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ORIGINAL ARTICLE – PANCREATIC TUMORS

The Prognostic Relevance of the New 8th Edition of the Union for International Cancer Control Classification of TNM Staging for Ampulla of Vater Carcinoma

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ABSTRACT

Objective. The aim of this study was to investigate the clinical relevance of the 8th edition of the Union for International Cancer Control classification of TNM staging for ampulla of Vater carcinoma (AC).

Methods. A total of 104 consecutive patients who underwent macroscopic curative resection for AC between January 2002 and September 2017 were investigated.

Results. Significant differences in recurrence-free survival (RFS) were found between T1a and T1b ($p = 0.0030$), but not between T1b and T2 ($p = 0.9319$), T2 and T3a ($p = 0.0732$), or T3a and T3b ($p = 0.2118$). The prognostic impact of the depth of duodenal invasion and pancreatic invasion, which define the T category, were evaluated. With regard to duodenal invasion, significant differences in RFS were found between the negative and submucosa classifications ($p = 0.0012$) and the muscularis propria and serosa classifications ($p = 0.0131$), but not between the submucosa and muscularis propria classifications ($p = 0.6390$). With regard to pancreatic invasion, significant differences in RFS were found between the negative and ≤ 0.5 cm classifications ($p = 0.0001$), and ≤ 0.5 cm and > 0.5 cm classifications ($p = 0.0062$). A Cox proportional hazard analysis for RFS revealed that duodenal invasion (submucosa or muscularis propria/negative, hazard ratio [HR] 5.08; serosa/negative, HR 7.42), and pancreatic invasion (≤ 0.5 cm/negative, HR 8.23; > 0.5 cm/negative, HR 9.81) were independent prognostic factors. An alternative new T category was proposed, based on the HRs, as follows: T1, tumor limited to the ampulla of Vater or sphincter of Oddi; T2, duodenal invasion (submucosa or muscularis propria); T3, pancreatic invasion (≤ 0.5 cm) or duodenal invasion (serosa); and T4, pancreatic invasion (> 0.5 cm). This alternative T category can well classify each subgroup with prognostic differences.

Conclusions. Reconsideration of the T category based on the prognostic impact of TNM factors, including the depth of duodenal and pancreatic invasion, are required in the 8th edition T category.

Ampulla of Vater carcinoma (AC) presents with symptoms in the early phase of the disease course due to biliary obstruction, therefore a higher resection rate and better prognosis have been reported with this tumor than with other periampullary malignancies.[1] However, a poor prognosis has been reported in AC patients with pancreatic invasion and/or positive lymph nodes.[2,3] AC is rare, accounting for only 0.2% of gastrointestinal cancers and approximately 7% of all periampullary cancers.[4,5] The low incidence of AC, as well as the limited clinical data regarding AC, makes it difficult to establish evidence of clinical practice and outcomes. Therefore, the prognostic relevance of various staging systems for resected AC remains controversial.

The TNM classification of malignant tumors published by the Union for International Cancer Control (UICC) has been recognized as the standard protocol for cancer

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staging. In 2017, the latest update of the UICC classification (8th edition) was released based on the 8th edition staging system of the American Joint Committee on Cancer (AJCC), and includes considerable changes for several cancers, including AC. In particular, the definition of the T category has changed markedly. In the 7th edition, the T category was defined only by the presence or absence of duodenal invasion and pancreatic invasion, whereas in the 8th edition, the detailed depth of duodenal invasion and pancreatic invasion were newly employed as factors indicating the T category. In addition, a further N category classification, according to the number of positive lymph nodes, was newly adopted. However, the prognostic relevance of these newly adopted factors remains unclear, without adequate evidence or validation.

The aim of this study was to compare the 7th and 8th editions of the UICC/AJCC staging and to investigate the prognostic impact of the factors that have been newly incorporated into the definitions in order to validate the significance of the new UICC/AJCC staging and to help update the process of the TNM classification for AC.

METHODS

Study Population of Ampulla of Vater Carcinoma (AC) Patients

This study was approved by the Institutional Review Board of the Shizuoka Cancer Centre, and each study subject provided written informed consent. A retrospective review was performed of a prospectively maintained AC database. A total of 104 patients underwent macroscopic curative resection and were diagnosed with AC between January 2002 and September 2017.

Surgical Strategy and Surgical Procedures for AC

Pancreaticoduodenectomy (PD) with regional lymph node dissection was performed as the standard treatment for AC, as previously described.[6] For patients with tumors limited to the mucosa of the ampulla, local resection, such as ampullectomy or pancreas-sparing duodenectomy, was planned. For AC patients undergoing local resection, frozen sections of the cut end of the specimen and/or regional lymph nodes sampled were examined. PD was performed when the examination of a frozen section revealed tumor involvement at the resection margin or lymph nodes. Endoscopic ampullectomy was not indicated for cancer.

Postoperative Follow-Up

Resected specimens were examined by pathologists and were evaluated based on the 7th and 8th edition UICC/AJCC staging system classifications. The final surgical margins were considered positive if tumor cells were microscopically detectable at any of the resected margins. R1 resection included a positive surgical margin or positive peritoneal lavage cytology in the current study. Para-aortic lymph node metastasis (LNM) was defined as M1 and stage IV disease. Adjuvant therapy after surgery was not performed as a standard treatment during the study periods. The administration of S-1 was performed as adjuvant therapy after surgery in nine patients according to the protocol of the clinical trials for the evaluation of the efficacy of adjuvant therapy for cholangiocarcinoma.

Statistical Analyses

Survival curves were estimated using the Kaplan–Meier method, and statistical differences were examined using the log-rank test. The Cox proportional hazard model was used for further evaluations of a multivariate analysis. All statistical analyses were performed using the JMP software package, version 14 for Mac (SAS Institute Inc., Cary, NC, USA), and a p value < 0.05 was considered statistically significant.

RESULTS

Clinicopathological and Treatment Factors in Patients Enrolled in This Study

PD with lymphadenectomy was performed in 99 patients (95%), ampullectomy was performed in 4 patients (4%), and pancreas-sparing duodenectomy was performed in 1 patient (1%). The present study enrolled patients who underwent R1 resection. Of these, three patients (3%) had a positive surgical margin, and one patient (1%) had positive peritoneal lavage cytology. All stage IV disease in this study was due to para-aortic LNM. No patients received neoadjuvant therapy, but nine patients (9%) received adjuvant chemotherapy, mainly with S-1. Of these, 38 patients (37%) experienced disease recurrence. For recurrent disease, gemcitabine-based chemotherapy was generally performed. The 5-year overall survival (OS) rate was 70.1%, and the recurrence-free survival (RFS) rate was 57.6%. At a median follow-up of 47.4 months (range 1.6–188.3), the 3- and 5-year OS rate was 75.0% and 70.1%, respectively. Clinicopathological and treatment factors are described in Table 1. Figure 1 shows the prognosis according to the 8th edition classification (Fig. 1a, T category; Fig. 1b, N category; Fig. 1c, stage),

TABLE 1 Clinicopathologic characteristics of patients who underwent surgical resection for ampullary carcinomas

		N	% or range
Clinical variables			
Sex	Male	60	58
	Female	44	42
Age, years		69.0	40–87
Operation type	Pancreaticoduodenectomy	99	95
	Ampullectomy	4	4
	Pancreas-sparing duodenectomy	1	1
Operation time, min		393.5	120–648
Blood loss, ml		664.5	51–4158
Number of retrieved lymph nodes		22.5	0–62
Number of metastatic lymph nodes		0	0–17
Pathologic variables			
Tumor size, mm		22.0	1.0–60.0
Histological type	Well- or moderately differentiated	96	92
	Poorly differentiated	8	8
Duodenal invasion	Absent	33	32
	Submucosa	17	16
	Muscularis propria	41	39
	Serosa	13	13
Pancreatic invasion	Absent	71	68
	$\leq$ 5 mm	26	25
	$>$ 5 mm (without invasion to the peripancreatic tissues)	1	1
	Peripancreatic tissues, or other adjacent organs or structures	6	6
Lymphatic invasion	Present	62	60
Venous invasion	Present	22	21
Perineural invasion	Present	18	17
Surgical margin	Positive	3	3
Peritoneal lavage cytology	Positive	1	1
Para-aortic lymph node metastasis	Positive	4	4

while electronic supplementary Fig. S1 shows the prognosis according to the 7th edition classification (Fig. S1a, T category; Fig. S1b, N category; Fig. S1c, stage).

Comparison of the Prognostic Stratification between the 7th and 8th Edition T Categories

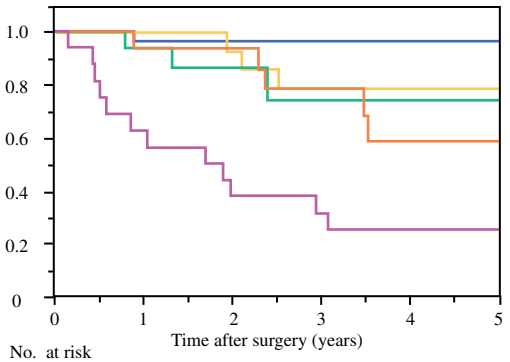
Table 2 shows the definition of each category and the total population. When the 7th edition T category was applied (electronic supplementary Fig. S1a), significant differences in OS and RFS were found between T1 and T2 (OS, $p = 0.0121$; RFS, $p = 0.0015$) and T3 and T4 (OS, $p = 0.0047$; RFS, $p = 0.0042$), but not between T2 and T3 (OS, $p = 0.5151$; RFS, $p = 0.2602$). When the 8th edition T category was applied (Fig. 1a), no patients were classified as T4. Significant differences in OS were found between T1 and T2 ($p = 0.0499$) and T3a and T3b ($p = 0.0189$), but not between T1b and T2 ($p = 0.6286$) and T2 and T3a ($p = 0.8889$). Significant differences in RFS were found between T1a and T1b ($p = 0.0030$), but not between T1b and T2 ($p = 0.9313$), T2 and T3a ($p = 0.0732$), or T3a and T3b ($p = 0.2118$).

Prognostic Impact According to the Depth of Duodenal and Pancreatic Invasion

The detailed depth of duodenal invasion was classified as negative, submucosa, muscularis propria, and serosa, while pancreatic invasion was classified as negative, ≤ 0.5 cm, and > 0.5 cm based on the findings of the histological evaluation. With regard to duodenal invasion, significant prognostic differences were found between the

8th UICC/AJCC

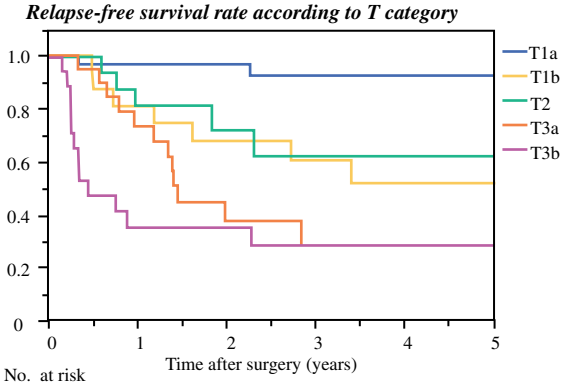
(a) *Overall survival rate according to T category*



No. at risk

T1a	33	27	24	20	16	11
T1b	16	15	13	10	9	7
T2	18	15	9	5	2	0
T3a	20	16	12	9	6	5
T3b	17	10	6	5	4	4

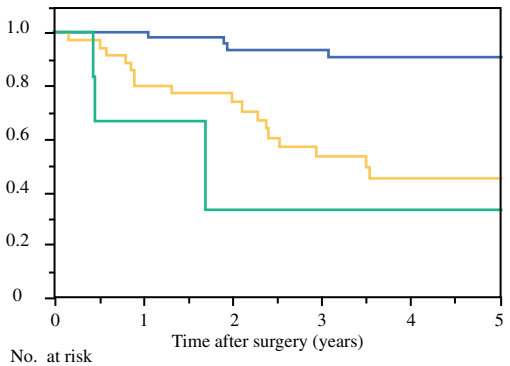
Relapse-free survival rate according to T category



No. at risk

T1a	33	27	24	19	15	10
T1b	16	13	9	7	5	4
T2	18	13	8	5	1	1
T3a	20	13	5	3	3	2
T3b	17	6	4	4	4	4

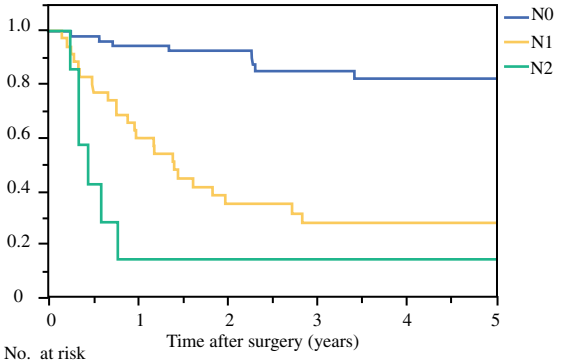
(b) *Overall survival rate according to N category*



No. at risk

N0	61	53	41	33	26	19
N1	36	29	22	15	10	7
N2	7	3	1	1	1	1

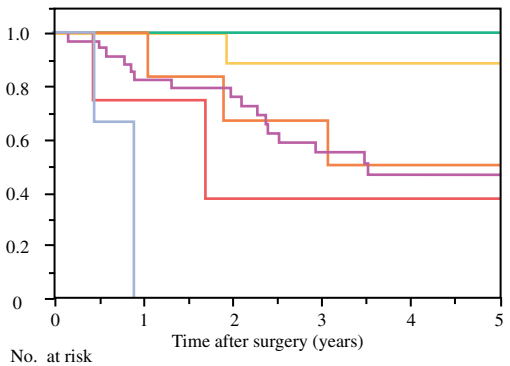
Relapse-free survival rate according to N category



No. at risk

N0	61	50	40	30	23	16
N1	36	21	10	7	4	3
N2	7	1	1	1	1	1

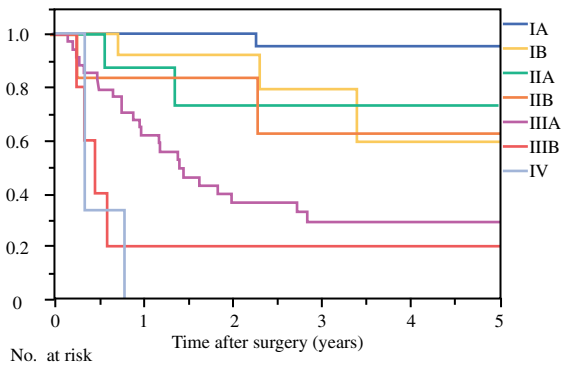
(c) *Overall survival rate according to Stage*



No. at risk

IA	32	27	24	20	16	11
IB	14	13	8	5	3	2
IIA	9	7	5	4	4	3
IIB	6	5	4	4	3	3
IIIA	34	18	22	15	10	7
IIIB	5	3	1	1	1	1
IV	4	0	0	0	0	0

Relapse-free survival rate according to Stage



No. at risk

IA	32	27	24	19	15	10
IB	14	12	8	5	2	1
IIA	9	6	4	3	3	2
IIB	6	5	4	3	3	3
IIIA	34	21	10	7	4	3
IIIB	5	1	1	1	1	1
IV	4	0	0	0	0	0

◀**FIG. 1** Prognostic stratification according to the 8th edition UICC/AJCC staging. **a** Significant differences in OS were found between T1 and T2 ($p = 0.0499$) and T3a and T3b ($p = 0.0189$), but not between T1b and T2 ($p = 0.6286$) or T2 and T3a ($p = 0.8889$). Significant differences in RFS were found between T1a and T1b ($p = 0.0030$), but not between T1b and T2 ($p = 0.9313$), T2 and T3a ($p = 0.0732$), or T3a and T3b ($p = 0.2118$). **b** Significant differences in OS were found between N0 and N1 ($p < 0.0001$), but not between N1 and N2 ($p = 0.2811$). Significant differences in RFS were found between N0 and N1 ($p < 0.0001$) and N1 and N2 ($p = 0.0259$). (**c**) Significant differences in OS were not found in any intergroup, however significant differences in RFS were found between stages IA and IB ($p = 0.0175$), but not between the other subgroups. *UICC* Union for International Cancer Control, *AJCC* American Joint Committee on Cancer, *OS* overall survival, *RFS* recurrence-free survival

negative and submucosa classifications (OS, $p = 0.0407$; RFS, $p = 0.0012$) and the muscularis propria and serosa classifications (OS, $p = 0.0059$; RFS, $p = 0.0131$), but not between the submucosa and muscularis propria classifications (OS, $p = 0.5143$; RFS, $p = 0.6390$) (Fig. 2a). No significant differences were noted in histologic lymphatic or venous invasion, or the incidence of LNM between duodenal invasion (submucosa) and duodenal invasion (muscularis propria) (lymphatic, $p = 0.8376$; venous, $p = 0.9864$; LNM, $p = 0.9750$). With regard to pancreatic invasion, significant prognostic differences were found between the negative and ≤ 0.5 cm classification (OS, $p = 0.0155$; RFS, $p = 0.0001$) and the ≤ 0.5 cm and $>$ 0.5 cm classification (OS, $p = 0.0059$; RFS, $p = 0.0062$) (Fig. 2b).

Comparison of the Prognostic Stratification between the 7th and 8th Edition N categories

Table 2 shows the definition of each category and the total population. When the 7th edition N category was applied (electronic supplementary Fig. S1b), significant differences in OS and RFS were found between N0 and N1 (OS, $p < 0.0001$; RFS, $p < 0.0001$), and when the 8th edition N category was applied (Fig. 1b), significant differences in OS were found between N0 and N1 ($p < 0.0001$), but not between N1 and N2 ($p = 0.2811$). Significant differences in RFS were found between N0 and N1 ($p < 0.0001$) and N1 and N2 ($p = 0.0259$).

Multivariate Analysis Using Cox's Proportional Hazard Model for Recurrence-Free Survival to Evaluate the Prognostic Impact among TNM Factors

To evaluate and compare the prognostic impact of each TNM-related factor, a multivariate analysis was performed and the hazard ratio (HR) of each factor was calculated (Table 3). Duodenal invasion (submucosa or muscularis propria/negative, HR 5.08; serosa/negative, HR 7.42), pancreatic invasion (≤ 0.5 cm/negative, HR 8.23; > 0.5 cm/negative, HR 9.81), N category (N1/N0, HR 5.16; N2/N0, HR 7.06), and M category (M1/M0, HR 11.46) were identified as independent prognostic factors in patients with AC.

Alternative Proposal for T Category and Stage

Inadequate prognostic stratification of the 8th edition T category and stage (Fig. 1c) implies the need for alternative T category and stage grouping. An alternative T category and stage were proposed based on the results of the preceding analysis (Table 2). The key points of the proposal are as follows: duodenal invasion (submucosa) and duodenal invasion (muscularis propria) are classified as one category (T2) because no prognostic difference was found between these two categories (Fig. 2a); pancreatic invasion (≤ 0.5 cm) and duodenal invasion (serosa) are classified as T3 based on the HRs (Table 3); pancreatic invasion (> 0.5 cm) is classified as T4. Significant differences in OS were found between T1 and T2 ($p = 0.0279$) and T3 and T4 ($p = 0.0066$), while significant differences in RFS were found between T1 and T2 ($p = 0.0037$), T2 and T3 ($p = 0.0211$), and T3 and T4 ($p = 0.0127$) (Fig. 2c).

An alternative stage was also proposed, as shown in Table 2. The key point of the proposal is that N2 and T4 are classified as the same category (stage IIIB) based on the HRs. Significant differences in OS and RFS were found between stages I and II (OS, $p = 0.0111$; RFS, $p = 0.0103$), stages II and III (OS, $p = 0.0205$; RFS, $p = 0.0008$), and stages III and IV (OS, $p = 0.0168$; RFS, $p = 0.0304$) (Fig. 2d).

DISCUSSION

The results of the present study showed that the 8th edition T category does not better stratify the prognosis than the previous 7th edition, regardless of the detailed classification of duodenal and pancreatic invasion. The newly adopted separate categorization of duodenal invasion (submucosa) and duodenal invasion (muscularis propria) as T1b and T2, respectively, was not justified based on the finding of no prognostic difference between duodenal invasion (submucosa) and duodenal invasion (muscularis propria). However, the further subclassification of T3 according to the depth of invasion into the pancreas was found to be reasonable. In addition, the biased population in each subgroup is a major concern in the 8th edition classification. The population in the subgroups is biased according to T category and stage in the 8th edition

TABLE 2 Seventh and eighth edition UICC/AJCC classifications and our proposal for alternative staging for ampullary cancer

7th Edition UICC/AJCC				8th Edition UICC/AJCC				Proposed alternative staging			
Category	*N*	%	Definition	Category	*N*	%	Definition	Category	*N*	%	Definition
T1	33	31.7	Tumor limited to ampulla of Vater or sphincter of Oddi	T1a	33	31.7	Tumor limited to ampulla of Vater or sphincter of Oddi	T1	33	31.7	Tumor limited to Ampulla of Vater or sphincter of Oddi
				T1b	16	15.4	Tumor invades beyond the sphincter of Oddi (perisphincteric invasion) and/or into the duodenal submucosa				
T2	37	35.6	Tumor invades the duodenal wall	T2	18	17.3	Tumor invades the muscularis propria of the duodenum	T2	35	33.6	Tumor invades beyond the sphincter of Oddi (perisphincteric invasion) and/or into the duodenal submucosa or the muscularis propria
T3	27	26.0	Tumor invades the pancreas	T3	37	35.6	Tumor invades the pancreas	T3	29	27.9	Tumor invades $\leq$ 0.5 cm into the pancreas or tumor invades the duodenal serosa
				T3a	20	19.2	Tumor invades $\leq$ 0.5 cm into the pancreas				
				T3b	17	16.3	Tumor invades $>$ 0.5 cm into the pancreas or extends into the peripancreatic tissue or duodenal serosa but without involvement of the celiac axis or the superior mesenteric artery				
T4	7	6.7	Tumor invades the peripancreatic soft tissues, or other adjacent organs or structures	T4	0	0	Tumor with vascular involvement of the superior mesenteric artery or celiac axis, or common hepatic artery	T4	7	6.7	Tumor invades $>$ 0.5 cm into the pancreas or extends into the peripancreatic tissue
N0	61	58.7	No regional lymph node metastasis	N0	61	58.7	No regional lymph node metastasis	N0	61	58.7	No regional lymph node metastasis
N1	43	41.3	Regional lymph node metastasis	N1	36	34.6	Metastasis in 1–3 regional lymph nodes	N1	36	34.6	Metastasis in 1–3 regional lymph nodes
				N2	7	6.7	Metastasis in $\geq$ 4 regional lymph nodes	N2	7	6.7	Metastasis in $\geq$ 4 or more regional lymph nodes
Stage IA	32	30.8	T1, N0, M0	Stage IA	32	30.8	T1a, N0, M0	Stage I	32	30.8	T1, N0, M0
Stage IB	16	15.4	T2, N0, M0	Stage IB	14	13.5	T1b, T2, N0, M0				
Stage IIA	13	12.5	T3, N0, M0	Stage IIA	9	8.7	T3a, N0, M0	Stage IIA	15	14.4	T2, N0, M0
Stage IIB	33	31.7	T1, T2, T3, N1, M0	Stage IIB	6	5.8	T3b, N0, M0	Stage IIB	14	13.5	T3, N0, M0
Stage III	6	26.0	T4, any N, M0	Stage IIIA	34	32.7	T1a, T1b, T2, T3, N1M0	Stage IIIA	32	30.8	T1–3, N1, M0
				Stage IIIB	5	4.8	Any T, N2, M0 T4, any N, M0	Stage IIIB	8	7.7	T1–3, N2, M0 T4, any N, M0
Stage IV	4	3.8	Any T, any N, M1	Stage IV	4	3.8	Any T, any N, M1	Stage IV	3	2.9	Any T, any N, M1

UICC/AJCC Union for International Cancer Control/American Joint Committee on Cancer

TABLE 3 Univariate and multivariate analyses for relapse-free survival of ampulla of Vater carcinoma patients using Cox's proportional hazard model

	Variable	Univariate analysis	Multivariate analysis		
		p Value[a]	HR	95% CI	*p* Value[b]
Duodenal invasion	Serosa	<0.0001*	7.42	1.52–43.18	0.0128*
	Submucosa or muscularis propria		5.08	1.88–13.42	0.0017*
	Negative		1.000		
Pancreatic invasion	> 0.5 cm	<0.0001*	9.81	1.18–70.86	0.0345*
	≤ 0.5 cm		8.23	1.10–58.43	0.0402*
	Negative		1.000		
N category	N2	<0.0001*	7.06	2.77–20.27	<0.0001*
	N1		5.16	0.65–39.82	0.1187
	N0		1.000		
M category	M1	<0.0001*	11.46	1.96–55.94	0.0093*
	M0		1.000		

*Indicates significant values

[a]Kaplan–Meier method. Significance was determined using the log-rank test

[b]A multivariate survival analysis was performed using Cox's proportional hazard model

HR hazard ratio, *CI* confidence interval

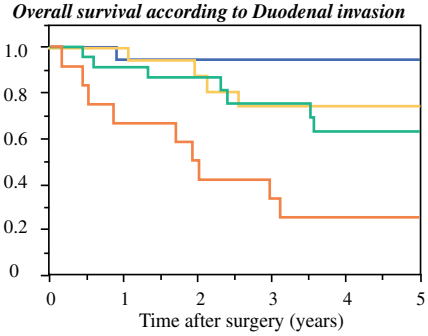
classification. For example, no patient was classified as T4 category, and only 14% of the patients were classified as stage II, according to the 8th edition. This uneven distribution might not be appropriate for the standard protocol for cancer staging. Following these findings, an alternative T category and stage were proposed, which were able to better stratify the prognosis than the new current standards. The present study provides further evidence of the prognostic impact of the depth of duodenal and pancreatic invasion, and will therefore help to update the process of the TNM classification for AC.

In other gastrointestinal cancers, invasion into the submucosa and muscularis propria are classified into different T categories based on reports that invasion into the muscularis propria is associated with increased lymphovascular invasion, an increased risk of LNM, and a worse prognosis than that into the submucosa.[7] However, specifically in AC, several groups, as well as the present study, have shown no significant difference in prognosis between duodenal invasion (submucosa) and duodenal invasion (muscularis propria).[8,9] Furthermore, the present study revealed no significant difference in lymphatic or venous invasion, or incidence of LNM, between duodenal invasion (submucosa) and duodenal invasion (muscularis propria). This difference from other gastrointestinal cancers might be caused by the anatomical complexity of the ampulla of Vater. The perisphincteric tissues or duodenal submucosa exist between the sphincter of Oddi and duodenal muscularis propria, and the sphincter of Oddi surrounds the bile duct and pancreatic duct, which penetrate through all layers of the duodenal wall.[10] Therefore, duodenal invasion (muscularis propria) does not mean deeper vertical invasion than duodenal invasion (submucosa) in some cases.

Pancreatic invasion has been recognized as a factor predicting worse prognostic outcomes;[11] however, the prognostic impact and optimum cut-off value of the depth of invasion into the pancreas are still unclear. In the 8th edition, 0.5 cm was newly employed as a cut-off value of the depth of invasion into the pancreas. The results of the present study support this revision as valid. In addition, in the present study, 94% (16/17) of ACs with pancreatic invasion (> 0.5 cm) invaded into the peripancreatic soft tissues or other adjacent organs or structures.[12] Furthermore, AC patients with pancreatic invasion (> 0.5 cm) showed a limited median survival time of 7.2 months. Accordingly, it is acceptable to classify AC with pancreatic invasion (> 0.5 cm) as T4, as outlined in the proposal, although further accumulation of evidence and validation of these findings are needed.

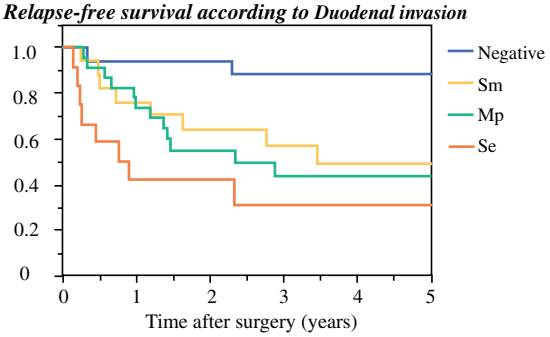
Tumors with vascular involvement of the superior mesenteric artery, celiac axis, or common hepatic artery are defined as T4 in the 8th edition. Generally, AC can often be diagnosed in the early stages of disease; thus, resected AC classified as T4 in the new 8th edition seems to be extremely rare.[9] Indeed, none of the cases in the present study

(a) ***Overall survival according to Duodenal invasion***



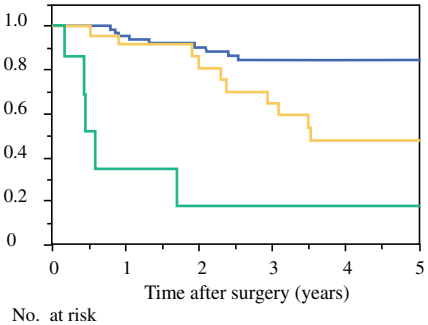
No. at risk						
Negative	33	27	24	20	16	11
Sm or mp	58	49	35	25	18	13
Se	13	8	5	4	3	3

Relapse-free survival according to Duodenal invasion



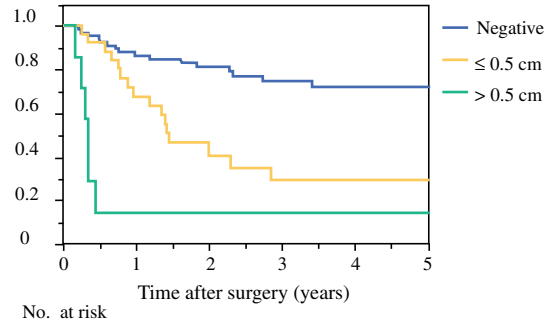
No. at risk						
Negative	33	27	24	19	15	10
Sm or mp	58	40	23	16	10	7
Se	13	5	4	3	3	3

(b) ***Overall survival according to Pancreas invasion***



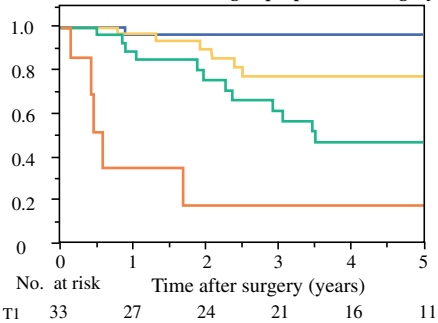
No. at risk						
Negative	71	61	49	36	28	20
≤ 0.5 cm	26	21	15	12	8	7
> 0.5 cm	7	2	1	1	1	1

Relapse-free survival according to Duodenal invasion



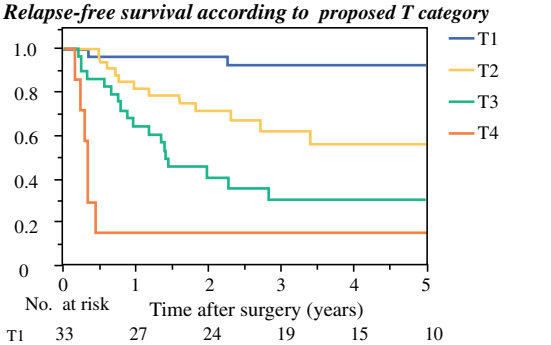
No. at risk						
Negative	71	56	43	32	22	15
≤ 0.5 cm	26	16	7	5	5	4
> 0.5 cm	7	1	1	1	1	1

(c) ***Overall survival according to proposed T category***



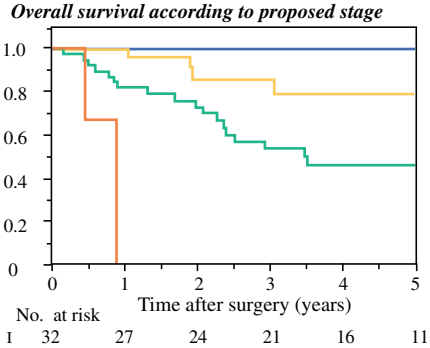
No. at risk						
T1	33	27	24	21	16	11
T2	35	32	23	16	11	7
T3	29	23	16	14	9	8
T4	7	2	1	1	1	1

Relapse-free survival according to proposed T category



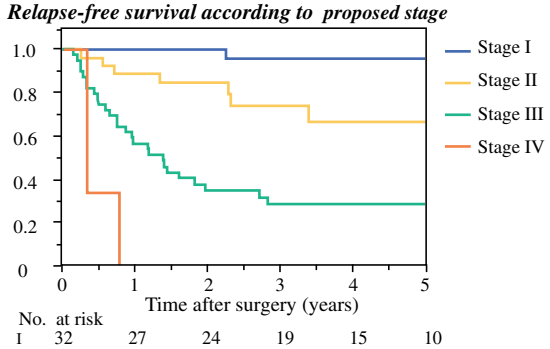
No. at risk						
T1	33	27	24	19	15	10
T2	35	27	18	12	6	4
T3	29	17	8	6	6	5
T4	7	1	1	1	1	1

(d) ***Overall survival according to proposed stage***



No. at risk						
I	32	27	24	21	16	11
II	29	26	17	13	10	8
III	39	31	23	16	11	8
IV	4	0	0	0	0	0

Relapse-free survival according to proposed stage



No. at risk						
I	32	27	24	19	15	10
II	29	23	16	11	8	6
III	39	22	12	8	5	4
IV	4	0	0	0	0	0

◀**FIG. 2** Evaluation of the prognostic impact according to the extent of duodenal invasion and pancreatic invasion, and prognostic stratification of the proposed alternative T category and staging. **a** OS and RFS according to the depth of duodenal invasion. Significant prognostic differences were found between the negative and submucosa classifications (OS, $p = 0.0407$; RFS, $p = 0.0012$) and the muscularis propria and serosa classifications (OS, $p = 0.0059$; RFS, $p = 0.0131$), but not between the submucosa and muscularis propria classifications (OS, $p = 0.5143$; RFS, $p = 0.6390$). Submucosa: tumor invades the duodenal submucosa; muscularis propria: tumor invades the duodenal muscularis propria; serosa: tumor invades the duodenal serosa. **b** OS and RFS according to the depth of pancreatic invasion. Significant prognostic differences were found between the negative and ≤ 0.5 cm classifications (OS, $p = 0.0155$; RFS, $p = 0.0001$) and the ≤ 0.5 cm and > 0.5 cm classifications (OS, $p = 0.0059$; RFS, $p = 0.0062$). ≤ 0.5 cm: tumor invades ≤ 0.5 cm into the pancreas; > 0.5 cm: tumor invades > 0.5 cm into the pancreas. **c** OS and RFS according to the proposed T category. The 5-year OS and RFS rates were as follows: T1: OS 96.6%, RFS 92.6%; T2: OS 77.2%, RFS 55.8%; T3: OS 46.3%, RFS 30.2%; and T4: OS 17.1%, RFS 14.3%. Significant differences in OS were found between T1 and T2 ($p = 0.0279$) and T3 and T4 ($p = 0.0066$). Significant differences in RFS were found between T1 and T2 ($p = 0.0037$), T2 and T3 ($p = 0.0211$), and T3 and T4 ($p = 0.0127$). **d** OS and RFS according to the proposed staging. The 5-year OS and RFS rates were as follows: stage I: OS 100.0%, RFS 95.7%; stage II: OS 78.9%, RFS 66.4%; stage III: OS 45.9%, RFS 27.9%; stage IV: OS 0.0%, RFS 0.0%. Significant differences in OS and RFS were found between stages I and II (OS, $p = 0.0111$; RFS, $p = 0.0103$), stages II and III (OS, $p = 0.0205$; RFS, $p = 0.0008$), and stages III and IV (OS, $p = 0.0168$; RFS, $p = 0.0304$). *Sm* submucosa, *Mp* muscularis propria, *Se* serosa, *OS* overall survival, *RFS* recurrence-free survival

were defined as T4. Consequently, tumors invading > 0.5 cm into the pancreas should be categorized as T4, as mentioned in the above paragraph.

The number of positive nodes is also an established prognostic factor in various malignant tumors, including AC.[9,13] In the 8th edition classification, the number of positive lymph nodes was newly adopted as the N category definition, and the present study demonstrated a significant difference in RFS between N1 and N2 ($p = 0.0259$). In the present study, the median survival time for N2 patients was 20.7 months, which is shorter than that for N1 but longer than that reported for patients treated with chemotherapy for unresectable biliary tract cancers (7.7–12.5 months).[14–16] These findings suggest that surgical resection has a prognostic benefit for N2 patients, and AC diagnosed as N2M0 that is classified not as stage IV but as stage IIIB therefore seems to be reasonable. However, evidence supporting the cut-off value and details of further classifications are lacking at present, therefore validation is warranted.

Several limitations associated with the present study warrant mention. One major limitation is the small number of cases in this single-center, retrospective study. In the 8th edition in particular, the populations in each subgroup are biased and are relatively small in some subgroups, potentially leading to statistical type II error. Therefore, larger sample sizes are needed in order to prove that the stratification of the prognosis in the 8th edition is insufficient. We plan to validate the present results and our proposed classification in a large-scale, multi-institutional cohort. This project is currently under evaluation and our results are expected to be reported in the near future.

CONCLUSION

The new 8th edition T category cannot stratify the prognosis well in resected AC patients. Reconsideration of the T category based on the prognostic impact of the depth of duodenal and pancreatic invasion is required. The results of the present study should therefore be considered to help update the process of the TNM classification for AC.

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COMPLIANCE WITH ETHICAL STANDARDS

CONFLICT OF INTEREST Taisuke Imamura, Yusuke Yamamoto, Teiichi Sugiura, Yukiyasu Okamura, Takaaki Ito, Ryo Ashida, Katsuhisa Ohgi, and Katsuhiko Uesaka declare that they have no conflicts of interest.

DISCLOSURES Taisuke Imamura, Yusuke Yamamoto, Teiichi Sugiura, Yukiyasu Okamura, Takaaki Ito, Ryo Ashida, Katsuhisa Ohgi, and Katsuhiko Uesaka affirm that they have no financial or personal affiliations (including research funding) or other involvement with any commercial organization that has a direct financial interest in any matter included in this work.

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