with the general clinical picture in patients with borderline resectable pancreatic carcinoma, simplified information regarding detection is urgently needed. The aim of the present study was to identify indicators that can predict patients with PDAC at high risk for unresectability and to clarify who should receive precise evaluations for distant metastasis and locally advanced unresectability based on an analysis of clinical factors and the initial serum levels of carcinoembryonic antigen (CEA), CA 19-9, DUPAN-2 (pancreatic cancer-associated antigen) and CA 125 among 200 consecutive patients with PDAC.

Patients and methods

Patients

A total of 200 consecutive patients with pancreatic ductal adenocarcinoma (PDAC) who presented to the outpatient clinic of Wakayama Medical University Hospital (WMUH) between June 2009 and October 2012 were analyzed retrospectively. All tumor markers were routinely measured at the outpatient service unit without relation to prior biliary drainage. Consequently, all patients were diagnosed with PDAC or invasive ductal carcinoma derived from intraductal papillary mucinous neoplasm (IPMN) using either one or two specimens obtained with the following examinations: surgical resection, endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), percutaneous liver biopsy, peritoneal biopsy on laparoscopy or endoscopic duodenal biopsy. Patients who had undergone any prior therapies against PDAC or other types of pancreatic carcinoma, including noninvasive intraductal papillary mucinous carcinoma, acinar cell carcinoma, anaplastic carcinoma or endocrine carcinoma, were excluded from this study. Unresectable cases that were found to be progression of the disease after NACRT were also excluded from analysis due to the prediction of unresectability.

Definition of locally advanced and borderline resectable disease

The extent of pancreatic cancer was defined as resectable (stage I or II), locally advanced (stage III) according to NCCN criteria. The subset of tumors that blurs distinction between resectable and locally advanced disease were diagnosed as borderline resectable pancreatic carcinoma. Borderline resectable pancreatic carcinoma was defined as resectable at increased risk of disseminated disease and higher likelihood of an incomplete (R1 or R2) resection after surgery without relation to portal vein involvement.

Tumor markers

The levels of four tumor markers (CEA, CA19-9, DUPAN-2 and CA 125) were obtained on the initial medical examination in this study. The normal ranges of each tumor marker in WMUH were as follows: CEA: 0–5 ng/ml, CA19-9: 0–37 U/ml, DUPAN-2: 0–150 U/ml and CA 125: 0–34 U/ml.

Diagnosis of distant metastasis based on the examinations

In this study, the initial diagnostic imaging evaluations of distant metastases were performed based on the findings of plain/dynamic multidetector computerized tomography (MD-CT) and abdominal ultrasonography. The conditions for dynamic MD-CT imaging were as follows: contrast material injection: 99 ml/60 kg, 4 ml/sec (0–25 sec), shooting on 30 sec (early arterial phase), 45 sec (late arterial phase), 65 sec (portal venous phase) and 180 sec (equilibrium phase), 1.25 mm thick from the neck to the pelvis (GE Healthcare, Light Speed VCT). Only the patients who were scheduled to undergo neoadjuvant chemoradiation therapy (NACRT) received closer examinations of MRI and PET-CT for distant metastasis. During the period of this study, no patients underwent sampling or dissection of para-aortic lymph nodes. The metastasis of para-aortic lymph node was diagnosed only by preoperative MD-CT.

Indications for staging laparoscopy

Until January 2010, patients with borderline resectable pancreatic carcinoma underwent surgery first and received subsequent adjuvant chemotherapy. Between January 2010 and October 2011, all patients with pancreatic carcinoma that was initially diagnosed as borderline resectable underwent staging laparoscopy to rule out peritoneal or hepatic metastasis before receiving NACRT as local therapy. Starting in November 2011, patients with borderline resectable carcinoma received neoadjuvant chemotherapy as systemic therapy after histopathological results of PDAC were confirmed without the use of staging laparoscopy.

Cytology via peritoneal lavage

Peritoneal lavage was basically performed for cytology on all patients who underwent staging laparoscopy or laparotomy just after laparotomy. However, the results of cytology did not influence the decision for resection.

Statistical analysis

Statistical comparisons between two groups were made using the χ^2 test, Fisher's exact test or the Mann–Whitney

U-test, where appropriate. The baseline characteristics and clinical variables were compared between the resected and unresected patients and between the patients with normal and abnormal CA 125 levels using the χ^2 test for continuous and categorical variables, respectively. Univariate analyses (χ^2 test) were primarily used to select variables based on a *P*-value of <0.05. The significant variable factors were subjected to a forward logistic regression analysis to determine the net effect for each predictor while controlling the effects of the other factors. A value of $P < 0.05$ was considered to indicate statistical significance. All analyses were performed using the statistical software package SPSS II (version 20.0; SPSS, Chicago, IL, USA).

Results

Patient characteristics and the diagnostic/therapeutic flow of the 200 patients

The patient characteristics of the 200 PDAC patients revealed there were 117 males and 83 females, of whom 157 patients were symptomatic and 43 were asymptomatic. The tumors were located in the pancreatic head in 98 patients and the body/tail in 102 patients. The median age and tumor size (longest diameter) in all patients were 69 (38–86) years and 30 (10–80) mm, respectively. Positive symptoms included abdominal pain, back pain, jaundice, appetite loss, body weight loss, abdominal discomfort and emerging or exacerbation of diabetes mellitus. Negative symptoms included incidentaloma or abnormalities in tumor markers. Figure 1 presents a diagnostic and therapeutic flowchart of the 200 patients. Initially, 60 (30.0%) patients were diagnosed as being positive for distant metastasis (n = 45, 22.5%) or locally advanced unresectable tumors (n = 15, 7.5%), while 140 (70.0%) patients were diagnosed with borderline resectable or resectable pancreatic carcinoma based on the findings of MD-CT and US. Twenty-four patients underwent staging laparoscopy, two of whom were found to have peritoneal metastasis laparoscopically based on histopathological examinations. After receiving NACRT, two patients were found to have new metastases to the liver or disease progression of the primary lesion. Surgery in anticipation of resection was scheduled for 136 (68.0%) patients, 17 (8.5%) of whom were found to have unexpected peritoneal or liver metastases intraoperatively, and two (1.0%) of whom were found intraoperatively unresectable due to local extension of primary disease. Ultimately, 117 (58.5%) patients underwent successful tumor resection and 83 (41.5%) patients did not undergo resection and instead received anticancer agents (Fig. 1). In this series, unresectability was diagnosed due to locally advanced unresectable tumors (n = 18, 9.0%) or distant metastasis

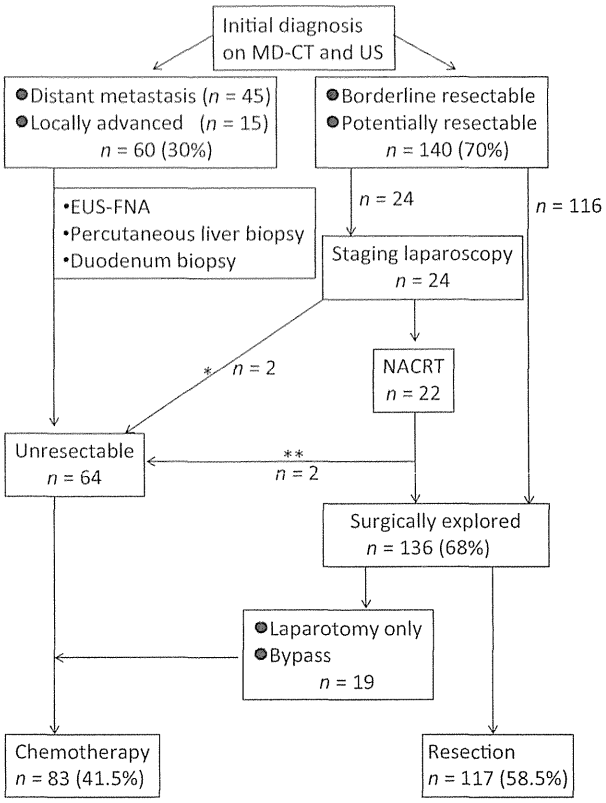

Fig. 1 A diagnostic and therapeutic flowchart of the 200 patients with pancreatic ductal adenocarcinoma. Ultimately, 117 patients underwent successful tumor resection and 83 patients did not undergo tumor resection and instead received anticancer agents. *Two of 24 patients were found to have peritoneal metastasis histopathologically based on staging laparoscopy. **Two patients were found to have new metastases to the liver or disease progression of the primary lesion after receiving neoadjuvant chemoradiation therapy (NACRT), and they were excluded from analysis about the prediction of unresectability. *EUS-FNA* endoscopic ultrasound-guided fine-needle aspiration

(n = 65, 32.5%). The sites of distant metastasis included the peritoneum (n = 16, 8.0%), liver (n = 43, 21.5%), lungs (n = 8, 4.0%), para-aortic lymph nodes (n = 19, 9.5%), adrenal glands (n = 1, 0.5%) and supraclavicular lymph nodes (n = 1, 0.5%). Sixteen patients (8.0%) were diagnosed with distant metastases at more than one site.

Factors predicting unresectability

To determine which factors are independent predictors of unresectability in patients with PDAC, a univariate analysis was used for preliminary screening of variables followed by a stepwise logistic regression analysis of the risk of unresectability using the significant univariate predictors. The univariate analysis (Table 1) identified two clinical factors and three tumor markers (a symptomatic status, tumor size [≥30 mm] and the levels of CEA, DUPAN-2 and

Table 1 Univariate analysis of factors predicting unresectability

Factor		Resection (n = 117)	Unresection (n = 81)	Total (n = 198)	P-value
Age	≥69	63	36	99	0.124
	<69	54	45	99	
Sex	Male	71	45	116	0.283
	Female	46	36	82	
Symptom	Symptomatic	83	72	155	0.002
	Asymptomatic	34	9	43	
Location of the tumor	Head	62	36	98	0.150
	Body/tail	55	45	100	
Tumor size (mm)	≥30	52	63	115	<0.001
	<30	65	18	83	
CEA	Normal	86	44	130	0.004
	Abnormal	31	37	68	
CA 19-9	Normal	24	17	41	0.536
	Abnormal	93	64	157	
DUPAN-2	Normal	60	15	75	<0.001
	Abnormal	54	63	117	
CA 125	Normal	92	37	129	<0.001
	Abnormal	17	38	55	

CA 19-9 carbohydrate antigen 19-9, *CEA* carcinoembryonic antigen, *n* number of patients

Table 2 Multivariate analysis of factors predicting unresectability

Factor	P-value	Odds ratio	95% confidence interval
Symptomatic	0.144	2.148	0.770–5.995
Tumor size ≥ 30 mm	0.002	3.257	1.516–7.000
CEA > 5 ng/ml	0.387	1.402	0.652–3.015
DUPAN-2 > 150 U/ml	0.014	2.648	1.217–5.763
CA 125 > 34 U/ml	<0.001	3.960	1.843–8.509

CA 19-9 carbohydrate antigen 19-9, *CEA* carcinoembryonic antigen

Table 3 Validity of combined screening using three independent factors predicting unresectability

Positive factors	Sensitivity (%)	Specificity (%)	Accuracy (%)
0 factor	12.8	51.0	43.0
1 factor	18.9	49.6	40.9
2 factors	59.7	67.7	65.1
3 factors	78.8	66.7	68.8

CA 125) to be associated with increased unresectability in patients with PDAC. Table 2 shows the five factors that were retained in the multivariate logistic regression analysis. Tumor size (≥30 mm) and abnormalities in the levels of DUPAN-2 and CA 125 remained significant predictors for unresectability even after controlling for the other variables (P = 0.002, 0.014, < 0.001; odds ratio [OR]: 3.257, 2.648, 3.960; 95% confidence interval [CI]: 1.516–7.000, 1.217–5.763, 1.843–8.509, respectively). In this study, the sensitivity, specificity and accuracy for unresectability were analyzed to compare the findings of combined tests using the three independent predictors. Among the four tumor markers, the serum CA 125 level demonstrated the highest sensitivity (69.6%) and accuracy (70.4%), while the DUPAN-2 level exhibited the highest specificity (80.0%). Tumor size demonstrated a specificity of 78.3% and an accuracy of 65.0% for unresectability. The patients with triple positive findings for the three predictors, including tumor size and the levels of DUPAN-2 and CA 125, presented with the highest sensitivity (78.8%) (Table 3).

Table 4 illustrates the prediction rate for distant metastasis using combined screening with the three independent predicting factors. Triple positive findings for the three factors were identified in six patients (40.0%) with peritoneal metastases, 14 patients (35.0%) with liver metastases, five patients (71.4%) with lung metastases and nine patients (50.0%) with para-aortic lymph node metastases in patients with distant metastasis (n = 45). Seven in 13 (53.8%) triple positive patients with borderline/potentially resectable pancreatic carcinoma (n = 140) revealed to be unresectable finally.

Discussion

The aim of the present study was to identify indicators that can predict unresectability in patients with PDAC. The tumor size and the levels of DUPAN-2 and CA 125 were found to be independent predictors of unresectability.

Table 4 The prediction rate for distant metastasis using combined screening

Positive factors	The sites of distant metastases (n = 45)				Borderline/potentially resectable (n = 140[a])	
	Peritoneum (n = 15)	Liver (n = 39)	Lung (n = 7)	LN (n = 18)	n	Finally unresectable
0 factor	1 (6.7%)	3 (7.7%)	0	0	44	4 (9.1%)
1 factor	1 (6.7%)	5 (12.8%)	0	3 (16.7%)	47	2 (4.3%)
2 factors	7 (46.7%)	17 (43.6%)	2 (28.6%)	6 (33.3%)	27	9 (33.3%)
3 factors	6 (40.0%)	14 (35.9%)	5 (71.4%)	9 (50.0%)	13	7 (53.8%)

LN para-aortic lymph node, *n* number of patients

[a] Three factors were available in 131 patients

Recently, the prognostic and therapeutic value of the CA 19-9 level in patients with pancreatic carcinoma treated with resection, radiotherapy and chemotherapy has been reported and is well established [3–10]. Previous studies reported that the serum concentrations of CA 19-9 and CA 125 exhibit significant increases in cases of disseminated carcinoma [15, 16]. In patients with potentially resectable PDAC, the presurgical and postresection CA 19-9 levels correlate with resectability or overall survival [3, 4]. However, in patients with advanced PDAC, elevated pretreatment levels of CA 19-9 are associated with adverse patient outcomes [17]. Approximately 5% to 10% of the general population is Lewis^{a-b-}; these individuals cannot increase their serum CA 19-9 levels [18, 19]. Those Lewis^{a-b-} patients were termed nonsecretors and were analyzed as a separate group even in the recent literature with one of the largest series of patients [3, 4]. Furthermore, there was the strong association between CA19-9 and biliary obstruction. In the present study, 46 patients (23%) had evidence of jaundice at the time of measurement of tumor markers. Presumably, these features of serum CA 19-9 explain why it was not found to be a predictor for unresectability in this study.

It has been reported that binding of MUC16 and mesothelin expressed by cancer cells mediates heterotypic cell adhesion and may contribute to the metastasis and invasion of ovarian cancer [20]. We previously reported that MUC16, which carries the peptide epitope CA125 [21], clinically represents a prognostic biomarker for PDAC, demonstrating that MUC16 is involved in pancreatic cancer cell invasion and migration [22]. Under the assumption of the presence of a CA 125-presenting disseminated status in PDAC patients, since 2009 we have prospectively investigated the clinical value of the serum CA 125 level by collecting it as an initially obtained tumor marker along with the levels of CA 19-9, CEA and DUPAN-2 and analyzing the data retrospectively with simple clinical factors. The present study demonstrated that tumor size (≥30 mm) and the levels of DUPAN-2 and CA 125 remained significant predictors of unresectability and that the level CA 125 demonstrated the highest accuracy compared to other tumor markers in patients with PDAC. In particular, in regard to the three independent predictors, the patients with triple positive findings presented with the highest sensitivity in all patients, and 7 in 13 (sensitivity 53.8%, specificity 87.3%, accuracy 84.0%) triple positive patients who were diagnosed as borderline/potentially resectable tumor in initial imaging studies revealed to be unresectable finally. Therefore triple positive for these factors is valuable to predict unresectablity in addition to recent modern imaging studies. We suggest using not only the CA 19-9 level to detect the existence of pancreatic carcinoma, but also the DUPAN-2 and CA 125 levels to evaluate the disseminated status as a favorable combination of tumor markers that should be obtained at the initial medical visit in patients with pancreatic tumors.

In conclusion, the CA 125 level is a useful indicator of unresectability in patients with PDAC, and patients with triple positive findings for a tumor size ≥30 mm, a DUPAN-2 level >150 U/ml and a CA 125 level >34 U/ml should receive precise evaluations, including laparoscopy, thin-slice high-resolution MD-CT, magnetic resonance imaging and positron emission tomography/computerized tomography, to assess distant metastasis or locally advanced unresectability.

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Conflict of interest None declared.

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Postoperative prognosis of pancreatic cancer with para-aortic lymph node metastasis: a multicenter study on 822 patients

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Abstract
Background The prognosis of pancreatic cancer patients with metastatic para-aortic lymph node (PALN) has been reported to be extremely poor. In general, PALN metastasis has been considered as a contraindication for pancreatic resection. The aim of this study was to reevaluate the postoperative prognostic value of PALN metastasis in pancreatic cancer and to determine the validity of pancreatic surgery.
Methods Retrospective multicenter analysis of 882 patients who have undergone curative-intent pancreatic resection with pathological evaluation of PALNs for pancreatic ductal adenocarcinoma between 2001 and 2012 was conducted. Clinicopathological data and outcomes were evaluated with univariate and multivariate analysis.
Results In total, 102 (12.4 %) patients had positive metastasis in PALN. Patients with metastatic PALN had significantly poorer survival than those without (17 vs. 23 months; $p < 0.001$). Multivariable analysis of 822 patients identified adjuvant chemotherapy, primary tumor status, regional lymph node metastasis, portal vein invasion, pre- and post-operative serum CA19-9 levels, and tumor grade as independent prognostic factors. In contrast, PALN metastasis did not have a significant prognostic value. Furthermore, the multivariate prognostic analysis in patients with PALN metastasis revealed that adjuvant chemotherapy and the number of metastatic PALN were significantly associated with long-term survival. Lung metastasis as initial recurrence was observed more often in patients with PALN metastasis in comparison with those without.
Conclusions Some pancreatic cancer patients with metastatic PALN may survive for longer than expected after pancreatectomy. Adjuvant chemotherapy and the number of metastatic PALN were critical factors for long-term survival of those patients.

Keywords Pancreatic cancer · Para-aortic lymph node metastasis · Postoperative prognosis

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Introduction

Pancreatic cancer has been increasing in incidence, and it is one of leading causes of cancer-related deaths worldwide [1, 2]. Despite significant progress in the treatment, the overall survival of patients remains extremely poor [3, 4]. Although surgery offers the only chance for cure or long-term survival, the majority of patients were found to be unresectable at diagnosis [5–7]. Common reasons for unresectability include vascular invasion excluding limited portal vein invasion that can be reconstructed, distant lymph node metastases, hepatic metastases, peritoneal metastases, and extra-abdominal metastases including pulmonary metastases. These surgical indications have not been much changed for many years [5, 8].

According to the TNM classification for pancreatic cancer, para-aortic lymph node (PALN) is regarded as distant lymph node and PALN metastasis is classified as distant metastasis [9, 10]. Therefore, if PALN metastasis in pancreatic cancer is suspected by preoperative images or defined by intraoperative pathological examination, pancreatic surgery is generally contraindicated. In fact, several previous studies have emphasized that the patients with metastatic PALN often had early recurrence after surgery and had extremely poor survival [11–16]. Therefore, they concluded that surgical resection did not provide survival benefit in such patients. They also discussed the need for adjuvant treatment or alternative therapeutic strategies for longer survival. However, the number of clinical studies on this issue is limited and the number of patients evaluated in each study is relatively small. Thus, there is limited clinical evidence that PALN metastasis without other distant metastasis is an absolute contraindication to pancreatic resection. In addition, due to treatment advancement including the introduction of new chemotherapeutic agents for pancreatic cancer, we occasionally see unexpected favorable outcome in daily clinical practice [17–20]. Therefore, pancreatic surgery may provide survival benefits to patients with PALN metastasis in some cases.

To address various clinical questions in the surgical treatment for pancreatic cancer including surgical indication, postoperative complications, as well as predictions of recurrence and prognosis, we have recently established a common database of seven high-volume surgical centers in Japan (Multicenter Study Group of Pancreatobiliary Surgery: MSG-PBS). By using this large-scale database, we reevaluate the postoperative prognosis of pancreatic cancer patients with PALN metastasis as a collaborative study. We further investigated risk factors for PALN metastasis and also analyzed the possibility of long-term survival in patients with metastatic PALN.

Patients and methods

Study design and data collection

This study was approved by the institutional review board of each center. We collected and registered consecutive patients who had undergone R0 or R1 pancreatic resection between 2001 and 2012 for pancreatic ductal adenocarcinoma in the database. Patients with R2 resection were not included in the database. Furthermore, patients with distant metastasis such as liver or peritoneal metastasis were also excluded from the database, even if the combined resection of metastatic sites with the primary lesion was performed. From 1,414 patients registered in the database, 592 whose PALNs had not been sampled for pathological examination were excluded. The data of a total of 822 patients with pathological proof of PALN status were collected from the database.

Para-aortic lymph nodes were sampled by harvesting the lymphocellular aortocaval tissue from the upper part of the celiac trunk to the upper part of the origin of the inferior mesenteric artery [11–13]. These lymph nodes were classified as No. 16, according to the Japanese classification [21].

Clinical data included gender, age, body mass index (BMI), neoadjuvant treatment, adjuvant chemotherapy, pre- and post-operative serum CA19-9 level, tumor location, and operation type. For tumors, pathological data included T and N status according to the 7th AJCC/UICC TNM classification, tumor size, histological type, surgical margin status, and portal vein invasion [9, 10]. Some patients received neoadjuvant treatment using chemotherapy or chemoradiotherapy depending on each institution's decision with informed consent. Postoperative adjuvant treatment of gemcitabine- or S-1-based chemotherapy was employed depending on the physicians' choice or the patients' condition.

The primary endpoint of this study was to evaluate the postoperative prognosis of pancreatic cancer patients with PALN metastasis in comparison with those without. Secondary endpoints included the assessment of risk factors for PALN metastasis and the analysis of prognostic factors in patients with PALN metastasis.

Statistical analysis

The clinicopathological parameters were compared between patients with and without PALM metastasis using Student's t test, the Chi-square test, or Fisher's exact test as appropriate. Continuous variables were expressed as mean values ± standard deviation. The median survival was estimated using the Kaplan–Meier method, and the difference was tested using the log-rank test. Patients alive at the time of follow-up point were censored. Date of last

follow-up was June 2013. Univariate and multivariate analyses were performed by the Cox proportional hazards model to evaluate significant prognostic predictors and their relative role. Statistical analyses were performed using JMP statistical discovery software (JMP version 11.0, SAS Institute, Cary, NC, USA). A p value < 0.05 was considered statistically significant.

Results

Correlations of clinicopathological factors with para-aortic lymph node metastasis

Among a total of 822 patients, pancreatoduodenectomies were performed in 617 patients (75.1 %), distal pancreatectomies in 161 patients (19.6 %), and total pancreatectomies in 44 patients (5.3 %). The 30-day and 90-day mortality rates were 0.7 and 2.9 %, respectively. The mean and median numbers of PALNs sampled for pathological examination were 4.3 (standard deviation, 4.2) and 3 (range, 1–27), respectively. As a result, while PALNs were negative for metastasis in 720 patients, they were positive in 102 patients (12.4 %). The mean and median numbers of metastatic PALNs were 1.9 (standard deviation, 1.6) and 1 (range, 1–11), respectively. Sixty patients (58.8 %) had single metastasis in PALNs, while 42 (41.2 %) had multiple metastasis.

Between patients with and without PALN metastasis, there were no significant differences in various clinicopathological factors including gender, age, BMI, neoadjuvant treatment, adjuvant chemotherapy, tumor size, tumor location, tumor differentiation, and portal vein invasion (Table 1). In contrast, PALN metastasis significantly correlated with R1 resection, advanced primary tumor status, regional lymph node metastasis, and elevated pre- and post-operative serum CA19-9 levels. In patients with metastatic PALN, only three patients had T1 tumor and/or no regional lymph node metastasis. While approximately two-thirds (72.3 %) of the patients without PALN metastasis had normal CA19-9 levels after surgery, more than half (55.0 %) of patients with PALN metastasis still had elevated CA19-9 levels.

Table 1 Clinicopathological characteristics for patients with pancreatic adenocarcinoma

Variables	Para-aortic lymph node metastasis		p value
	Absent ($n = 720$)	Present ($n = 102$)	
Gender, male, n (%)	401 (56 %)	46 (45 %)	0.056
Age, mean ± SD (years)	66.5 ± 9.5	65.6 ± 9.3	0.422
Body mass index (BMI), mean ± SD (kg/m^2)	21.6 ± 3.2	21.1 ± 2.8	0.098
Neoadjuvant treatment			0.061
Yes	214 (30 %)	21 (21 %)	
No	506 (70 %)	81 (79 %)	
Adjuvant chemotherapy			0.113
Yes	373 (52 %)	44 (43 %)	
No	347 (48 %)	58 (57 %)	
Tumor size, mean ± SD (cm)	2.9 ± 1.2	3.0 ± 1.3	0.241
R status			<0.001
R0	566 (79 %)	44 (43 %)	
R1	154 (21 %)	58 (57 %)	
T status			0.016
T1-2	61 (9 %)	2 (2 %)	
T3-4	659 (91 %)	100 (98 %)	
N status			<0.001
Negative	279 (39 %)	2 (2 %)	
Positive	441 (61 %)	100 (98 %)	
Portal vein invasion			0.911
No	474 (66 %)	67 (66 %)	
Yes	242 (34 %)	35 (34 %)	
Preoperative CA19-9 (units/ml)			<0.001
<100	368 (51 %)	32 (31 %)	
>100	352 (49 %)	70 (69 %)	
Postoperative CA19-9 (units/ml)			<0.001
<37	485 (72 %)	45 (45 %)	
>37	186 (28 %)	55 (55 %)	
Tumor location			0.598
Head/whole	574 (80 %)	84 (82 %)	
Body/tail	146 (20 %)	18 (18 %)	
Tumor differentiation			0.248
G1	185 (27 %)	19 (19 %)	
G2	447 (65 %)	70 (71 %)	
G3/4	59 (8 %)	10 (10 %)	

Survival of patients according to para-aortic lymph node metastasis status

There was a significant difference in overall survival between patients with and without PALN metastasis ($p < 0.001$; Fig. 1a). The median survival time (MST) for patients with and without PALN metastasis were 16.9 and 22.6 months, respectively. The 1-, 2-, 3-, and 5-year survival rates were for patients with PALN metastasis were 63.8, 30.0, 16.7, and 6.8 %, respectively, compared with 74.6, 48.4, 35.6, and 25.4 % for patients without PALN metastasis.

To evaluate the change and improvement of treatment outcome during the study period, we compared the prognosis of patients with PALN metastasis treated in the first 5 years of 2001–2005 with that in the latter 5 years of

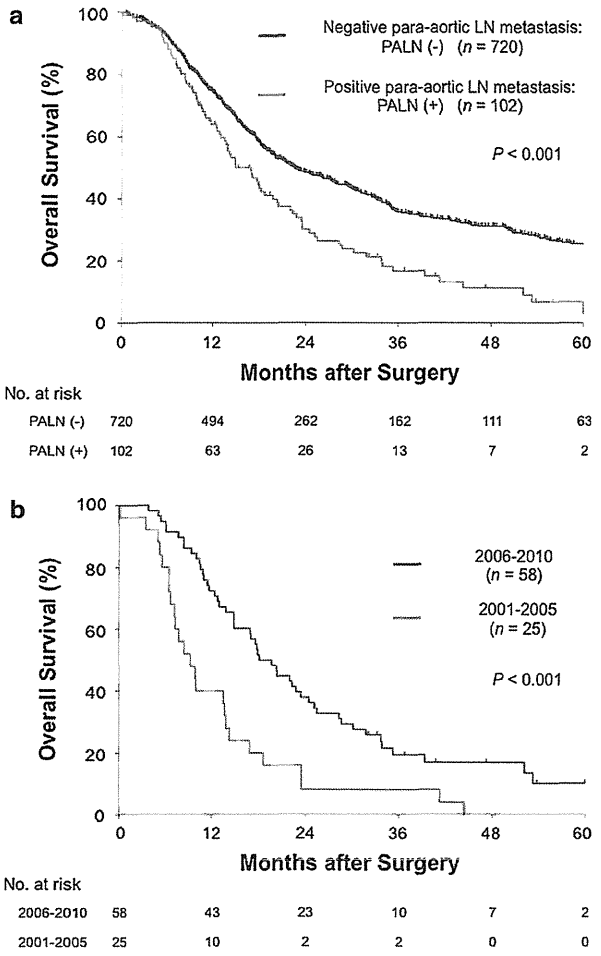

Fig. 1 Kaplan–Meier analysis of overall survival. **a** Patients with para-aortic lymph node (PALN) metastasis ($n = 102$) had worse survival compared to those without ($n = 720$). **b** Postoperative survival of patients with PALN metastasis operated in the year of 2006–2010 ($n = 58$) was better than that in 2001–2005 ($n = 25$)

2006–2010. For data accuracy, we excluded patients operated on between 2011 and 2012 with a follow-up of less than 30 months from this analysis. The survival of patients with PALN metastasis treated in the latter period was significantly better than that of patients in the first half period ($p < 0.001$; Fig. 1b). The MST for patients treated in the first and latter half period were 9.3 and 18.2 months, respectively.

Univariate and multivariate survival analyses

Using the Cox proportional hazards model, we examined prognostic factors in 822 patients with pancreatic adenocarcinoma. In univariate analysis, factors associated with better patient survival included the administration of adjuvant chemotherapy, R0 resection, T1-2 tumor, negative regional lymph node metastasis, no portal vein invasion, a preoperative value of CA19-9 $\leq$100 units/ml, normal level of postoperative CA19-9, high-grade differentiation of tumor, and negative PALN metastasis (Table 2). On the other hand, gender, age, neoadjuvant treatment, and tumor location did not correlate with prognosis. Multivariable analysis indicated that adjuvant chemotherapy, T status, N status, portal vein invasion, and pre- and post-operative CA19-9 level, and tumor grade had significant prognostic value (Table 2). In contrast, not only *R* status but also PALN metastasis did not have prognostic value.

Factors for long-term survival in patients with para-aortic lymph node metastasis

Among 102 patients with PALN metastasis, 39 (38.2 %) died within 1 year after surgery. On the other hand, 63 patients (61.8 %) survived for over 1 year, 26 (25.5 %) for over 2 years, 13 (12.7 %) for over 3 years, and two (2.0 %) for over 5 years. To investigate predictive factors for long-term survival in patients with PALN metastasis, we further performed survival analysis in these patients. As a result, adjuvant chemotherapy and the number of metastatic PALN were found to be significant independent predictors of long-term survival (Table 3). In contrast, the total number of metastatic regional lymph nodes and postoperative CA19-9 level did not have significant prognostic value in patients with PALN metastasis. The MST of patients with adjuvant chemotherapy was 23.6 months, while that without adjuvant chemotherapy was 10.6 months (Fig. 2a). In addition, the MST of patients with single PALN metastasis was 22.1 months, while that with multiple PALN metastasis was 12.8 months. Furthermore, MST of patients with two metastatic PALNs was 11.7 months, and that with more than two metastatic PALNs was 16.9 months. Although the difference between these two groups was not significant, both were significantly worse that that of patients with single PALN metastasis (Fig. 2b).

Postoperative recurrence pattern according to para-aortic lymph node metastasis status

At the time of analysis, 516 patients (71.7 %) without PALN metastasis had recurrence. On the other hand, there were significantly more recurrences in patients with PALN metastasis ($n = 91$, 89.2 %, $p < 0.001$). Finally, we compared the initial recurrence pattern between patients with PALN metastasis and those without (Table 4). There were no significant differences in the frequency of hepatic, local, and peritoneal recurrence as initial recurrence. In contrast, lung metastasis was observed more often in patients with PALN metastasis than those without ($p = 0.012$).

Table 2 Univariate and multivariate analysis of prognostic factors in 822 patients with pancreatic adenocarcinoma

Variable	No. of patients (%)	Univariable analysis		Multivariable analysis		
		Hazard ratio	*P* value	Hazard ratio	95 % CI	*P* value
Gender			0.817			
Male	447 (54)	1.000				
Female	375 (46)	0.980				
Age (years)			0.085			
<70	499 (61)	1.000				
>70	323 (40)	1.166				
Neoadjuvant treatment			0.783			
Yes	235 (29)	1.000				
No	587 (71)	1.028				
Adjuvant chemotherapy			<0.001			<0.001
Yes	417 (51)	1.000		1.000	–	
No	405 (49)	3.047		2.730	2.253–3.313	
R status			<0.001			0.968
R0	610 (74)	1.000		1.000	–	
R1	212 (26)	1.620		1.005	0.811–1.250	
T status			<0.001			0.002
T1-2	63 (8)	1.000		1.000	–	
T3-4	759 (92)	3.030		1.925	1.264–3.085	
N status			<0.001			<0.001
Negative	281 (34)	1.000		1.000	–	
Positive	541 (66)	2.003		1.854	1.483–2.330	
Portal vein invasion			<0.001			0.002
No	541 (66)	1.000		1.000	–	
Yes	277 (34)	1.649		1.360	1.116–1.654	
Preoperative CA19-9, units/ml			<0.001			0.046
<100	400 (49)	1.000		1.000	–	
>100	422 (51)	1.767		1.250	1.004–1.556	
Postoperative CA19-9, units/ml			<0.001			0.006
<37	530 (69)	1.000		1.000	–	
>37	241 (31)	2.140		1.376	1.097–1.724	
Tumor location			0.269			
Head/whole	658 (80)	1.000				
Body/tail	164 (20)	0.889				
Tumor differentiation			<0.001			0.047
G1	204 (26)	1.000		1.000	–	
G2	517 (65)	1.488		1.181	0.944–1.490	
G3/4	69 (9)	1.774		1.565	1.095–2.207	
Para-aortic lymph node metastasis			<0.001			0.335
Positive	102 (12)	1.000		1.145	0.867–1.496	
Negative	720 (88)	0.592		1.000	–	

Discussion

In the past several years, some progress has been made in the treatment for pancreatic cancer [5]. However, patient prognosis remains extremely poor and surgical indication has not been greatly changed. In general, pancreatic cancer with distant metastasis such as liver, lung, and peritoneal metastasis is thought to be systemic and incurable disease. Therefore, even if clinically apparent distant metastasis is a single lesion, surgery has usually been contraindicated. Para-aortic lymph nodes have been classified as non-regional lymph nodes and cancer cells existing in PALN are recognized as distant metastasis [9, 10]. To date, there are only a limited number of studies on the postoperative

Table 3 Univariate and multivariate analysis of prognostic factors in 102 patients with para-aortic lymph node metastasis

		Univariate Analysis		Multivariate analysis		
	No. of patients (%)	Hazard ratio	*p* value	Hazard ratio	95 % CI	*p* value
Gender			0.488			
Male	46 (45)	1.000				
Female	56 (55)	0.855				
Age			0.901			
<70	65 (64)	1.000				
>70	37 (36)	1.029				
Neoadjuvant treatment			0.306			
Yes	21 (21)	1.000				
No	81 (79)	1.361				
Adjuvant chemotherapy			<0.001			0.003
Ye s	44 (43)	1.000		1.000	–	
No	58 (57)	2.405		2.060	1.270–3.384	
Number of metastatic regional LN			0.013			0.161
<3	28 (27)	1.000		1.000	–	
>4	74 (73)	1.864		1.474	0.860–2.619	
R status			0.083			
R0	44 (43)	1.000				
R1	58 (57)	1.481				
Preoperative CA19-9			0.057			
<100	32 (31)	1.000				
>100	70 (69)	1.578				
Postoperative CA19-9			0.005			0.307
<37	45 (45)	1.000		1.000	–	
>37	55 (55)	1.918		1.288	0.794–2.113	
Tumor location			0.065			
Head/Whole	84 (82)	1.000				
Body/Tail	18 (18)	0.586				
Tumor differentiation			0.218			
G1	19 (19)	1.000				
G2	70 (71)	1.605				
G3/4	10 (10)	1.176				
Number of metastatic PALN			<0.001			0.017
Single	60 (59)	1.000		1.000	–	
Multiple	42 (41)	2.200		1.840	1.115–3.062	

prognosis in patients with PALN metastasis [11–16]. These previous studies reported that the median survival time of patients with metastatic PALN was only between 5.1 and 15.7 months. Furthermore, early recurrence and little benefit of surgery have been described [11, 13]. These clinical data have supported that PALN metastasis is a common reason for unresectability in pancreatic cancer. However, this large-scale collaborative study has demonstrated that the prognosis of pancreatic cancer patients with PALN metastasis in the current study seems to be better than that in previous studies (Table 5). Furthermore, this study also clarified that the prognosis of those patients has been improved during the study period. The median overall survival was approximately 9 months in patients treated between the years 2001 and 2005. This is comparable to that shown in previous reports. In contrast, the median overall survival is up to 18 months in patients treated in the most recent 5 years. In fact, whereas Doi et al. reported that PALN metastasis was the only independent prognostic factor for resectable pancreatic cancer, multivariable analysis of this study demonstrates that it no longer has an independent prognostic value [13]. Recent clinical trials to evaluate new chemotherapeutic regimens including FOLFILINOX or nab-paclitaxel plus gemcitabine have demonstrated significantly improved survival for metastatic pancreatic cancer with the median survival times of 11.1

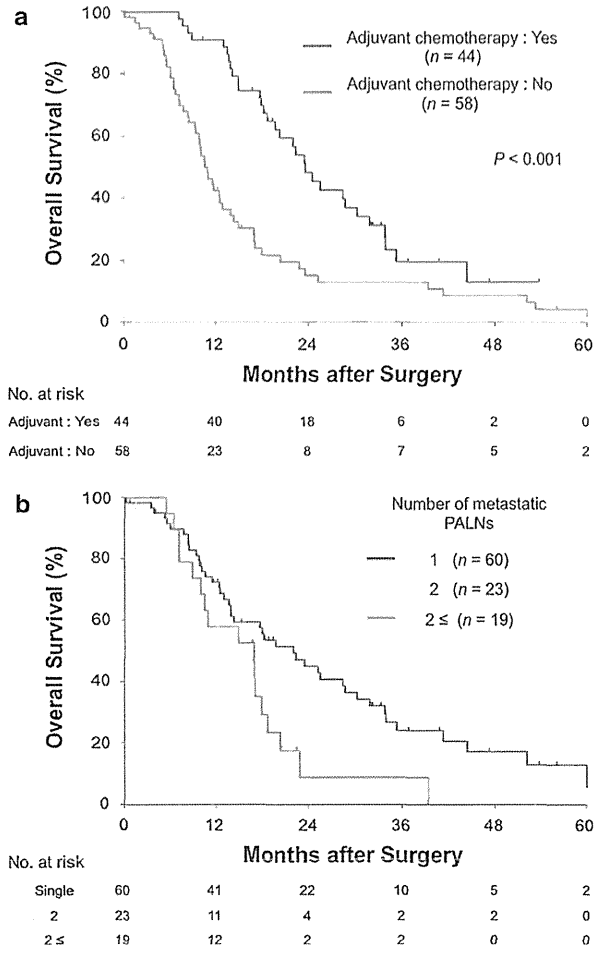

Fig. 2 Kaplan–Meier analysis of overall survival in patients with para-aortic lymph node (PALN) metastasis. **a** Patients with adjuvant chemotherapy ($n = 44$) had better survival than those without ($n = 58$) ($p < 0.001$). **b** Patients with single PALN metastasis ($n = 60$) had better survival than those with two metastatic PALNs ($p = 0.001$, $n = 23$) or more than two metastatic PALNs ($p = 0.018$, $n = 19$)

and 8.5 months, respectively [22, 23]. Even in comparison with these latest data for metastatic pancreatic cancer, the median overall survival of about 18 months is likely to be better, suggesting that there may be some differences in the tumor behavior of pancreatic cancer between PALN metastasis and other types of distant metastasis.

The precise reasons for the improved survival of patients with PALN metastasis are not fully elucidated. One of the major reasons is most likely to perform adjuvant chemotherapy. In Japan, gemcitabine was approved in 2001 and S-1 in 2006 for the treatment of pancreatic cancer. These chemotherapeutic reagents occasionally bring unexpectedly favorable clinical outcomes. In addition, recent randomized clinical trials indicating the efficacy of gemcitabine in adjuvant settings encourage surgeons and

Table 4 Recurrence pattern according to para-aortic lymph node metastasis status

	Para-aortic lymph node metastasis		p value
	Absent ($n = 516$)	Present ($n = 91$)	
Liver	194 (38 %)	29 (32 %)	0.346
Local	180 (35 %)	26 (29 %)	0.280
Peritoneum	112 (22 %)	19 (21 %)	1.000
Lung	73 (14 %)	23 (25 %)	0.012

Table 5 Comparison of other series with prognosis of patients with para-aortic lymph node metastasis

Author	Year	Study period	No. of total patients	No. of patients with para-aortic lymph node metastasis (%)	MST (months)
Present	2014	2001–2012	822	102 (12)	16.9
Schwarz et al.	2014	2000–2010	111	17 (15)	15.7
Kanda et al.	2011	1981–2009	429	49 (11)	8.3
Murakami et al.	2010	1992–2008	103	18 (17)	12.4
Doi et al.	2007	1980–2000	133	19 (14)	5.1
Shimada et al.	2006	1999–2003	133	29 (22)	13

MST median survival time

oncologists to employ adjuvant chemotherapy more actively than before [24, 25]. In this study, approximately 20 % of patients with PALN metastasis received neoadjuvant treatment and 43 % received adjuvant chemotherapy. Other various efforts in an adjuvant setting and after postoperative recurrence might have contributed to improve patient survival [20, 26, 27].

Preoperative diagnosis of PALN metastasis is not always easy, even when using the latest imaging technology [28, 29]. In daily clinical practice, enlarged PALNs suspicious of metastasis or inflammation are sometimes encountered. The enlarged PALN may be thought to be a distant metastasis and the reason for unresectability in some institutions, even if it is not pathologically proven. In the United States and Europe, the sampling of PALNs does not seem a routine procedure during surgery. Therefore, the actual rate of metastatic PALN in pancreatic cancer is unknown. However, even with the small number of PALN sampling of 4.3, the metastatic rate in PALN of 12 % in this analysis is not low and cannot be ignored. Previous studies have demonstrated that several factors including tumor size, surgical margin, postoperative CA19-9 level, extrapancreatic nerve invasion, age, and portal vein

invasion were associated with PALN metastasis [11, 12, 30]. Our data, including R status, pre- and post-operative CA19-9 levels, corroborate some of the previous reports. On the other hand, Nagai et al. have reported that even T1 and T2 primary tumors of pancreatic cancer had a relatively high rate of PALN metastasis [31]. In this series, two T1 primary tumors had PALN metastasis. Furthermore, Hirono et al. have reported that there is a direct lymphatic drainage pathway from the pancreatic head to the PALN area [32]. Taken together, although PALN metastasis is a common feature of pancreatic cancer, it may occur at a relatively early stage before metastasizing to other distant organs.

Previous studies have shown that there were no or very few long-term survivors after pancreatic resection for the patients with PALN metastasis [11–13]. In contrast, 26 out of 102 patients with metastatic PALN survived for over 2 years and 13 for over 3 years. We then analyzed the conditions for long-term survival after pancreatic resection for patients with PALN metastasis. As a result, adjuvant chemotherapy and the number of metastatic PALNs were independent prognostic factors in patients with PALN metastasis. Data suggested that multimodal treatment including surgery and chemotherapy might lead to long-term survival in some patients, especially with single PALN metastasis. To consider future strategy, we analyzed the initial recurrence pattern. The pattern did not differ much between patients with PALN metastasis and those without. However, only lung metastasis was observed more often in patients with PALN metastasis, although the underlying mechanism is unclear at present. Data suggested that a more effective systemic anticancer treatment was needed. As demonstrated in recent clinical trials, several promising chemotherapy regimens may further improve postoperative prognosis of PALN-positive patients [22, 23].

There are several limitations in this study. Firstly, the sampling of PALNs was performed based on the surgeon's decision at each institution. Furthermore, massive PALN metastases even in patients without any other distant metastases might be considered to be contraindications in most cases. Therefore, actual status of PALN remained unknown in all patients. Secondly, this study is retrospective and the true significance of pancreatic resection remains unknown. Thirdly, since this is multi-institutional study, each institution has different treatment strategies including neoadjuvant and adjuvant treatment. Such inter-institutional differences can affect the analyzed data. Therefore, in order to obtain medical evidence and to evaluate surgical indications precisely, prospective clinical studies, especially under current circumstances, need to be done. However, since this study is the largest as well as the first multicenter investigation to explore the postoperative prognosis of patients with PALN metastasis, our data may provide useful information on surgical indications and multimodal treatment for advanced pancreatic cancer.

In conclusion, some pancreatic cancer patients with PALN metastasis may survive for longer than expected after pancreatectomy. To expect long-term survival in those patients, adjuvant chemotherapy and single PALN metastasis are critical factors.

Conflict of interest The authors declare no conflicts of interest.

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ORIGINAL ARTICLE

Clinicopathological features and surgical outcomes of adenosquamous carcinoma of the pancreas: a retrospective analysis of patients with resectable stage tumors

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Abstract
Purpose Adenosquamous carcinoma of the pancreas is a rare subtype of pancreatic cancer. We herein describe the clinicopathological features of surgically resected cases of adenosquamous carcinoma of the pancreas.
Methods From 2001 to 2011, 132 patients underwent R0 resection for Stage IIA or IIB pancreatic cancer. The survival rate, pathological features and recurrence status were reviewed.
Results Out of 132 patients, 121 patients had tubular adenocarcinoma, and only seven had adenosquamous carcinoma (ASC). The incidence of ASC increased with the tumor size. The overall survival and disease-free survival periods of the patients with ASC were significantly shorter than those of patients with tubular adenocarcinoma ($p = 0.0153$ and $p = 0.0045$). The histological findings revealed more marked venous invasion in ASC compared to tubular adenocarcinoma (G1, G2 and G3). The proportion of v3 cases, which denotes the most severe venous invasion, was 31.3 % in G1, 47.3 % in G2, 60.0 % in G3 and 71.4 % in ASC cases, respectively. Other factors, including lymphatic and nerve invasion, were not correlated with the histological subtypes. The incidence of ASC was 11.1 % in the tumors more than 6 cm in diameter, and 0 % in those less than 2 cm in diameter.
Conclusions We revealed that adenosquamous carcinoma of the pancreas is associated with a poor outcome, and also clarified its clinicopathological features.

Keywords Adenosquamous carcinoma · Pancreatic carcinoma · Distant metastasis · Venous invasion

Introduction

Adenosquamous carcinoma (ASC) is defined as an admixture of two distinct components of adenocarcinoma and squamous carcinoma, in which the squamous component should account for at least 30 % [1–3]. ASC of the pancreas is an uncommon subtype of pancreatic cancer, associated with aggressive behavior and less favorable survival rates [4–7]. ASC of the pancreas is reported to represent only 1.0 % of pancreatic neoplasms according to the Pancreatic Cancer Registry in Japan, in which 25,582 patients were recorded from 1981 to 2002 [4]. Another large-scale analysis, based on the California Cancer Registry database, in which 24,604 patients with pancreatic neoplasms were recorded from 2000 to 2007, showed a 0.39 % incident rate of ASC [8]. The median overall survival after curative resection was reported to be 6–14 months, and the 3-year overall survival rate was reported to be 14.0 % [5, 9, 10]. ASC is also found in the breast, lung, stomach, colon, rectum, anus, uterus and cervix. ASCs in these organs are also rare and regarded as a

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disease with a dismal prognosis compared to the most common types of the cancers [11–17]. However, there have been few well-documented studies about ASC of the pancreas because of its rarity, and therefore, the cause of the unfavorable prognosis has not yet been clarified.

In this study, we examined the clinicopathological features in patients with ASC of the pancreas in comparison with those with tubular adenocarcinoma (TAC) and attempted to identify the causes of the poor prognosis. We hope that a better understanding of ASC of the pancreas will lead to novel therapeutic strategies that provide prolonged survival for affected patients.

Methods

Registry and population

We performed a retrospective analysis of the prospective database kept at the Division of Hepato-Biliary Pancreatic Surgery, Tohoku University, Japan. Between 1961 and 2011, a total of 1,278 patients with pancreatic neoplasms were recorded, including those with pancreatic cancer, endocrine tumors and non-epithelial neoplasms. All patients were Japanese, and the tumor extent was recorded according to the classifications of both the Japan Pancreatic Society (JPS) and the UICC. The stage description below is the conclusive stage from the surgical and pathological findings based on the UICC classification, unless otherwise specified. Since the approval of gemcitabine in 2001 in Japan had a significant impact on the patient's survival, we focused on the 195 patients with surgically resected invasive pancreatic cancer treated from January 2001 to January 2011 [18]. In order to clarify the biological behavior of ASC at similar disease extent as TAC, patients with Stage III and IV tumors who were not suitable for surgical resection and those with Stage IA and IB tumors who had obviously favorable prognoses were excluded. As a result, 132 of 195 patients were selected who had been histologically diagnosed to have Stage IIA or IIB pancreatic cancer with R0 resection. The surgical procedures performed were pancreaticoduodenectomy (including substomach-preserving pancreaticoduodenectomy and pylorus-preserving pancreaticoduodenectomy), distal pancreatectomy and total pancreatectomy. Among the patients, TAC was the most common histological type, comprising 121 cases, whereas there were only seven cases of ASC and four cases of other diseases. Invasive pancreatic cancers derived from intraductal papillary mucinous tumors and mucinous cystic tumors were excluded. We finally chose the 128 patients with TAC ($n = 121$) and ASC ($n = 7$) to compare the survival rates, pathological features and recurrent status between these two subtypes. The recurrence status was retrospectively examined for the patients with TAC and ASC. The sites of distant metastasis, including the liver, lungs, brain and bone, were examined. Of the 128 patients, 100 with TAC and six with ASC had sufficient information available to analyze the recurrence status.

Pathological analysis

The pathological features including venous invasion, lymphatic invasion, intrapancreatic nerve invasion and the growth patterns of tumors infiltrating the surrounding tissue were analyzed in the patients with TAC and ASC. To evaluate the invasion status, we examined the tumor sections made from the maximum diameter of the tumor. Elastica–Masson staining was performed to assess the venous invasion, and hematoxylin–eosin staining was performed to analyze the other factors. These factors were evaluated routinely according to the JPS classification, and were classified into three or four levels [3]. The degrees of venous invasion were defined in the classification as follows: v0, no venous invasion; v1, slight venous invasion; v2, moderate venous invasion and v3, marked venous invasion. For unbiased assessment, the criteria had been administered in our institute according to the previously published article: v0 for no invasion detected per slide, v1 for one or two areas of invasion, v2 for three or four areas of invasion and v3 for more than five areas of invasion per slide [19].

Lymphatic invasion and intrapancreatic nerve invasion were defined identically as venous invasion. The growth patterns of tumors infiltrating the surrounding tissue were classified into three levels: INF alpha, an expanding pattern of growth characterized by a distinct border with the surrounding tissue; INF beta, a pattern intermediate between infiltration alpha and infiltration gamma and INF gamma, a diffusely infiltrating pattern of growth characterized by an indistinct border that shows infiltration of the surrounding tissue.

Statistical analysis

The clinical characteristics were analyzed using Pearson's Chi-square test or Fisher's exact test for categorical and dichotomous variables, and Student's t test was used for comparisons of continuous variables. The overall survival (OS) was calculated using the dates of the initial surgical or chemotherapeutic treatment when neo-adjuvant chemotherapy was performed and the date of occurrence of either death from any cause or last contact. The disease-free survival (DFS) was defined as the duration of time the patient remained free of disease after a surgical operation. The Kaplan–Meier method was used to create survival curves, and the differences were assessed with the log-rank

Table 1 The clinical features of the 128 patients with TAC and ASC

	TAC ($n = 121$)	ASC ($n = 7$)	p value
Age, mean (years)	64.2 (27–83)	62.0 (51–77)	0.5782*
Sex			
Male	70 (57.9)	5 (71.4)	0.6988†
Female	51 (42.1)	2 (28.6)	

TAC tubular adenocarcinoma, *ASC* adenosquamous carcinoma

* Student's t test, † Fisher's exact test

Table 2 The clinicopathological findings, including the tumor location, T, N, M and UICC stage

	TAC ($n = 121$)		ASC ($n = 7$)		p value
	n	%	n	%	
Location					
Head	86	71.1	5	71.4	0.1131*
Body	27	22.3	0	0.0	
Tail	5	4.1	1	14.3	
Two segments of pancreas	3	2.5	1	14.3	
All segments of pancreas	0	0.0	0	0.0	
T					
Tis	0	0.0	0	0.0	0.6489*
T1	1	0.8	0	0.0	
T2	7	5.8	1	14.3	
T3	113	93.4	6	85.7	
T4	0	0.0	0	0.0	
N					
N0	34	28.1	1	14.3	0.4253*
N1	87	71.9	6	85.7	
M					
M (−)	121	100.0	7	100.0	–
M (+)	0	0.0	0	0.0	
Stage					
IIA	34	28.1	1	14.3	0.6729*
IIB	87	71.9	6	85.7	

TAC tubular adenocarcinoma, *ASC* adenosquamous carcinoma

* Pearson's Chi-square test

test. All analyses were conducted using the JMP 9 software program (SAS Institute, Cary, NC, USA). Statistical significance was assumed for a two-tailed p value <0.05.

Results

Patient characteristics

Tubular adenocarcinoma (TAC) was the most common histological type, totaling 121 cases, whereas only seven patients had ASC, two had acinar cell carcinoma and two had undifferentiated carcinomas. TAC was divided into three subtypes: well differentiated (G1, $n = 16$), moderately differentiated (G2, $n = 95$) and poorly differentiated (G3, $n = 10$). Among the patients, the 128 patients with TAC ($n = 121$) and ASC ($n = 7$) were enrolled in the analysis. The clinical features of these patients are shown in Table 1. No significant differences were found in the mean age and sex proportion between the TAC and ASC patients. The clinicopathological findings, including the tumor location, T, N, M and stage, are shown in Table 2. The distributions of the TNM and stage were similar for TAC and ASC. Cancer located in the pancreatic head, including the uncinate process, was far more common compared to that in the pancreatic body and tail. Regional lymph node metastasis was positive in more than 70 % of the patients, who were categorized into Stage IIB. Neoadjuvant chemotherapy with gemcitabine or a gemcitabine/S1 combination was administered to 31.4 % (38/121) of the patients with TAC and 14.3 % (1/7) of those with ASC. Adjuvant chemotherapy was administered to 83.1 % of the patients with TAC and 71.4 % of those with ASC. There were no significant differences between the two groups in terms of the clinicopathological findings or treatment with chemotherapy (data not shown).

Overall survival

The overall survival of the 35 patients with Stage IIA disease and 93 patients with Stage IIB disease, including both TAC and ASC cases, is shown in Fig. 1a. The median survival times (MSTs) of the resected patients with Stage IIA and Stage IIB disease were 24.5 and 17.9 months, respectively. No statistically significant difference was detected between the two stages ($p = 0.0931$). Therefore, we analyzed these patients together in the subsequent analyses.

The overall survival of the 121 patients with TAC and seven patients with ASC, including both Stage IIA and IIB disease, is shown in Fig. 1b. The MSTs of the resected patients with TAC and those with ASC were 20.3 and 8.8 months, respectively, demonstrating that ASC had a significantly worse prognosis than TAC ($p = 0.0153$).

Pathological features

Venous invasion, lymphatic invasion, intrapancreatic nerve invasion and the growth patterns of tumors infiltrating the surrounding tissue were analyzed. Representative microscopic images are shown in Fig. 2. The pathological features were compared among the three differentiation subtypes of TAC (G1, G2 and G3) and the ASC patients. The groups had similar proportions in terms of the tumor location, T, N, M and stage (data not shown).

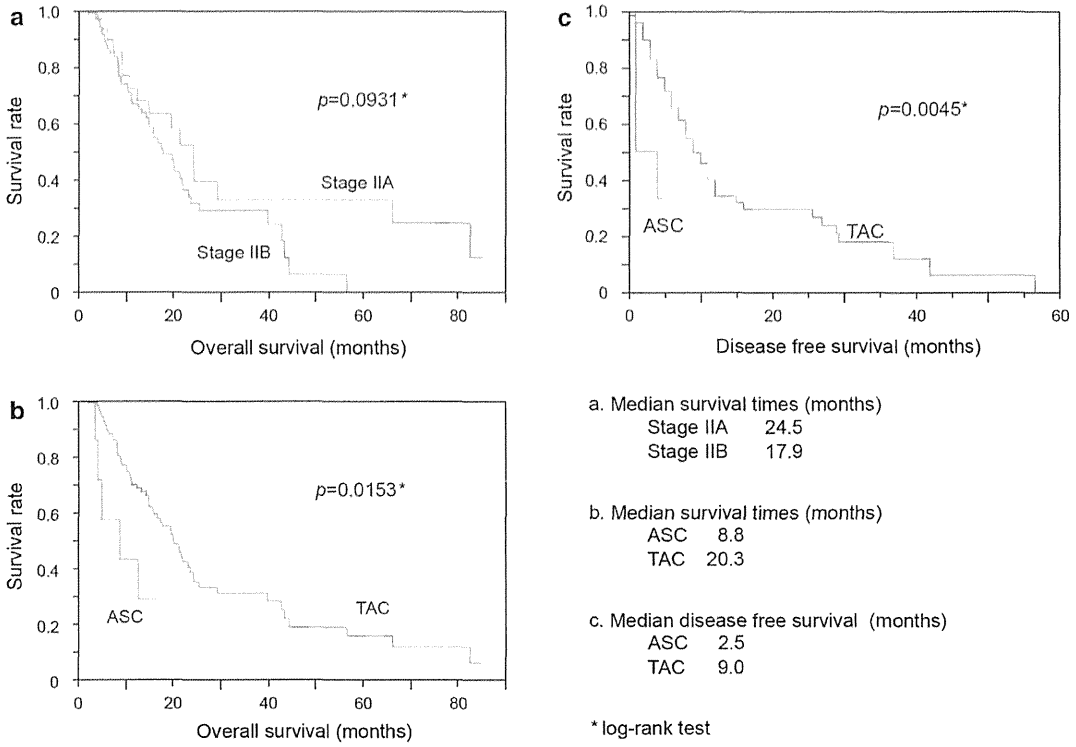

Fig. 1 The survival curves of the patients. **a** The overall survival curves of 35 patients with Stage IIA and 93 with Stage IIB. The median survival times (MSTs) of the patients with Stage IIA and those with Stage IIB were 24.5 and 17.9 months, respectively. There was no significant difference between the two stages ($p = 0.0931$). **b** The overall survival curves of the 121 patients with TAC and seven patients with ASC. The MSTs of the patients with TAC and ASC were 20.3 and 8.8 months, respectively, demonstrating that ASC patients had a significantly less favorable survival than did TAC patients ($p = 0.0153$). **c** The disease-free survival (DFS) curves of 121 patients with TAC and seven patients with ASC. The median DFS of the patients with TAC and ASC was 9.0 and 2.5 months, respectively, indicating that the time to relapse of the patients with ASC was significantly shorter than that of the patients with TAC after R0 surgical resection ($p = 0.0045$)

The venous invasion among the four histological types demonstrated an interesting distribution (Fig. 3a). As the differentiation of TAC decreased, the venous invasion became more severe. Furthermore, ASC showed more severe venous invasion compared with all three subtypes of TAC (G1, G2 and G3). The proportions of cases with v3 status (the most severe venous invasion) were 31.3 % in G1, 47.3 % in G2, 60.0 % in G3 and 71.4 % in ASC patients, respectively. The increase in the prevalence of v3 in the ASC patients was not statistically significant, but showed a trend toward significance compared to the G1 TAC patients ($p = 0.0737$, v3 vs. others).

In contrast, the distributions of lymphatic invasion, intrapancreatic nerve invasion and growth patterns of tumors infiltrating the surrounding tissue showed no tendencies among the four histological subtypes (Fig. 3b–d). The relationship between the tumor size and the histological type is shown in Fig. 4, demonstrating that the incidence of ASC and G3 tended to increase with the tumor size (statistical significance was not detected; $p = 0.5410$).

Recurrent status

The disease-free survival (DFS) curves of the 121 patients with Stage IIA and IIB TAC and the seven patients with ASC are shown in Fig. 1c. The median DFS of the patients with TAC and the patients with ASC was 9.0 and 2.5 months, respectively, indicating that the time to recurrence in the patients with ASC was significantly shorter than that in the patients with TAC after R0 surgical resection for the same extent of disease ($p = 0.0045$).

We then analyzed the recurrence between TAC and ASC patients in two categories; distant metastasis and local recurrence (Online Resource 1). The median follow-up periods of the TAC and ASC patients were 11.2 and 8.8 months, respectively. In the TAC group, the local recurrence rate was slightly higher than the distant metastasis rate (37 vs. 34 %). On the other hand, distant metastasis occurred more frequently compared to local recurrence in the ASC group, but the difference was not statistically significant (50 vs. 33 %). In the TAC group, 17

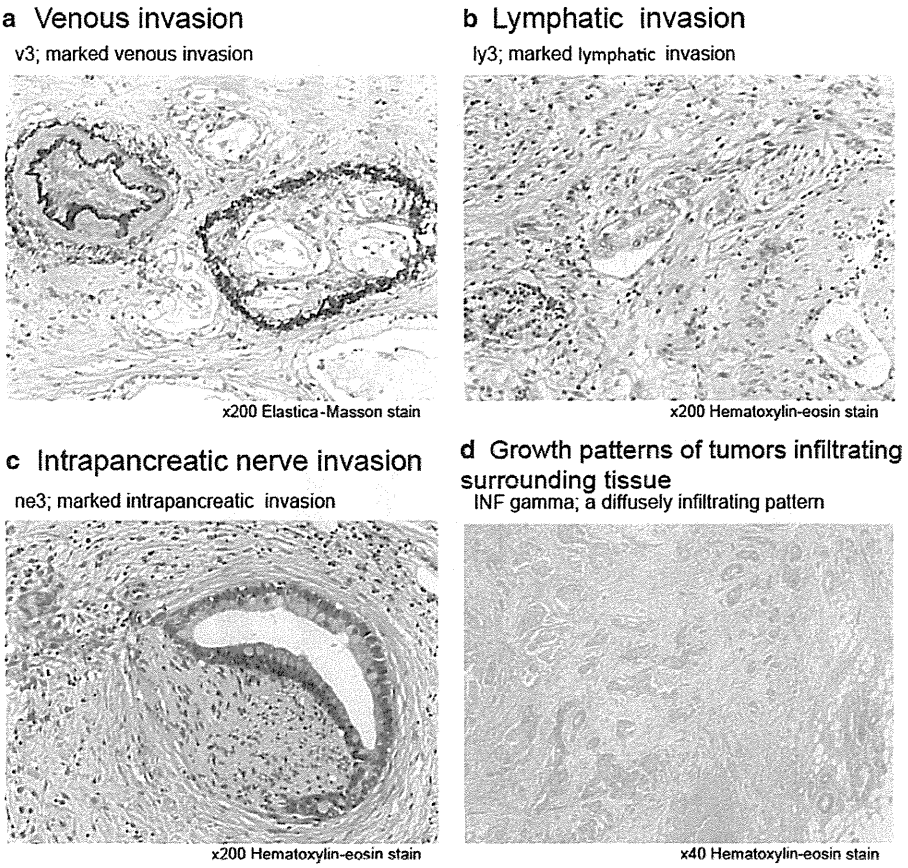

Fig. 2 Representative pathological images. **a** Marked venous invasion (v3) is demonstrated. **b** Marked lymphatic invasion was noted. **c** Marked intrapancreatic nerve invasion (ne3) was present. **d** The tumor cells show a diffusely infiltrating pattern of growth characterized by an indistinct border (INF gamma)

patients (14.0 %) had both distant and local recurrence, while there was no patient with both types of recurrence among those with ASC. No recurrence occurred in the patients without venous invasion (v0), while local recurrence was more common than distant metastasis in patients with v1 (data not shown).

Discussion

Adenosquamous carcinomas are found in many organs, including the pancreas. All of the ASCs are reported to be rare, and are regarded as having a dismal prognosis in comparison to the more common types of the cancer [11–17]. There have been few well-documented studies about ASC of the pancreas because of its rarity [5–7]. Most of the previous studies on pancreatic ASC analyzed heterogeneous populations, and focused on the resectability, curability of surgery and histological stages. Therefore, the cause of the unfavorable prognosis of ASC of the pancreas has not yet been clarified. In addition, proposals for multidisciplinary treatment have been based on unorganized methods. This is the first study to describe a comparison of TAC and ASC in comparable Stage IIA and IIB patients who had undergone a complete (R0) resection after 2001, when gemcitabine started to be routinely used as an adjuvant treatment. We excluded patients with Stage III and IV disease, because these tumors are too advanced to compare their biology, and ASC of Stage IA and IB is too rare to analyze statistically, so we also excluded these patients [4, 20, 21]. Since there was no statistically significant difference in the survival between patients with Stage IIA and IIB disease, we analyzed them together in the present study (Fig. 1).

In our department, the lymph nodes are dissected to the same extent in all patients that underwent pancreatic surgery, including the right side of the superior mesenteric artery and the paraaortic area, and they are fully examined pathologically. There is little chance for a stage migration to occur. The presence of lymph node metastasis in the paraaortic area is regarded to be a distant metastasis (M1), and patients with these tumors were excluded from this analysis. As shown in Table 2, more than 70 % of the patients had regional lymph node metastasis (N1) at the time of surgery and were classified into Stage IIB. The other patients with no lymph node metastasis were

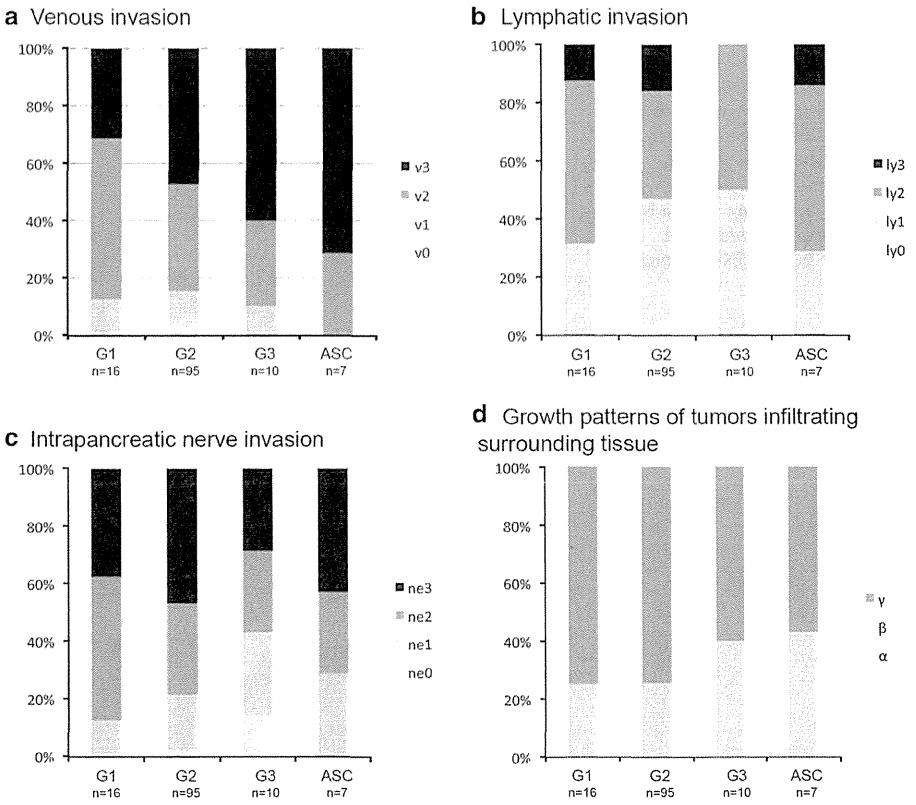

Fig. 3 The pathological features of the patients with the four histological types of pancreatic cancer; three differentiation subtypes of TAC (G1, G2 and G3) and ASC. **a** As the differentiation of TAC decreased, the venous invasion became more severe. ASC showed the most severe venous invasion of the four groups, and more than 70 % of the patients were classified to have v3 tumors. **b–d** The distributions of the lymphatic invasion, intrapancreatic nerve invasion and growth patterns of tumors infiltrating the surrounding tissue showed no specific tendencies among the TAC subtypes and ASC

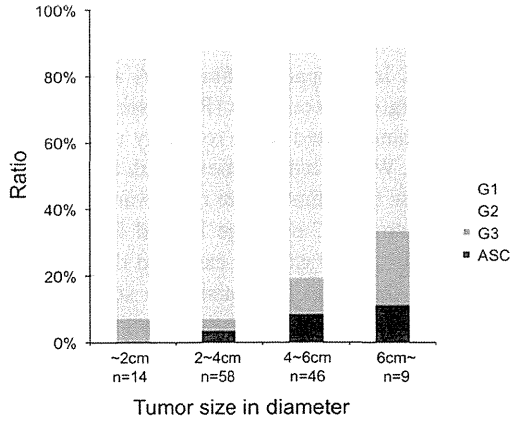

Fig. 4 The clinical features of ASC. The relationship between the tumor size and histological types. The incidence of ASC and G3 TAC increased with the tumor size, but not to the same extent as that of TAC ($p = 0.5410$, Pearson's Chi-square test)

classified into Stage IIA. Therefore, the ratios of N0/N1 and Stage IIA/IIB patients in this study were the same. While Stage IIB includes T1-T3 with N1 tumors, Stage IIA includes only T3 with N0, which resulted in the high rate of T3 tumors in this group. This may be another reason why the survival rates of the patients with Stage IIA and IIB were similar in our study.

As shown in Table 2, the tumors involved the head of the pancreas in more than 70 % of the patients, followed by the tail or body. Previous literature reviews have reported similar incident rates with ASC of the pancreatic head (66.7–71.8 %) among patients who underwent surgical resection, although other studies, including those on non-surgical treatment, reported a 42.9–56.7 % rate of pancreatic head cancer [10, 22–24]. Pancreatic head cancer may be detectable at smaller sizes, because symptoms such as icterus are easy to observe. Hence, these patients are more likely to undergo surgery at early stages, while the patients with pancreatic body and tail tumors tend to be found when they have non-resectable large tumors. The distribution of TNM was not significantly different between TAC and ASC, thus assuring that the tumor extent was similar in these two categories.

However, among the resected patients with Stage IIA and IIB tumors, the survival curves of the TAC and ASC groups were clearly divergent ($p = 0.0153$, Fig. 1b), supporting the notion that ASC has a less favorable outcome in comparison with TAC. Only one previous study has reported a comparison between ASC and TAC of the pancreas in a uniformly distributed setting. Hsu et al. [5] reported that the survival rate of ASC patients with Stage IIB pancreatic cancer ($n = 7$) was poorer than that of