB, T1-3 N1 M0 Stage III, AnyT N2 M0, T4 AnyN M0 Stage IV, AnyT AnyN M1
AJCC 7th edition	T1, Tumor limited to the pancreas, $\leq$ 2 cm in maximal diameter	N0, No regional LN metastasis	M0, No distant metastasis	Stage IA, T1 N0 M0
	T2, Tumor limited to the pancreas, $>$ 2 cm in maximal diameter	N1, Regional LN metastasis	M1, Distant metastasis	Stage IB, T2 N0 M0
	T3, Tumor extends beyond the pancreas but without involvement of the CA or the SMA			Stage IIA, T3 N0 M0
	T4, Tumor involves the CA or the SMA (unresectable primary tumor)			Stage IIB, T1-3 N1 M0 Stage III, T4 AnyN M0 Stage IV, AnyT AnyN M1

Abbreviations: AJCC, American Joint Committee on Cancer; PDA, pancreatic ductal adenocarcinoma; CA, celiac axis; SMA, superior mesenteric artery; LN, lymph node.

univariate analyses. A Cox proportional hazard model was used to compute hazard ratios. All statistical analyses were performed using IBM SPSS, version 22 for Windows (IBM Inc., US) and R version 3.2.3 (The R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org). A two-sided *p*-value of < 0.05 was considered statistically significant.

Results

Baseline characteristics

Of the 3,748 PDA patients enrolled in the K-PaC registry, 815 patients underwent pancreatectomy (Fig. 1). Among them, 114 patients who underwent neoadjuvant chemotherapy/radiotherapy or who had peritoneal metastasis during surgery were excluded from the analysis. Finally, the clinical data of 701 PDA patients were reviewed and analyzed.

The demographic characteristics of the included patients are shown in Table 2. The median age was 65.4 years, and 405 (57.8%) patients were male. The median body mass index was 22.5 kg/m^2. The median values of the tumor markers at the time of diagnosis was 37.3 ng/mL for carcinoembryonic antigen (CEA) and 650.4 U/mL for carbohydrate antigen 19-9 (CA 19-9). Of the 701 patients, 441 (62.9%) underwent pancreaticoduodenectomy (pylorus-sparing pancreaticoduodenectomy, 315 (44.9%); Whipple procedure, 126 (18.0%)) and the remaining 37.1% underwent distal pancreatectomy. The median tumor size was 3.0 cm (range, 0.3–14.0 cm), and 544 (77.6%) of the patients had moderately differentiated malignancies. The average number of harvested LNs per patient was 21.3 (range, 1-46), and the average number of metastatic LNs per patient was 2.4 (range, 0-12). Majority (63.6%) of patients had an LNR of 0.01–0.35, while 31% and 5.4% had LNR of 0 and ≥ 0.35, respectively.

Table 2
Baseline clinicopathological characteristics of the 701 PDA patients who underwent pancreatectomy.

Characteristics	All patients (n = 701)
Age, mean ± SD (yrs)	65.4 ± 10.1
18-59, n (%)	182 (26.0%)
60-75, n (%)	388 (55.3%)
>76, n (%)	131 (18.7%)
Male, n (%)	405 (57.8%)
Height, mean ± SD (cm)	160.8 ± 9.0
Weight, mean ± SD (kg)	58.4 ± 10.3
BMI, mean ± SD (kg/m^2)	22.5 ± 3.1
BSA, mean ± SD (m^2)	1.6 ± 0.2
CEA, mean ± SD (ng/mL)	37.3 ± 563.5
CA 19-9, mean ± SD (U/mL)	650.4 ± 2654.9
Type of surgery, n (%)	
PPPD	315 (44.9%)
Whipple's operation	126 (18.0%)
Distal pancreatectomy	260 (37.1%)
Median tumor size (cm)	3.0 ± 1.8
Grade of differentiation	
Well differentiated	67 (9.6%)
Moderately differentiated	544 (77.6%)
Poorly differentiated	90 (12.8%)
Number of resected LNs	21.3 ± 11.8
Number of metastatic LNs	2.4 ± 3.1
Positive LN ratio	
0	217 (31.0%)
0.01–0.35	446 (63.6%)
>0.35	38 (5.4%)
Resection margin	
R0	590 (84.2%)
R1	111 (15.8%)

Abbreviations: PDA, pancreatic ductal adenocarcinoma; SD, standard deviation; BMI, body mass index; BSA, body surface area; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; PPPD, pylorus-sparing pancreaticoduodenectomy; LN, lymph node; R0, no cancer cells seen microscopically at the resection margin; R1, cancer cells present microscopically at the resection margin.

Overall survival for TNM staging

Table 3 shows the stage at which PDA patients in the K-PaC registry were classified according to the protocols of AJCC 7th and 8th edition. In addition, the survival time of patients in each group was represented (Fig. 2(a) and (b)). During a median follow-up of 24.5 months, the median OS for all 701 PDA patients was 21.7 months. According to the AJCC 7th edition, only 20 (2.9%) patients and 13 (1.9%) patients had stage IA and IB, respectively, and most patients had stage II (stage IIA, 180 (25.7%); stage IIB, 474 (67.6%)). Meanwhile, according to the AJCC 8th edition, 55 (7.8%), 129 (18.4%), 29 (4.1%), 304 (43.4%), and 184 (26.2%) had stage IA, IB, IIA, IIB, and III, respectively. Moreover, the median OS according to the AJCC 8th edition staging system was as follows: stage IA, 73.5 months; stage IB, 41.9 months; stage IIA, 24.2 months; stage IIB, 18.3 months; and stage III, 16.8 months, with significant difference with that according to the 7th edition ($p < 0.01$). The risk of death was significantly higher for stage IIA [hazard ratio (HR), 2.466; 95% CI, (1.224–4.970; $p = 0.01$], IIB (HR, 2.956; 95% CI, 1.864–4.688; $p < 0.01$) and III (HR, 3.656; 95% CI, 2.283–5.856; $p < 0.01$) than for stage IA. The distribution of the PDA stage according to the 7th and 8th edition of the AJCC is shown in Supplement table. Majority of patients had stage IIB disease (67.6% in the 7th edition and 43.4% in the AJCC 8th edition).

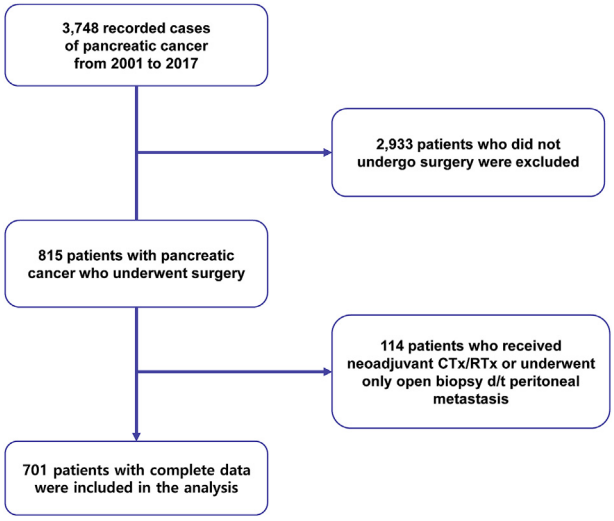

Fig. 1. Flowchart of the study.

Overall survival for T- and N-category

According to the T-category of the AJCC 7th edition, most of the patients (648 patients, 92.4%) had pT3, while 18 (2.6%) and 14 (2.0%) had pT2 and pT4, respectively. The median OS of each T-category was as follows: pT2, 101.2 months; pT3, 21.3 months; and pT4, 13.8 months. The small number of patients with pT1 and pT2 resulted to no significant difference in survival between these patients ($p = 0.55$; Table 3 and Fig. 2(c)). Patients with pT3 in the AJCC 7th edition were categorized according to tumor size from pT1 to pT3 in the AJCC 8th edition. According to the new T-category, there were 90 (12.8%) pT1 tumors, 457 (65.2%) pT2 tumors, 140 (20.0%)

Table 3
Comparison of staging and median OS of PDA patients based on the AJCC 7th and the 8th edition staging system.

Characteristics	AJCC 7th edition				AJCC 8th edition			
	n (%)	Median OS (months)	HR (95% CI)	*p*-value	n (%)	Median OS (months)	HR (95% CI)	*p*-value
Stage, n (%)								
Stage IA	20 (2.9%)	-	1 (reference)		55 (7.8%)	73.5	1 (reference)	
Stage IB	13 (1.9%)	92.6	1.010 (0.271–3.762)	0.99	129 (18.4%)	41.9	1.502 (0.909–2.480)	0.11
Stage IIA	180 (25.7%)	39.3	2.231 (0.906–5.494)	0.08	29 (4.1%)	24.2	2.466 (1.224–4.970)	0.01
Stage IIB	474 (67.6%)	18.0	4.418 (1.825–10.699)	<0.01	304 (43.4%)	18.3	2.956 (1.864–4.688)	<0.01
Stage III	14 (2.0%)	13.8	8.019 (2.853–22.544)	<0.01	184 (26.2%)	16.8	3.656 (2.283–5.856)	<0.01
T-category, n (%)								
pT1	21 (3.0%)	-	1 (reference)		90 (12.8%)	40.8	1 (reference)	
pT2	18 (2.6%)	101.2	0.828 (0.253–2.715)	0.76	457 (65.2%)	23.2	1.816 (1.299–2.539)	<0.01
pT3	648 (92.4%)	21.3	3.067 (1.369–6.872)	0.01	140 (20.0%)	15.1	2.839 (1.961–4.111)	<0.01
pT4	14 (2.0%)	13.8	6.634 (2.516–17.190)	<0.01	14 (2.0%)	13.8	4.220 (2.248–7.921)	<0.01
N-category, n (%)								
pN0	217 (31.0%)	43.5	1 (reference)		217 (31.0%)	43.5	1 (reference)	
pN1	484 (69.0%)	17.5	2.156 (1.725–2.696)	<0.01	311 (44.4%)	18.1	2.018 (1.591–2.561)	<0.01
pN2	-	-	-	-	173 (24.7%)	16.9	2.430 (1.871–3.157)	<0.01
Positive LN ratio								
0	-	-	-	-	217 (31.0%)	43.5	1 (reference)	
0.01–0.35	-	-	-	-	446 (63.6%)	18.0	2.035 (1.609–2.574)	<0.01
>0.35	-	-	-	-	38 (5.4%)	13.0	2.469 (1.882–3.238)	<0.01
Resection margin, n (%)								
R0	-	-	-	-	590 (84.2%)	23.2	1 (reference)	
R1	-	-	-	-	111 (15.8%)	16.8	1.714 (1.360–2.160)	<0.01

Abbreviations: AJCC, American Joint Committee on Cancer; PDA, pancreatic ductal adenocarcinoma; OS, overall survival; HR, hazard ratio; 95% CI, 95% confidence interval; LN, lymph node; R0, no cancer cells seen microscopically at the resection margin; R1, cancer cells present microscopically at the resection margin.

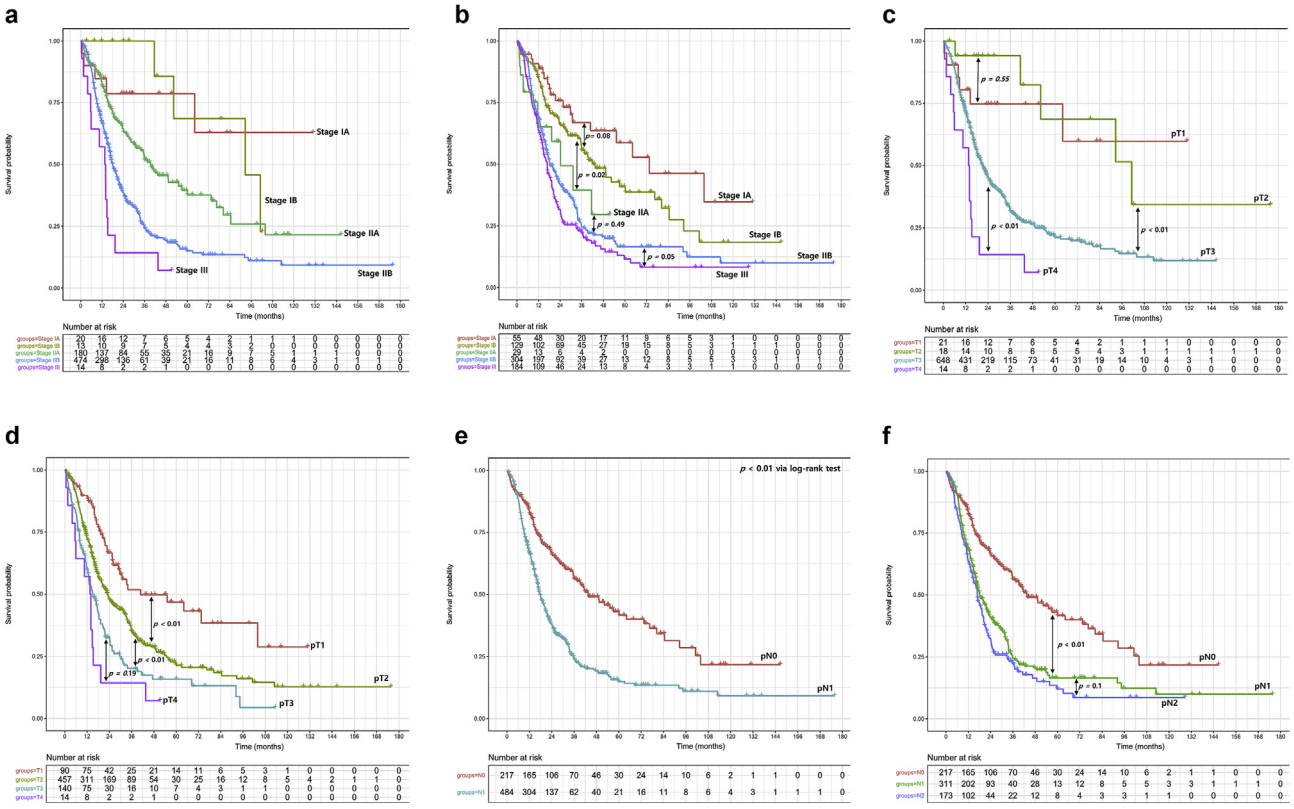

Fig. 2. Kaplan-Meier curves for overall survival of the 701 patients who underwent resection for pancreatic cancer (a) Survival curve according to AJCC 7th edition staging (b) Survival curve according to the AJCC 8th edition staging (c) T-category according to the AJCC 7th edition (d) T-category according to the AJCC 8th edition (e) N-category according to the AJCC 7th edition (f) N-category according to the AJCC 8th edition.

pT3 tumors, and 14 (2.0%) pT4 tumors. The median survival time for each stage was significantly different between the T-categories of the 7th and 8th edition; in the AJCC 8th edition, the median survival for pT1 was 40.8 months; pT2, 23.2 months; pT3, 15.1 months; pT4, 13.8 months ($p < 0.01$). The risk of death was significantly higher for pT2, pT3 tumors and pT4 tumors than for pT1 tumors. (with pT1 as the reference; pT2 HR, 1.816; pT3, 2.839; pT3, 4.220; $p < 0.01$; Table 3 and Fig. 2(d))

We investigated whether the number of metastatic LNs could be a predictor of survival in PDA patients. Of the 484 (69.0%) patients with pN1 in the 7th edition, 311 (44.4%) and 173 (24.7%) were categorized into pN1 and pN2 in the 8th edition, respectively. Based on the N-category of the previous AJCC 7th edition, there was a significant difference in the median OS between node-negative patients and positive patients (pN0, 43.5 months; pN1, 17.5%; $p < 0.01$; Table 3 and Fig. 2(e)). Meanwhile, according to the N-category of AJCC 8th edition, there was a statistically significant difference in the median OS between pN0 and pN1 (43.5 months vs 18.1 months; $p < 0.01$), but not between pN1 and pN2 (18.1 months vs 16.9 months; $p = 0.10$; Fig. 2(f)). Meanwhile, with respect to LNR, we found that the higher the LNR, the shorter the survival, with statistically significant differences (LNR 0, 43.5 months; LNR, 0.01–0.35, 18.0 months; LNR > 0.35, 13.0 months; $p < 0.01$; Table 3 and Fig. 3).

Stage III according to the new staging system

One of the major changes in the AJCC 8th edition was that pN2 patients were classified to have stage III disease regardless of tumor size (Table 1). We also analyzed the survival time of pT4 and pN2 patients using the K-PaC registry to determine the prognosis of unresectable PDA (stage III) patients. Only 14 patients had stage III disease in the AJCC 7th edition, but it increased to 184 in the AJCC 8th edition. Although pT4 and pN2 belong to the same stage III (AJCC 8th edition), pN2 has a significantly longer median OS than pT4 (16.9 months vs 11.2 months; $p < 0.01$; Supplement figure).

Resection margin status

In this study, we also analyzed the difference in survival time according to resection margin status in surgical specimens. Majority (84.2%) of the patients had R0, while 15.8% of patients had R1 (Table 2). The median OS was statistically significantly different between R0 and R1 (23.2 months vs 16.8 months; $p < 0.01$; Table 3). The risk of death was significantly higher for R1 [HR, 1.714; 95% CI, (1.360–2.160; $p = 0.01$] than for R0 (reference).

Discussion

Cancer staging is important not only in predicting patient prognosis but also in providing the optimal treatment approach. The TNM staging system has become a global standard and is widely used to collect, communicate, and exchange cancer information. The AJCC Cancer Staging Manual, 8th edition was published in October 2016, and it contained several significant changes compared to the previous edition. For the T-category in the new staging system for PDA, tumors are classified by size, and the N-category was subclassified according to the number of malignant

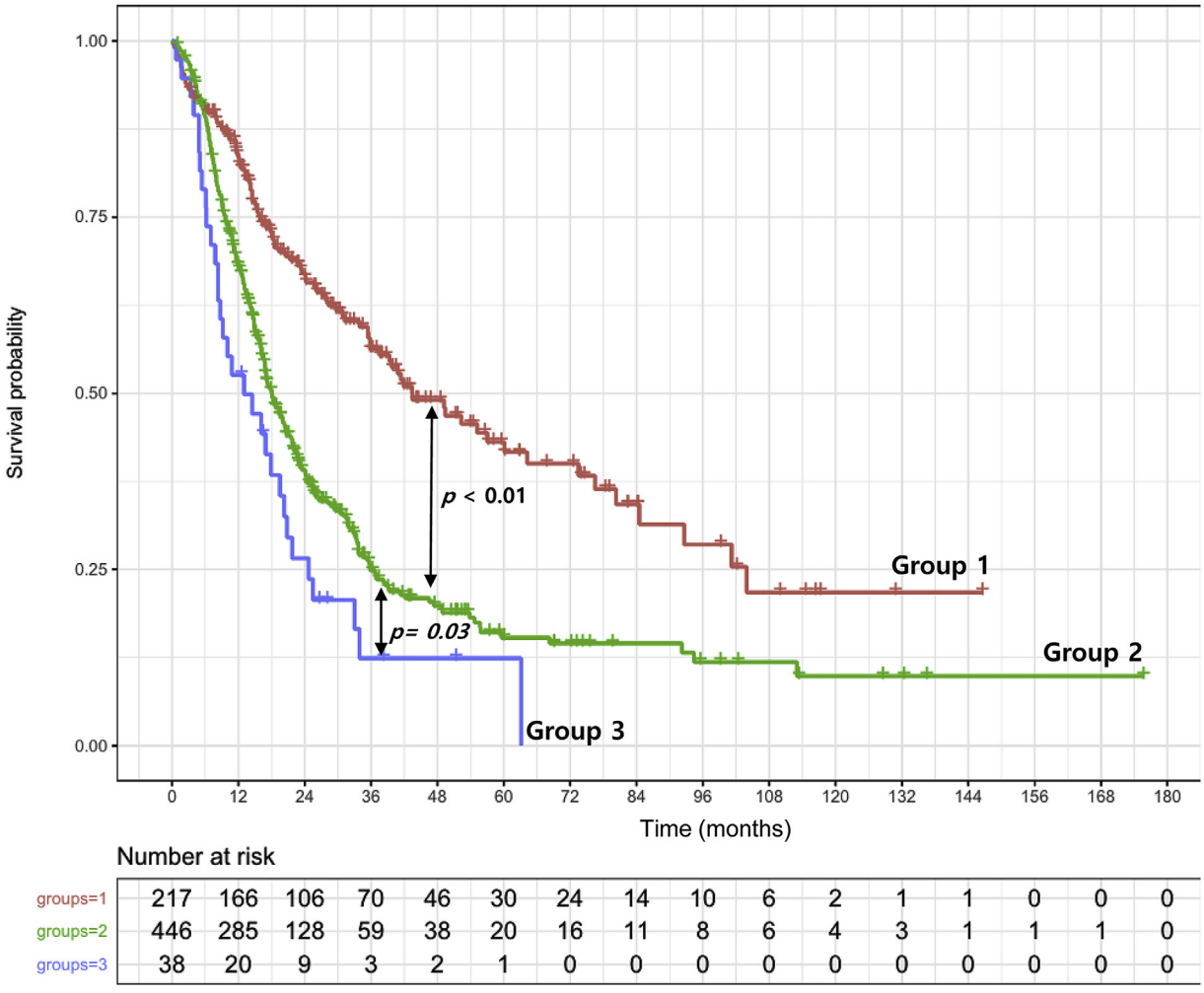

Fig. 3. Kaplan-Meier curve showing the survival time according to lymph node ratio (LNR) (Group 1: LNR = 0; Group 2: LNR > 0, ≤ 0.35; Group 3: LNR ≥ 0.35).

LNs. In the AJCC 7th edition, there was an inter-observer discrepancy on the interpretation of "extend to peripancreatic tissue (pT3)" between pathologists. Because PDA often extends to the surface, most PDAs are classified as pT3 tumors regardless of size in the conventional staging system. Moreover, because the pancreas does not have a capsule, distinguishing extrapancreatic extension from the pancreas can be challenging in the presence of fibrosis or inflammation [6]. Furthermore, the N-category of the 7th edition was also criticized because it was simply divided into pN0 and pN1 [8]. The previous AJCC staging system was not widely used due to low reproducibility of T-category and limited clinical applicability. In the actual clinical setting, the stage of PDA is categorized into the following four groups: 1) upfront resectable; 2) borderline resectable; 3) locally advanced; or 4) metastatic. However, there were also various consensus statements made by various entities regarding borderline resectable and locally advanced disease [9].

This study validated the revised staging system in 701 patients diagnosed with PDA using clinicopathologic data obtained from the K-PaC registry. With regard to staging according to the 7th edition, majority of patients had stage IIA and IIB disease because most were classified to have pT3. The survival period could not be predicted properly because of the limited number of patients with stage IA (2.9%) and IB (1.9%). The AJCC 8th edition allows for better stratification of the prognosis of PDA patients than the 7th edition. Recently, two large-scale studies based on the Surveillance, Epidemiology and End Results (SEER) database [10,11] and one multi-institutional study [12] evaluated the modified staging system (AJCC 8th edition) of PDA and found clinical relevance, reproducibility, and better stratification. These results are consistent with our findings and indicate that the revised staging system, particularly the T-category, can better predict the prognosis of PDA patients [13–15]. We concluded the proposed T-category criteria based only on size is more accurate and reproducible by eliminating the criteria of 'extend to peripancreatic tissue (pT3)', although some conflict data existed [8].

LN metastasis is one of the most important prognostic factors in PDA, and thus it should be adequately described. Many studies have reported that peripancreatic nodal involvement, regardless of direct extension or distant metastasis, is independently associated with poor prognosis [16–18]. In the 7th edition, the N classification was divided into two categories (pN0, node-negative; pN1, node-positive), while it was divided into three categories in the 8th edition (pN0, no positive LNs; pN1, 1-3 positive LNs; and pN2, $\geq$4 positive LNs). In this study, we evaluated the prognostic significance of the number of metastatic LNs using data from the K-PaC registry. When applying the new N classification, the median OS was longer in the pN0 group than that in the pN1 group, and the difference was statistically significant. Meanwhile, no significant differences in the median OS was noted between pN1 and pN2 (18.1 months vs. 16.9 months; $p = 0.10$). The statistical validity of the cutoff points in the latest N-category is controversial. In a retrospective analysis of 1,525 patients by Roessel et al., the revised N-category was highly prognostic [8]. Allen et al. also reported that the new N classification could adequately classify the prognosis [12]. However, similar to our findings, Schlitter et al. reported that the newly introduced pN1 and pN2 categories showed no prognostic differences [19]. In addition to the number of metastatic LNs, the LNR (i.e., the ratio of metastatic nodes to the total number of harvested LNs) has been recently introduced as another prognostic predictor of PDA [20–22]. We have identified the optimal cut-off points (0.35) of LNR using recursive partitioning and found that the survival time significantly shortened with increasing LNR.

In general, the pathologist classifies the surgical specimens into three categories according to whether cancer cells are present on the resection margin: R0, no cancer cells at the resection margin (at least a 1 mm tumor-free margin); R1, cancer cells are visible microscopically within 1 mm of the resection margin; R2, cancer cells present by gross examination [7]. In many studies, resection margin of PDA has been reported to be an independent prognostic factor affecting survival [23–27]. Although there was a difference in survival time between studies, it was generally found that the survival time was longer in R0 than R1. This K-PaC cohort also showed a difference in median OS depending on the status of the resection margin.

Another important change in the AJCC 8th edition staging system is the classification of pN2 into stage III. In this study, the median OS was significantly different between the pN2 group and the pT4 (16.9 months vs. 11.2 months; $p < 0.01$, Supplement figure). Therefore, we propose to subdivide stage III into IIIA (Tany N2 M0) and IIIB (T4 Nany M0). The pT4 involves the major arteries (celiac axis or superior mesenteric artery), while pN2 involves only more than four LNs. In general, pancreatectomy is not recommended in pT4 because it invades major arteries. Meanwhile, most cases of pN2 are pathologically diagnosed when cancer cells are identified in more than four LNs in surgical specimens. This shows that pT4 and pN2 have markedly different clinical courses and thus also have different prognosis.

This study has some limitations. First, this study is based on retrospective data analysis. Second, because this study was conducted based on the multi-institutional cohort, pathologic reports of several pathologists were reviewed. However, the AJCC 8th edition is based on objective measurements (e.g., tumor size, number of LNs), thus the results of our findings are reliable and reproducible, similar to those of other studies. Despite the relatively small number of patients with high LNR and using our own LNR cutoff, we found adequate evidence that the LNR is a more reliable predictor of prognosis than the new N-category.

Conclusion

In conclusion, the T-category based on tumor size adequately stratifies the prognosis of resected PDA, whereas the N-category based on the number of metastatic LNs failed to accurately classify the prognosis. Thus, the N-category needs to be further evaluated in more large-scale studies, and the use of an alternative prognostic predictor such as the LNR should be considered. Moreover, we propose that stage III disease in the AJCC 8th edition be divided into stage IIIA (Tany N2 M0) and stage IIIB (T4 Nany M0) as these showed differences in survival time. We hope that these findings will be reflected in the next revision of the staging system.

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Disclosures

The authors declare no conflict of interest.

Writing assistance

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Authors' contributions

DWS analyzed the data and drafted the article. JCL performed data handling and statistical analysis. JHH designed the study and edited the manuscript. JK, SMW, WJL, SSH, SJP, KSC, HSC, YSY, HSH,

and EKH contributed to the review of the manuscript. All authors approved the final version of the manuscript before submission.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.06.002.

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