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ORIGINAL ARTICLE – PANCREATIC TUMORS

Clinical Implications of the Degree of Pancreatic Invasion in Ampulla of Vater Carcinoma

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ABSTRACT

Background. Ampulla of Vater carcinoma (AVC) stage T3 was subdivided according to the degree of pancreatic invasion into T3a (≤ 0.5 cm) and T3b (> 0.5 cm) by the 8th edition of the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) cancer staging system. However, the differences in clinicopathological features and survival outcomes between the two categories have not been well discussed.

Patients and Methods. We retrospectively analyzed 133 consecutive patients who underwent pancreatoduodenectomy for AVC at our institution between 2002 and 2020. Clinicopathological features and survival outcomes of patients with AVC were analyzed, with a focus on the depth of pancreatic invasion. In addition, the survival outcomes of patients with T3 AVC were compared with those of patients with resectable pancreatic head carcinoma (R-PhC) who underwent pancreatoduodenectomy during the same period.

Results. The overall survival (OS) in patients with T3b AVC ($n = 12$) was significantly worse than that in patients with T3a AVC ($n = 39$) [median survival time (MST) 9.2 vs. 74.5 months, $p < 0.001$). A multivariate analysis identified T3b tumor (hazard ratio 5.64, $p = 0.009$) as an independent prognostic factor. The OS of patients with T3a AVC was significantly better than that of patients with R-PhC who received adjuvant chemotherapy ($n = 276$, MST 35.0 months, $p = 0.007$). In contrast, the OS of patients with T3b AVC tended to be worse than that of patients with R-PhC managed without adjuvant chemotherapy, although this difference was not statistically significant ($n = 163$; MST, 17.5; $p = 0.140$).

Conclusions. AVC with > 0.5 cm invasion into the pancreas was associated with poor survival and represented advanced tumor progression to systemic disease.

Symptoms of biliary obstruction make the ampulla of Vater carcinoma (AVC) more likely to be detected in the early phase, and patients are more likely to undergo curative resection compared to other periampullary malignancies.[1] In 2017, The Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) established a new 8th edition cancer staging system, including AVC.[2,3] The T category of the UICC/AJCC staging system had been revised, especially with respect to the depth of pancreatic invasion. T3 was divided into T3a, invasion to the pancreas (≤ 0.5 cm), and T3b, invasion to the pancreas (> 0.5 cm) or invasion into the duodenal serosa. A cutoff value of 0.5 cm was selected because it represents the shortest distance from the ampulla of Vater to the peripancreatic soft tissue or other adjacent organs or structures, excluding the pancreas such as the duodenal serosa. In the 8th edition of the UICC/AJCC staging system, tumors with pancreatic invasion (> 0.5 cm) as well as those invading peripancreatic soft tissue or other adjacent organs or structures other than the pancreas, which were classified as T4 in the 7th edition, are both categorized as T3b tumors.[4,5] While validation studies of this revision showed a significant difference in the survival outcomes of T3a and T3b tumors,[6,7] the differences

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in clinicopathological features between these two tumors have not been sufficiently clarified.

This study aimed to investigate the clinicopathological features and survival outcomes of patients with AVC, with a focus on the depth of pancreatic invasion according to the UICC/AJCC staging system. Furthermore, the survival outcomes of patients with AVC and pancreatic invasion were compared with those of patients with R-PhC.

PATIENTS AND METHODS

Study Population

This retrospective study included 133 consecutive patients who underwent pancreatoduodenectomy (PD) for AVC between October 2002 and December 2020 at Shizuoka Cancer Center. The 2002–2017 cohort overlapped with our previous AVC report.[6] Patients with tumors limited to the mucosa of the ampulla (Tis tumor) and those who underwent local resection (e.g., papillectomy or pancreas-sparing duodenectomy) were excluded. The current study was approved by our institutional review board (J2023-45-2023-1-3).

Preoperative Evaluation and Surgical Strategy

Preoperative work-up for AVC, including gross appearance, depth of tumor invasion, and resectability, was performed using upper gastrointestinal endoscopy, endoscopic ultrasonography, and multidetector-row computed tomography. None of the patients had received neoadjuvant therapy. Tumors clinically diagnosed as stage T1 or higher were treated with classical PD with regional lymph node dissection as the standard treatment for AVC, as previously described.[8,9] Clinical T4 tumors, including those involving the celiac axis or superior mesenteric artery, were considered unresectable. Patients who were preoperatively diagnosed with obvious distant metastases, including those in the para-aortic lymph nodes, were not candidates for surgery. Para-aortic lymph node sampling was typically conducted, and if the lymph node was positive for metastasis, the decision to proceed with PD was at the surgeon's discretion.

Histopathological Evaluation

All specimens were prepared in the usual manner for microscopic examination by hematoxylin-eosin staining. Tumor size, histological grade, microscopic lymphatic invasion, microscopic vascular invasion, microscopic perineural invasion, lymph node metastasis, staging, and invasion to other adjacent organs, including the pancreas, were recorded in accordance with the 8th edition of the UICC/AJCC staging system.[2,3]

An experienced pathologist (N.O.) reviewed these pathological findings for T3a cases characterized by tumor invasion into the pancreas (≤ 0.5 cm) and for T3b cases with tumor invasion into the pancreas (> 0.5 cm) or invasion into the duodenal serosa. Specifically, the malignant features identified in T3b tumors were extracted and examined to determine whether they were also present in T3a tumors.

Follow-Up

No adjuvant chemotherapy was administered. All patients were followed up at 3 to 6 months intervals after surgery with laboratory tests, including the measurement of tumor markers and imaging studies. Tumor recurrence was confirmed on the basis of either the radiological findings or histological evidence, and the initial recurrence sites were recorded. Gemcitabine-based regimens are primarily used to treat tumor recurrence.[10]

Comparisons of Survival Outcomes between Patients with AVC with Pancreatic Invasion and Patients with R-PhC

Survival outcomes were compared between patients with AVC with pancreatic invasion and 439 patients with R-PhC who did not receive neoadjuvant chemotherapy and who underwent PD during the same period at our institution. The resectability status of pancreatic carcinoma was defined according to the National Comprehensive Cancer Network (NCCN) guidelines.[11] As the treatment strategy for pancreatic cancer has dramatically changed over the last decade, patients with R-PhC were subdivided into two groups based on whether they received adjuvant chemotherapy. Gemcitabine was administered from 2006 to 2011[12] and S-1 has been used since 2012[13] as adjuvant chemotherapy.

Statistical Analyses

Continuous data are expressed as medians and ranges and compared using the Mann–Whitney *U* test or Kruskal–Wallis test. Categorical data were analyzed using Fisher's exact test. Overall survival (OS) was defined as the time from the date of resection to the date of death from any cause. Patients who were alive on the last follow-up examination were censored at that time. Relapse-free survival (RFS) was calculated from the date of resection to the date of disease recurrence or death from any cause. Patients without recurrence on the last follow-up examination were censored at that time. OS and RFS were estimated using the Kaplan–Meier method. Variables with a p value of < 0.05 in a univariate analysis were included in a multivariate Cox proportional hazards regression analysis to identify independent risk factors for OS. Statistical significance was set at

$p < 0.05$. All statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan).[14]

RESULTS

Patients with AVC

The clinicopathological characteristics of the 133 patients with AVC are shown in Table 1. Pancreatic invasion was observed in 51 patients (38.3%); 39 had pT3a tumors (29.3%) and 12 had pT3b tumors (9.0%). All T3b cases were on the basis of the evidence of pancreatic invasion, with no cases involving extrapancreatic tissue. Two deaths occurred within 90 days of surgery. One patient died on postoperative day 2, as a result of heart failure associated with myocardial infarction. The other patient died on postoperative day 73 because of bleeding from the gastroduodenal artery stump, which was associated with a pancreatic fistula. These patients had T1a and T2 tumors, respectively. Five patients were diagnosed with para-aortic lymph node metastases during surgery: one with a T1b tumor, one with a T2 tumor, one with a T3a tumor, and two with a T3b tumors. Among the 133 patients, 47 patients (35.3%) had tumor recurrence during the study period: 15 of the 41 patients (36.6%) with T2 tumors, 18 of 39 (46.2%) with pT3a tumors, and 11 of 12 (91.7%) with pT3b tumors. Systemic chemotherapy was administered to 29 of 47 patients with confirmed tumor recurrence. Gemcitabine alone was used in 16 cases, gemcitabine plus cisplatin in 11 cases, and other regimens were used in two cases. There was no difference in the OS between patients managed with and without systemic chemotherapy for recurrence [median survival time (MST): 27.8 vs. 28.9 months, $p = 0.336$] (Supplementary Fig. 1). Surgical resection for recurrent tumors was performed in 4 patients, two of whom had liver metastasis and two of whom had lung metastasis.

Survival Outcomes According to Pathological T Stage

Figure 1 compares the RFS and OS curves according to the T stage. The median observation period was 58.8 months (range: 3.2–224.9 months) in the censored cases. The survival time did not differ to a statistically significant

TABLE 1 Clinicopathological characteristics of the 133 patients with AVC

Characteristics	Whole patients $n = 133$
Age at surgery (years) *	69 (40–85)
Sex (male)	74 (55.6)
BMI (kg/m^2) *	22.3 (13.9–39.7)
CEA (ng/mL) *	2.3 (0.5–33.4)
CA19-9 (U/mL) *	16.5 (2–1479)
Surgical outcomes	
Operation time (min) *	401 (213–648)
Blood loss (mL) *	662 (92–3368)
Mortality	2 (1.5)
Morbidity (Clavien–Dindo ≥ III)	40 (30.1)
Postoperative hospital stays (days) *	25 (2–106)
Pathological findings	
Gross appearance (protruded type/ulcerative type)	103 (77.4)/30 (22.6)
Tumor size (mm) *	25 (1–133)
Differentiation (pap/tub/por/mix)	8 (6.0)/107 (83.5)/12 (6.0)/6 (4.5)
Lymphatic invasion (+)	82 (61.7)
Vascular invasion (+)	30 (22.6)
Perineural invasion (+)	30 (22.6)
Pathological T stage ** (T1a/T1b/T2/T3a/T3b)	24 (18.1)/17 (12.8)/41(30.8)/39 (29.3)/12 (9.0)
Pathological N stage** (N0/N1/N2)	81 (60.9)/38 (28.6)/14 (10.5)
Pathological Stage** (I/II/IIIA/IIIB/IV)	60 (45.1)/21 (15.8)/37 (27.8)/10 (7.5)/5 (3.8)

BMI body mass index, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9, *pap* papillary adenocarcinoma, *tub* tubular adenocarcinoma, *por* poorly differentiated adenocarcinoma, *mix* mixed adeno-neuroendocrine carcinoma (MANEC)

*Median (range)

**The 8th edition of UICC/AJCC classification

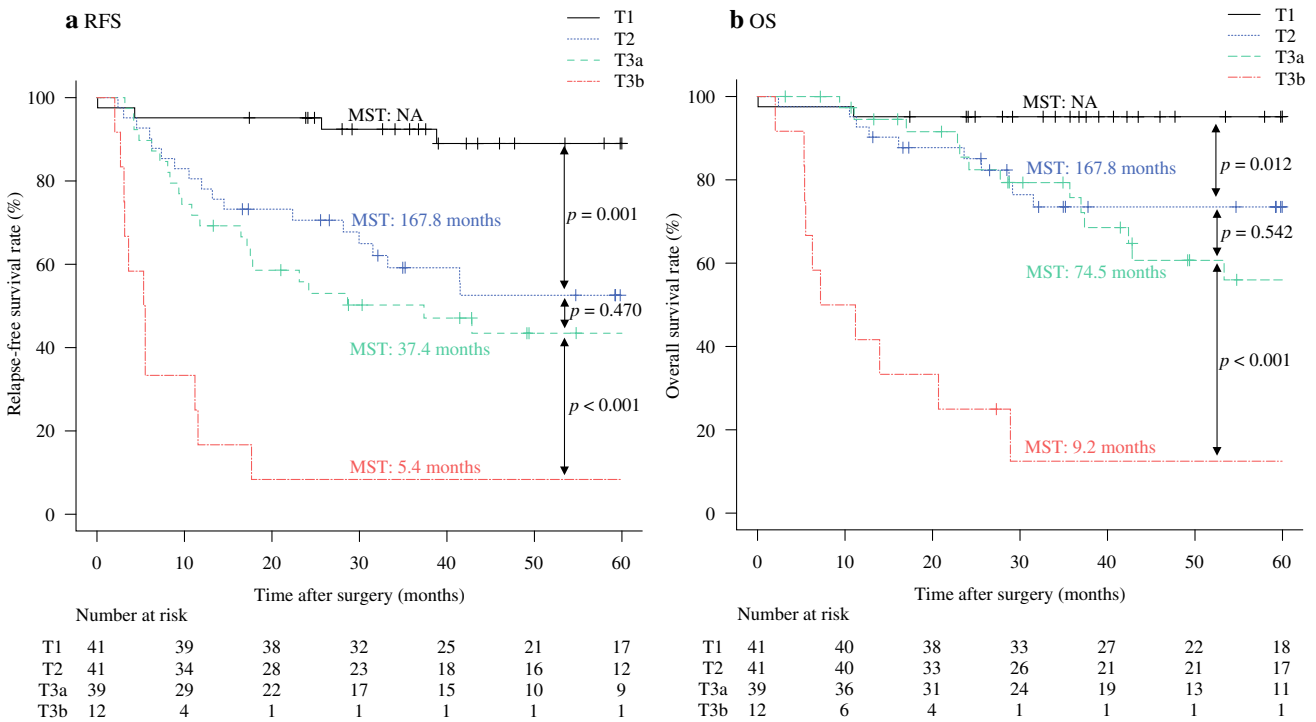

FIG. 1 **a** Relapse-free survival curves according to pathological T stage. **b** Overall survival curves according to pathological T stage. *MST* median survival time

extent between patients with T2 tumors (MST for RFS: 167.8 months; MST for OS: 167.8 months) and those with a T3a tumors (MST for RFS: 37.4 months; MST for OS: 74.5 months) (RFS, $p = 0.470$; OS, $p = 0.542$). Significant differences in RFS and OS were found between patients with T3a tumors and those with T3b tumors (MST for RFS: 5.4 months; MST for OS: 9.2 months) (RFS, $p < 0.001$; OS, $p < 0.001$).

Prognostic Factors for OS

Table 2 shows the results of univariate and multivariate analyses to identify the prognostic factors for OS. A multivariate analysis identified pathological N2 [hazard ratio (HR), 6.55; $p = 0.002$], pathological T3b tumor (HR, 5.64; $p = 0.009$), microscopic perineural invasion (HR, 2.79; $p = 0.013$), and pathological N1 (HR, 2.65; $p = 0.031$) as independent prognostic factors.

Histopathological Findings of T3b Tumors

Of the 12 T3b tumors, ten were observed as predominantly pancreaticobiliary-type tumors (Fig. 2a), specifically advanced regions of tumorous growth within the pancreas, which had infiltrated scirrhous tissue and exhibited lymphatic and/or vascular invasion (Fig. 2b, c). Five of these cases mainly presented with poorly differentiated components, among which one exhibited signet cell-like poorly differentiated cells (Fig. 2d). Tumors exhibiting a predominantly intestinal type also exhibited aggressive venous invasion (Fig. 2e). Other histological characteristics indicative of malignant tumor features included invasive micropapillary patterns in three cases (Fig. 2f), extranodal involvement of metastatic lymph nodes in two cases, and a mixture of neuroendocrine neoplasm components with sheet-like cell proliferation and positive synaptophysin in the cytoplasm (Fig. 2g, h).

Comparisons of Pathological Findings and Recurrence Patterns According to Pathological T Stage

Table 3 shows comparisons of pathological findings including the malignant tumor features identified in T3b tumors and recurrence patterns between patients with T3a and T3b tumors. Although the frequencies of microscopic lymphatic and perineural invasion were not significantly different between patients with a T3b and T3a tumors, there was a significant difference in the frequency of microscopic vascular invasion (75.0% vs. 28.2%, $p = 0.006$), and a significantly higher percentage of T3b tumors showed an invasive micropapillary pattern in comparison to T3a tumors (25.0% vs. 2.6%, $p = 0.036$). Additionally, 53.8% of patients with T3a tumors had no lymph node metastases, while all patients with T3b tumors had lymph node metastases,

TABLE 2 Univariate and multivariate analyses of the prognostic factors for the overall survival

Variable		*n*	Univariate†		Multivariate‡	
			MST (months)	*p* value	Hazard ratio (95% CI)	*p* value
Age (years)	≥ 70	66	73.3	**0.011**	1.90 (0.89–4.05)	0.097
	< 70	67	167.8			
Sex	Male	59	167.8	0.120		
	Female	74	NA			
BMI (kg/m^2)	≥ 21	92	NA	0.237		
	< 21	41	125.9			
CEA (ng/mL)	> 5.0	12	31.5	**0.014**	1.05 (0.39–2.83)	0.924
	≤ 5.0	118	167.8			
CA19-9 (U/mL)	> 37	33	73.3	0.055		
	≤ 37	97	167.8			
Gross appearance	Ulcerative	30	63.0	**0.002**	2.03 (0.95–4.32)	0.066
	Protruded	103	NA			
Differentiation	Pap, tub	115	167.8	0.103		
	Others	18	125.9			
Histologic type	Pancreatobiliary	59		**0.034**	1.07 (0.47–2.46)	0.868
	Intestinal	74	167.8			
Tumor size (mm)	≥ 25	69	74.5	**0.002**	1.43 (0.63–3.22)	0.395
	< 25	64	167.8			
ly	Present	82	74.5	**< 0.001**		
	Absent	51	NA			
v	Present	30	42.4	**< 0.001**	0.85 (0.37–1.95)	0.698
	Absent	103	167.8			
pn	Present	30	40.0	**< 0.001**	**2.79 (1.25–6.26)**	**0.013**
	Absent	103	167.8			
pT stage	T3b	12	9.2	**< 0.001**	**5.64 (1.53–20.73)**	**0.009**
	T3a	39	74.5		1.00 (0.41–2.47)	0.994
	T1/2	82	167.8			
pN stage	N2	14	24.2	**< 0.001**	**6.55 (2.01–21.38)**	**0.002**
	N1	38	63.0		**2.65 (1.09–6.44)**	**0.031**
	N0	81	NA			
pM stage	M1	5	11.0	**< 0.001**		
	M0	128	167.8			

MST median survival time, CI confidence interval, BMI body mass index, CEA carcinoembryonic antigen, CA19-9 carbohydrate antigen 19-9, ly microscopic lymphatic invasion, v microscopic vascular invasion, pn microscopic perineural invasion

Significant values are in bold. †Log rank test, ‡Cox proportional hazards model

58.3% of which had a pathological N stage of 2 ($p < 0.001$). Although the differences were not statistically significant, among patients with recurrence, patients with T3b tumors had a higher frequency of liver recurrence than those with T3a tumors (81.8% vs. 50.0%, $p = 0.125$).

A comparison of patients with T2 tumors is shown in Supplementary Table 1. The frequency of microscopic vascular invasion in patients with T2 and T3a tumors did not differ to a statistically significantly extent (22.0% vs. 28.2%, $p = 0.609$), but the frequencies of microscopic lymphatic and perineural invasion were significantly higher in patients with T3a tumors than in those with T2 tumors (lymphatic invasion, 73.2% vs. 92.3%, $p = 0.038$; perineural invasion, 17.1% vs. 46.2%, $p = 0.008$).

Comparisons of OS Between Patients with AVC with Pancreatic Invasion and Patients with R-PhC

Survival outcomes were compared between patients with T3 AVC and R-PhC who underwent PD without neoadjuvant chemotherapy. The clinicopathological characteristics of 439 patients with R-PhCs are presented in Supplementary Table 2. A comparison of the OS is shown in Fig. 3a. The OS of patients with T3a AVC was significantly better than

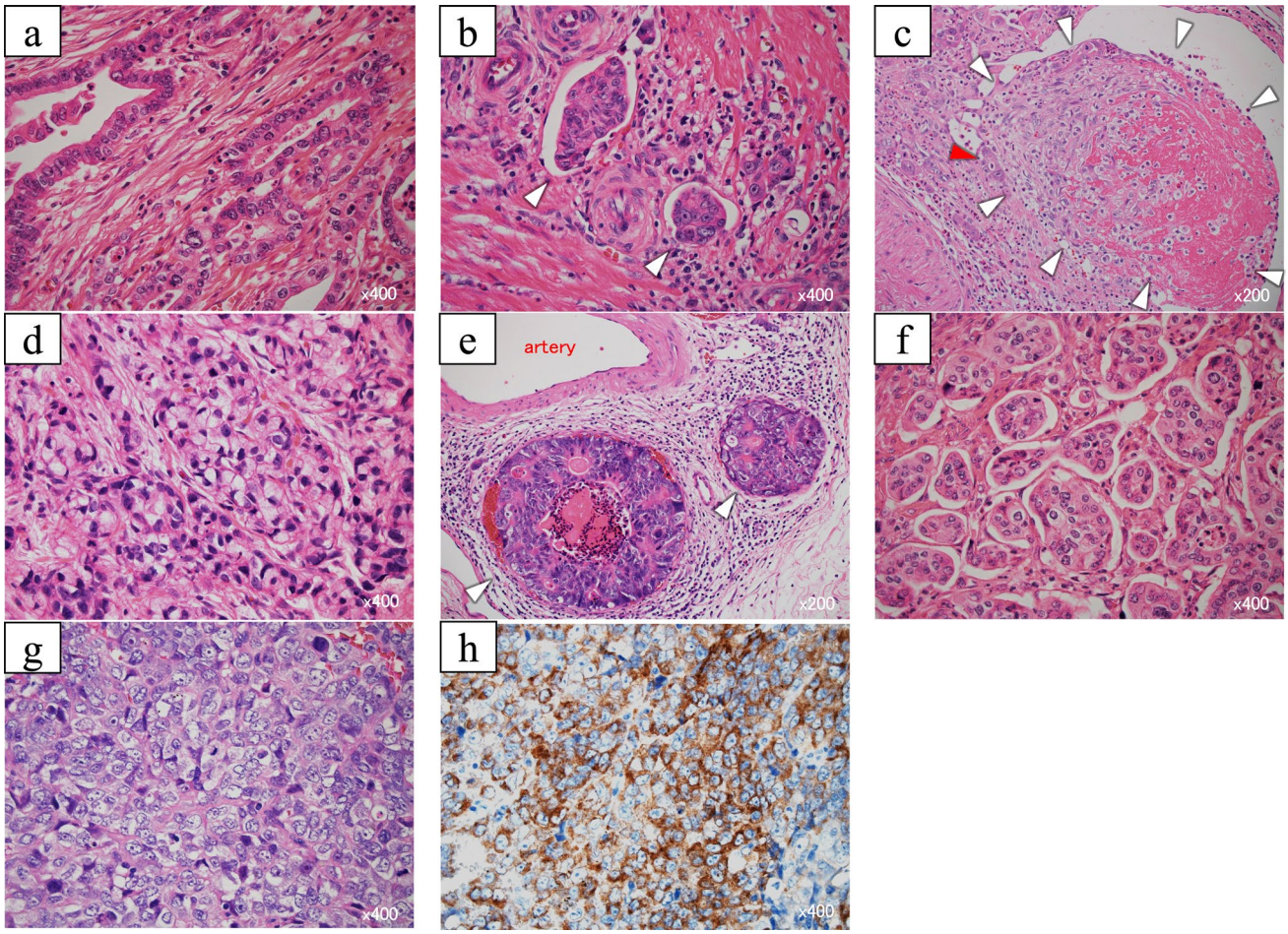

FIG. 2 Representative malignant microscopic findings of T3b tumors observed in this study. **a** A pancreaticobiliary-type tumor with abundant fibrous stroma and scirrhous proliferation. **b** Lymphatic invasion. **c** Venous invasion with thrombus. White arrowheads show the outline of the thrombus and red arrowhead shows tumor cells. **d** Poorly differentiated adenocarcinoma with signet cell-like cells. **e** Aggressive venous invasion of an intestinal-type tumor. White arrowheads show the tumor cells in the veins. **f** The invasive micropapillary pattern. **g** Neuroendocrine neoplasm components with sheet-like cell proliferation. **h** Positive synaptophysin in the cytoplasm in the specimen of **g**

that of patients with R-PhC (MST, 74.5 vs. 26.6 months, $p < 0.001$). In contrast, the OS of patients with T3b AVC was significantly worse than that of patients with R-PhC (MST, 9.2 months vs. 26.6 months, $p = 0.002$).

Subsequently, the patients with R-PhC were subdivided into two groups based on whether they received adjuvant chemotherapy. The OS of the patients with R-PhC who received adjuvant chemotherapy ($n = 276$, MST, 35.0 months) was significantly better than that of those who were managed without adjuvant chemotherapy ($n = 163$; MST, 17.5 months; $p < 0.001$). The OS of patients with T3a AVC was significantly better than that of patients with R-PhC who received adjuvant chemotherapy ($p = 0.007$). However, the OS of patients with T3b AVC tended to be worse than that of patients with R-PhC who were managed without adjuvant chemotherapy, although this difference was not statistically significant ($p = 0.140$) (Fig. 3b).

DISCUSSION

This study investigated the clinicopathological features and survival outcomes of patients with AVC, focusing on the depth of pancreatic invasion according to the UICC/AJCC staging system. Depth of pancreatic invasion was identified as an independent prognostic factor. Patients with T3a and T3b tumors showed significant differences in RFS and OS. Notably, patients with T3b tumors exhibited poor survival rates, which tended to be worse than those of patients with R-PhC who were managed without adjuvant chemotherapy, although this difference was not statistically significant. The clinicopathological characteristics, such as the frequency of poorly differentiated type, microscopic vascular invasion, advanced lymph node metastasis, invasive micropapillary pattern, and recurrence in the liver, were significantly different when the cutoff value of 0.5 cm was used to divide

TABLE 3 Pathological factors and recurrence patterns between patients with a T3a and T3b tumor

Characteristics	Pathological T stage		*p* value
	T3a	T3b	
	39	12	
Tumor size (mm) *	25 (13–48)	30 (18–60)	0.054
Poorly differentiated type	5 (12.8)	5 (41.7)	0.042
Lymphatic invasion (+)	36 (92.3)	11 (91.7)	1.000
Vascular invasion (+)	11 (28.2)	9 (75.0)	0.006
Perineural invasion (+)	18 (46.2)	5 (41.7)	1.000
Pathological N stage**			
N0	21 (53.8)	0 (0.0)	< 0.001
N1	13 (33.3)	5 (41.7)	
N2	5 (12.8)	7 (58.3)	
Pancreatobiliary type	26 (66.7)	10 (83.3)	0.470
Invasive micro papillary pattern	1 (2.6)	3 (25.0)	0.036
Extra-nodal involvement of LNM	1 (2.6)	2 (16.7)	0.134
Including NEN components	1 (2.6)	1 (8.3)	0.419
Cases of recurrence	18 (46.2)	11(91.7)	0.007
Initial recurrence site			
Liver	9 (50.0)	9 (81.8)	0.125
Lung	3 (16.7)	3 (27.3)	0.646
Lymph node	9 (50.0)	4 (36.4)	0.702
Local	4 (22.2)	3 (27.3)	1.000
Peritoneum	1 (5.6)	0 (0.0)	1.000

LNM lymph node metastasis, *NEN* neuroendocrine neoplasm

*Median (range)

**The 8th edition of UICC/AJCC classification

T3a and T3b. These results suggest that there was a significant difference in tumor progression between T3a and T3b tumors. Therefore, different treatment strategies may be necessary for T3a and T3b tumors.

Although RFS and OS were comparable between patients with T2 and T3a tumors, as in previous reports, the rates of microscopic lymphatic and perineural invasion were significantly higher in patients with T3a tumors than in those with T2 tumors. These results may suggest that pancreatic invasion within 0.5 cm indicates obvious pathological tumor progression. However, owing to the relatively good postoperative survival of patients with T3a AVC, they are excellent candidates for surgical treatment. In contrast, significant differences were observed in RFS and OS between patients with T3a and T3b tumors, and the rates of microscopic vascular invasion and multiple lymph node metastases were significantly higher in patients with T3b tumors than in those with T3a tumors. Focusing on recurrence patterns, among patients with recurrent disease, the rate of liver metastasis was higher in patients with T3b tumors than in those with T3a tumors. These results imply that pancreatic invasion deeper than 0.5 cm may represent hematogenous tumor extension and progression to systemic disease. This pattern appears to be consistent with the tumor progression patterns in pancreatic cancer. Therefore, patients with T3b tumors should be considered for multidisciplinary treatment.

A previous randomized phase III trial (ASCOT) showed that adjuvant chemotherapy improved OS in patients with resected biliary tract cancer who underwent curative resection, including patients with AVC.[15] Therefore, while patients with T2 and T3a tumors experience acceptable survival outcomes with PD alone, adjuvant treatment could potentially further enhance survival outcomes. Patients with T3b tumors, given their poor survival outcomes, obviously require adjuvant treatment. In addition, multidisciplinary treatment, including neoadjuvant therapy, may be needed, as T3b AVC tumors should be considered a potentially systemic disease. The effectiveness of neoadjuvant treatment has been established in patients with pancreatic carcinoma.[16–18] Although evidence of neoadjuvant treatment for AVC remains insufficient, clinical trials are underway for neoadjuvant treatment in patients with biliary tract cancer.[19–21]

Accurate preoperative diagnosis of the extent of pancreatic invasion is necessary to provide multidisciplinary treatment for patients with T3b AVC tumors. Various diagnostic methods are available to ascertain the extent of tumor invasion in AVC, with endoscopic ultrasonography being a significant modality.[22] However, the sensitivity of endoscopic ultrasonography in detecting tumor invasion is reported to be approximately 70–80%, and its accuracy for T-staging of AVC tumors is still a matter of debate.[22] Both the establishment of a treatment strategy and the advancement of diagnostic techniques for AVC are crucial for improving the outcomes of patients with T3b tumors.

The present study has several limitations. First, it was retrospective in nature and had a single institution setting with a limited number of patients with AVC. The population in each subgroup was relatively small, particularly in the T3b subgroup. Second, it must be taken into account that the diagnosis of the depth of pancreatic invasion may vary depending on the specimen preparation methods and individual pathologists. Third, adjuvant chemotherapy was not administered in the present study cohort, regardless of tumor progression. Owing to the rarity of AVC, an additional large-scale, multi-institutional study with a larger study population is required to validate the present findings.

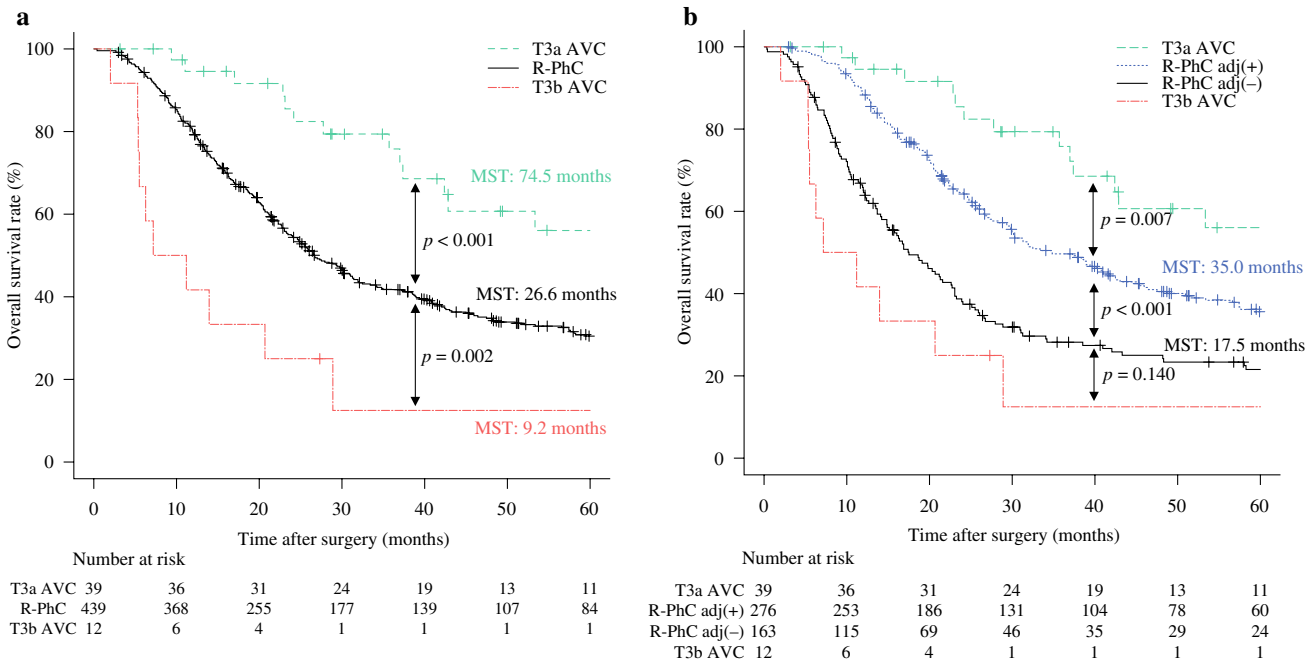

FIG. 3 **a** Overall survival curves in patients with T3a and T3b ampulla of Vater carcinoma and resectable pancreatic head carcinoma without neoadjuvant chemotherapy. **b** Patients with resectable pancreatic head carcinoma were subdivided according to whether adjuvant chemotherapy was performed. *MST* median survival time, *R-PhC* resectable pancreatic head carcinoma, *adj* adjuvant chemotherapy

In conclusion, significant differences were found in the survival outcomes between patients with T3a and T3b AVC. AVC with pancreatic invasion deeper than 0.5 cm (T3b) were associated with poor survival, comparable to that of R-PhCs, and may represent advanced tumor progression to systemic disease.

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AUTHOR CONTRIBUTIONS Y.M. and K.O. developed the main concepts and designed the study. Y.M., N.O., T.N., and T.S. were responsible for the acquisition of clinicopathological data. Y.M., K.O., and N.O. performed data analysis and interpretation and drafted the manuscript. R.A., M.Y., S.O., Y.K., K.U., and T.S. contributed to the editing and critical intellectual content. All authors have read and approved the final manuscript.

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DISCLOSURE The authors declare no conflicts of interest in association with the present study.

ETHICAL APPROVAL The study protocol for this research project was approved by a suitable Institutional Ethics Committee and conformed to the provisions of the Declaration of Helsinki. The Institutional Review Board of Shizuoka Cancer Center approved this study (approval no. J2023-45-2023-1-3).

REFERENCES

1. Riall TS, Cameron JL, Lillemoe KD, Winter JM, Campbell KA, Hruban RH, Chang D, Yeo CJ. Resected periampullary adenocarcinoma: 5 year survivors and their 6 to 10 years follow-up. *Surgery*. 2006;140:764–72.
2. Brierley JD, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumours. New York: Wiley; 2017.
3. Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, et al. AJCC cancer staging manual. 8th edn. New York: Springer; 2017.
4. Adsay NV, Bagci P, Tajiri T, Oliva I, Ohike N, Balci S, Gonzalez RS, Basturk O, Jang KT, Roa JC. Pathologic staging of pancreatic, ampullary, biliary, and gallbladder cancers: pitfalls and practical limitations of the current AJCC/UICC TNM staging system and opportunities for improvement. *Semin Diagn Pathol*. 2012;29:127–41.
5. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC cancer staging manual. 7th edn. New York, NY: Springer; 2009.
6. Imamura T, Yamamoto Y, Sugiura T, Okamura Y, Ito T, Ashida R, Ohgi K, Uesaka K. The prognostic relevance of the new 8th edition of the union for international cancer control classification of TNM staging for ampulla of Vater carcinoma. *Ann Surg Oncol*. 2019;26:1639–48.
7. Kim SJ, An S, Kang HJ, Kim JY, Jang MA, Lee JH, Song KB, Hwang DW, Cho H, Kim SC, Yu E, Hong SM. Validation of the of the 8th edition American joint committee on cancer staging system for ampulla of Vater cancer. *Surgery*. 2018;163:1071–9.
8. Kohga A, Yamamoto Y, Sano S, Sugiura T, Okamura Y, Ito T, Ashida R, Ishiwatari H, Matsubayashi H, Sasaki K, Uesaka K. Surgical strategy for T1 duodenal or ampullary carcinoma according to the depth of tumor invasion. *Anticancer Res*. 2017;37:5277–83.

9. Matsui S, Yamamoto Y, Sugiura T, Okamura Y, Ito T, Ashida R, Ohgi K, Imamura T, Uesaka K. The prognostic relevance of the number and location of positive lymph nodes for ampulla of Vater carcinoma. *World J Surg*. 2021;45:270–8.
10. Okusaka T, Nakachi K, Fukutomi A, Mizuno N, Ohkawa S, Funakoshi A, Nagino M, Kondo S, Nagaoka S, Funai J, Koshiji M, Nambu Y, Furuse J, Miyazaki M, Nimura Y. Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan. *Br J Cancer*. 2010;103:469–74.
11. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Pancreatic adenocarcinoma version 1. 2021. https://www2.tri-kobe.org/nccn/guideline/pancreas/english/pancreatic.pdf. Accessed 8 Dec 2022.
12. Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. *JAMA*. 2013;310:1473–81.
13. Uesaka K, Boku N, Fukutomi A, et al. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). *Lancet*. 2016;388:248–57.
14. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant*. 2013;48:452–8.
15. Nakachi K, Konishi M, Ikeda M, Mizusawa J, Eba J, Okusaka T, Ishii H, Fukuda H, Furuse J. A randomized phase III trial of adjuvant S-1 therapy vs. observation alone in resected biliary tract cancer: Japan clinical oncology group study (JCOG1202, ASCOT). *Jpn J Clin Oncol*. 2018;48:392–5.
16. Takahashi S, Ohno I, Ikeda M, et al. Neoadjuvant S-1 with concurrent radiotherapy followed by surgery for borderline resectable pancreatic cancer: a phase II open-label multicenter prospective trial (JASPAC05). *Ann Surg*. 2020;276(5):510–7.
17. Ielpo B, Duran H, Diaz E, Fabra I, Caruso R, Ferri V, Malavé L, Hidalgo M, Alvarez R, Plaza C, Quijano Y, Vicente E. Preoperative treatment with gemcitabine plus nab-paclitaxel is a safe and effective chemotherapy for pancreatic adenocarcinoma. *Eur J Surg Oncol*. 2016;42(9):1394–400.
18. Katz MH, Shi Q, Ahmad SA, Herman JM, Marsh Rde W, Collisson E, Schwartz L, Frankel W, Martin R, Conway W, Truty M, Kindler H, Lowy AM, Bekaii-Saab T, Philip P, Talamonti M, Cardin D, LoConte N, Shen P, Hoffman JP, Venook AP. Preoperative modified FOLFIRINOX treatment followed by capecitabine-based chemoradiation for borderline resectable pancreatic cancer: alliance for clinical trials in oncology trial A021101. *JAMA Surg*. 2016;151(8):e161137.
19. Goetze TO, Bechstein WO, Bankstahl US, Keck T, Königsrainer A, Lang SA, Pauligk C, Piso P, Vogel A, Al-Batran SE. Neoadjuvant chemotherapy with gemcitabine plus cisplatin followed by radical liver resection versus immediate radical liver resection alone with or without adjuvant chemotherapy in incidentally detected gallbladder carcinoma after simple cholecystectomy or in front of radical resection of BTC (ICC/ECC)–a phase III study of the German registry of incidental gallbladder carcinoma platform (GR)–the AIO/CALGP/ACO–GAIN-trial. *BMC Cancer*. 2020;20:122.
20. JCOG1920: a phase III trial of neoadjuvant Gemcitabine + Cisplatin + S-1 (GCS) vs. surgery first for resectable biliary tract cancer (NABICAT). https://jrct.niph.go.jp/en-latest-detail/jRCTs031200388. Accessed 8 Dec 2022.
21. Nara S, Esaki M, Ban D, Takamoto T, Mizui T, Shimada K. Role of adjuvant and neoadjuvant therapy for resectable biliary tract cancer. *Expert Rev Gastroenterol Hepatol*. 2021;15(5):537–45.
22. Trikudanathan G, Njei B, Attam R, Arain M, Shaukat A. Staging accuracy of ampullary tumors by endoscopic ultrasound: meta-analysis and systematic review. *Dig Endosc*. 2014;26(5):617–26.