Surgery Today (2019) 49:809–819
https://doi.org/10.1007/s00595-019-01807-8

ORIGINAL ARTICLE

Long-term outcomes after an aggressive resection of adenosquamous carcinoma of the pancreas

Takaaki Ito[1] · Teiichi Sugiura[1] · Yukiyasu Okamura[1] · Yusuke Yamamoto[1] · Ryo Ashida[1] · Katsuhisa Ohgi[1] · Keiko Sasaki[2] · Katsuhiko Uesaka[1]

Received: 27 December 2018 / Accepted: 15 March 2019 / Published online: 12 April 2019

Abstract

Purpose Adenosquamous carcinoma (ASC) of the pancreas is a rare malignancy, associated with a poor prognosis after surgical resection, with reported median survival times (MSTs) ranging from 4.4 to 13.1 months. We conducted this study to investigate the long-term outcomes of patients after the resection for ASC.

Methods Between 2002 and 2016, a total of 456 patients underwent resection for ASC or adenocarcinoma (AC) of the pancreas. ASC was confirmed in 17 (3.7%) of these patients. We analyzed the clinicopathological characteristics and survival of these 17 patients in comparison with those of patients with AC of the pancreas.

Results The operative procedures performed were pancreaticoduodenectomy ($n=6$) and distal pancreatectomy ($n=11$). Seven (41.2%) of the 17 patients underwent combined organ resection. R0 resection was achieved in 16 (94.1%) patients. The 5-year overall survival (OS) rate and MST were 40.3% and 20.9 months, respectively. A squamous component of ≥ 60% ($P=0.001$) and R1 resection ($P<0.001$) were significantly associated with poor OS for patients with ASC

Conclusion This study revealed longer survival and a higher R0 resection rate after aggressive combined resection in our ASC patients than those in previous studies. Although this was only a small series, our findings suggest that local control with aggressive resection may be an effective treatment protocol for ASC patients.

Keywords Pancreatic cancer · Adenosquamous carcinoma · Combined resection

Introduction

Among the gastrointestinal malignancies, pancreatic cancer continues to be associated with a poor prognosis because of its low rate of resectability. Surgical treatment provides the only chance of cure for patients with pancreatic cancer; however, fewer than 20% of patients have localized tumors that are potentially curable at the time of diagnosis [1–3]. Adenocarcinoma (AC) of the pancreas is the most common type of pancreatic cancer, whereas adenosquamous carcinoma (ASC) of the pancreas is a rare malignancy of the exocrine pancreas and a histological variant of pancreatic ductal adenocarcinoma. ASC accounts for 0.6–4% of pancreatic exocrine tumors [4–7]. The pancreatic body and tail are the most frequent sites of ASC, and ASC also tends to be larger in diameter than AC [5]. Surgery is more frequently performed for ASC than for AC [5], with an R0 resection rate of 58–67% [8–10]. Previous series have demonstrated a poor prognosis after surgical resection for ASC, with a median survival time (MST) of 4.4–13.1 months [4–11]. In a population-based review, patients with ASC had a similar survival time to those with AC [4]; however, the median survival time of those with ASC was approximately 12 months. In the largest previously published review, negative lymph node metastasis, R0 resection, and a history of adjuvant chemotherapy were reported to be independently associated with better overall survival following surgical resection [12].

The long-term outcomes after surgical treatment for ASC of the pancreas have not been clarified because of the rarity of the disease. To achieve R0 resection, we perform aggressive excision, including vascular and organ resection, in our institution. The aim of the present study was to evaluate

✉ Takaaki Ito
tak.ito@scchr.jp

[1] Division of Hepato-Biliary-Pancreatic Surgery, Shizuoka Cancer Center Hospital, 1007 Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka 411-8777, Japan

[2] Division of Diagnostic Pathology, Shizuoka Cancer Center Hospital, Shizuoka, Japan

the long-term outcomes of patients with ASC vs. those of patients with AC of the pancreas, following aggressive surgical resection.

Methods

Patient selection

We conducted a retrospective review, based on a prospectively collected database, of 469 patients who underwent surgical resection of AC or ASC of the pancreas, with curative intent, at the Shizuoka Cancer Center, between September, 2002 and December, 2016. After the exclusion of 13 patients who received neoadjuvant therapy, 456 patients were included in the final analysis. The confirmed pathological diagnoses were AC of the pancreas ($n = 439$) and ASC of the pancreas ($n = 17$; 3.7%). The study was approved by the institutional review board of the Shizuoka Cancer Center (30-J98-30-1-3).

Pre-operative assessment

Pre-operative examinations were conducted using multidetector-row computed tomography (MDCT) and ultrasonography (US). Magnetic resonance imaging and 18F-fluorodeoxyglucose positron-emission tomography were also performed, when necessary [13, 14]. Resectable pancreatic cancer was defined as follows: the absence of distant metastasis, no evidence of tumor extension to the superior mesenteric artery (SMA) or hepatic artery in pancreatic head cancer, and no evidence of tumor extension to the SMA in pancreatic body and tail cancer. Patients with resectable pancreatic cancer underwent up-front surgery (except for those included in the JASPAC 04 study; UMIN000014894). Patients with borderline resectable pancreatic cancer received neoadjuvant chemotherapy or chemoradiotherapy. Acceptable forms of combined resection included vascular resection (portal vein, aberrant hepatic artery) and organ resection (stomach, colon, kidney, left adrenal gland, and diaphragm). Distal pancreatectomy (DP) with celiac axis resection (DP-CAR) was considered appropriate surgery for pancreatic body/tail cancer [15].

Surgery and follow-up

Our standard method of pancreatoduodenectomy (PD) was followed by reconstruction using a modification of Child's method [16]. DP procedures consisted of en bloc resection of the distal pancreas and spleen. Combined adjacent organ or vascular (artery and portal vein) resection was performed if macroscopic invasion was confirmed during surgery. Prophylactic organ or vascular resection as a non-touch technique was not performed. The cut margin of the pancreas was examined using frozen sections. If the resected margin was positive, then additional resection of the pancreas was performed when applicable. The regional and peripancreatic lymph nodes were dissected routinely.

Staging and resection status of the specimens were defined according to the UICC classification (seventh edition) [17]. The standardization of the R status has been described previously [16]. Patients were followed up with imaging examinations and the measurement of tumor markers every 3–6 months after surgery. Recurrence was diagnosed based on radiological or histological evidence. The survival time was defined as the interval between the date of surgery and the date of the last follow-up examination. The median length of follow-up in the censored patients was 41.5 months.

Statistical analyses

Some of the continuous variables are expressed as medians with ranges and compared using the Mann–Whitney *U* test. The categorical variables were compared using the Chi-squared test or Fisher's exact test, as appropriate. Survival curves were generated using the Kaplan–Meier method, and differences in survival were compared using a log-rank test. The variables identified as potentially significant according to univariate analyses were subsequently chosen for multivariate analyses using the Cox proportional hazards model, to identify any independent predictors of survival. All tests were two sided. P values of < 0.05 were considered to indicate significance. All of the statistical analyses were performed using the Statistical Package for the Social Sciences software program (version 21.0J, IBM Japan Inc., Tokyo, Japan).

Results

Table 1 summarizes the details of the surgical procedures and survival outcomes of the 17 patients with ASC of the pancreas. PD was performed in 6 of these patients and DP was performed in 11. Combined other organ resection and vascular resection were performed in nine patients (52.9%) and seven patients (41.2%), respectively. Eight patients (47.1%) suffered post-operative morbidity of Clavien–Dindo classification ≥ 3a with a median hospital stay of 19 (7–47) days. The R0 resection rate was 94.1%. Four patients survived for more than 5 years after surgical resection without evidence of recurrence, including one patient (no. 11) who underwent combined stomach, left diaphragm, and left kidney resection (Fig. 1). Two patients who survived for more than 3 years after recurrence received long-term chemotherapy (nos. 3 and 14). ASC was not diagnosed

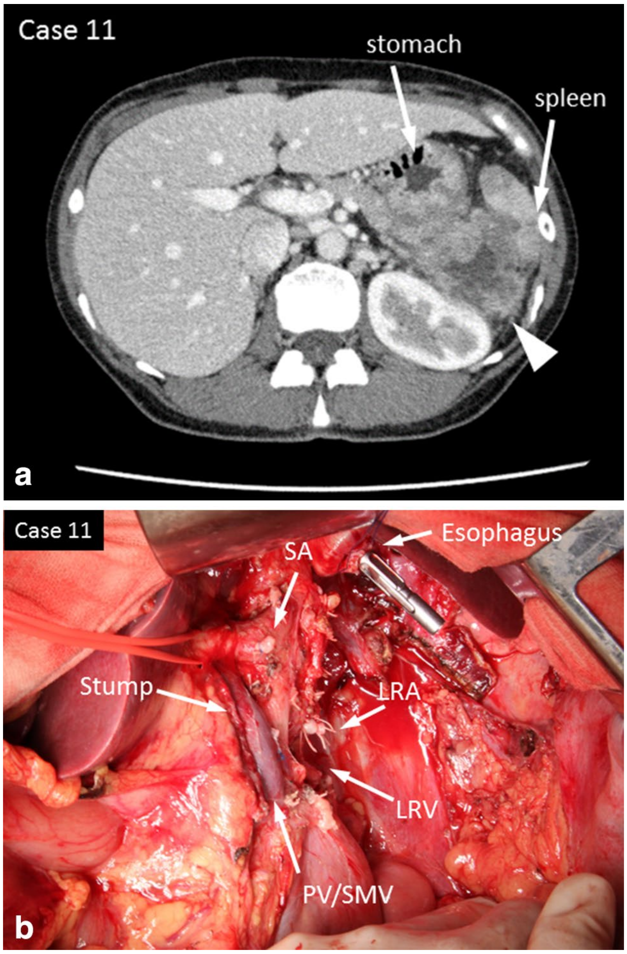

Fig. 1 Adenosquamous carcinoma in the pancreatic tail of a 52-year-old man (patient no. 11). The tumor (arrow head) was 70 mm in diameter and directly invaded the stomach, spleen, left kidney, and left diaphragm (**a**). An intra-operative photograph after distal pancreatectomy with en bloc proximal stomach, left diaphragm, and left kidney (**b**). *Stump* pancreatic stump, *SA* splenic artery, *PV/SMV* portal vein and superior mesenteric vein, *LRA* left renal artery, *LRV* left renal vein

pre-operatively based only on MDCT in any patient. Four patients underwent needle biopsy under endoscopic ultrasonography, and examination of the biopsy specimens revealed a squamous component in three and adenocarcinoma alone in one. Squamous cell cancer antigen (SCC-Ag) was measured in four patients, revealing a median value of 8.5 ng/mL.

Table 2 compares the patients with pancreatic AC vs. those with pancreatic ASC. ASC tumors were located more frequently in the pancreatic body and tail, and DP was more commonly performed for ASC than for AC. Although there was no significant difference in the vascular resection rates between the two groups ($P=0.264$), the combined other organ resection rate in the patients with ASC was significantly higher than that in the patients with AC (41.2% vs. 8.9%, $P<0.001$). Comparing patients who underwent non-combined resection ($n=10$) with those who underwent combined resection ($n=7$) for ASC, pathological invasion to other organs was observed more frequently in the patients who underwent combined resection (0% vs. 71.4%, $P=0.035$). There was no significant difference in the median tumor diameters (43 mm vs. 60 mm, $P=0.133$) or lymph node metastasis (80.0% vs. 42.9%, $P=0.162$).

Figure 2a, b shows the overall survival (OS) and relapse-free survival (RFS) curves according to the pathological diagnosis. Both OS and RFS were almost identical in the two groups ($P=0.954$ and $P=0.698$, respectively). The AC group patients who underwent combined organ resection had a poorer 5-year OS rate than those who did not undergo combined resection (14.2% vs. 35.3%, respectively; $P=0.011$; Fig. 3a). The ASC patients who underwent combined organ resection had a similar 5-year OS rate to those who did not undergo combined organ resection (42.9% vs. 37.5%, respectively; $P=0.926$; Fig. 3b). Under most conditions, the survival outcomes of the patients with AC vs. those with ASC did not differ significantly (Table 3). However, the ASC group patients who underwent R1 resection ($n=1$, 5.8%) had a poorer OS rate than their counterparts in the AC group ($n=54$, 12.3%; $P<0.001$).

Univariate analysis of the factors associated with the OS of patients with ASC revealed that a squamous component of ≥ 60% ($P=0.001$) and R1 resection ($P<0.001$) were significantly associated with poor OS (Table 4). There was a marginal difference in the OS rate between patients with T1–3 vs. those with T4 ($P=0.055$) as well as between patients with vs. those without microscopic venous invasion ($P=0.058$). However, the Cox proportional hazards analysis did not identify any independent prognostic factors for OS.

In comparing the effects of adjuvant chemotherapy, the 5-year survival rate of patients who received S-1 ($n=7$) vs. those who received Gemcitabine ($n=4$) was 42.9% (MST 20.9 months) vs. 25.0% (MST 12.0 months), respectively, which did not represent a significant difference according to univariate analysis ($P=0.905$).

Discussion

Although this was a small series, we were able to compare the long-term outcomes after aggressive surgical resection of patients with ASC vs. those with AC. ASC was significantly larger than AC and it arose more frequently in the body and tail of the pancreas than in the pancreatic head. We found that R0 resection for ASC was independently associated with better OS, and that the survival outcome of these patients was also favorable, even after combined organ resection.

Pancreatic cancer is a highly invasive tumor that sometimes spreads to the major arteries, such as the superior

Table 1 Surgical procedures and survival outcomes of 17 patients with adenosquamous carcinoma of the pancreas

Patient	Age	Sex	Location	Procedure	Combined resection	Vascular resection	R status	Squamous component (%)	Adjuvant	First recurrence	Treatment for recurrence	Survival
1	79	F	Pt	DP	Stomach, jejunum, colon, adrenal gland	None	0	40	None	None		67 months alive
2	77	F	Ph	PD	None	PV	0	40	None	None		69 months alive
3	32	M	Pb	DP	None	CeA	0	40	None	Local, peritoneum	GEM	137 months died
4	56	M	Pb	PD	None	None	0	50	GEM	None		112 months alive
5	73	M	Pt	DP	Stomach, colon, left adrenal gland	None	0	50	GEM	Liver, lymph node	BSC	12 months died
6	70	F	Pb	DP	Stomach, colon, left adrenal gland	PV, CeA, left renal vein	1	90	None	Liver	BSC	5 months died
7	69	F	Pb	DP	Colon	PV	0	30	GEM	Liver, lymph node	S-1	9 months died
8	69	M	Pb	DP	None	PV, CeA	0	90	GEM	Liver	S-1	31 months died
9	77	F	Ph	PD	None	PV	0	80	None	Liver	BSC	10 months died
10	71	F	Pt	DP	Stomach, colon, left adrenal gland	None	0	40	S-1	Liver	GEM	21 months died
11	52	F	Pb	DP	Stomach, left kidney, left diaphragm	PV	0	30	S-1	None		62 months alive
12	74	M	Pb	DP	None	None	0	90	S-1	Lung, peritoneum	BSC	9 months died
13	82	F	Ph	PD	None	PV	0	50	None	Liver	BSC	13 months died
14	52	F	Pb	DP	Stomach, left adrenal gland	None	0	50	S-1	Lung	Resection followed by S-1	51 months alive
15	64	M	Ph	PD	None	PV	0	70	S-1	Liver, lung, lymph node	GEM + nab-PTX	9 months died
16	61	M	Pt	DP	None	None	0	60	S-1	Liver	FOLFIRINOX	12 months died
17	69	M	Ph	PD	None	None	0	40	S-1	None		22 months alive

Ph pancreatic head, *Pb* pancreatic body, *Pt* pancreatic tail, *PV* portal vein, *CeA* celiac axis, *GEM* gemcitabine, *PTX* paclitaxel, *FOLFIRINOX* fluorouracil + leucovorin + oxaliplatin + irinotecan, *BSC* best supportive care

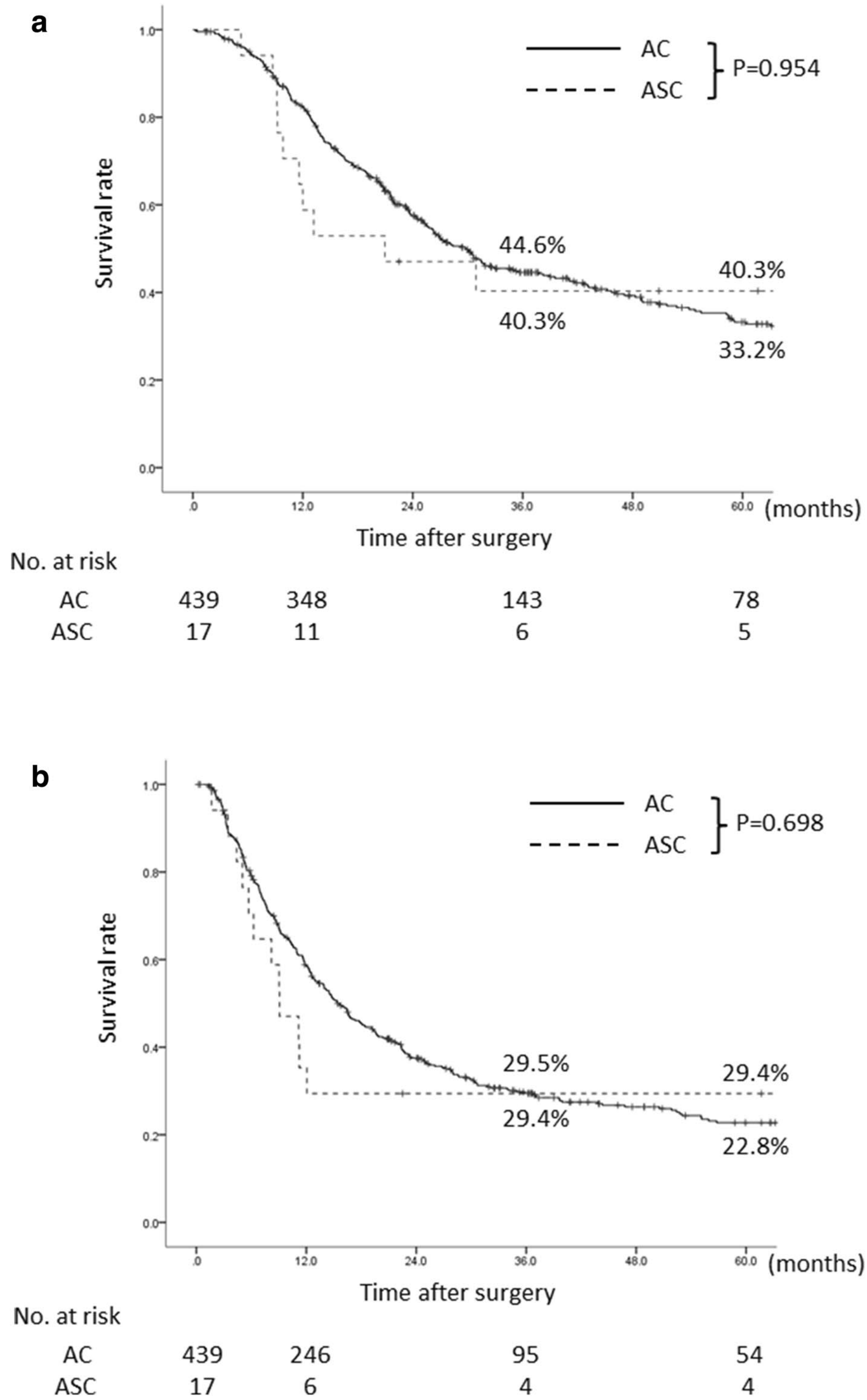

Fig. 2 Overall survival (OS) (**a**) and relapse-free survival (RFS) (**b**) according to the pathological diagnosis. *AC* adenocarcinoma of pancreas, *ASC* adenosquamous carcinoma of the pancreas. The OS and RFS of the patients with AC vs. those with ASC did not differ significantly ($P=0.954$ and $P=0.698$, respectively)

mesenteric artery, hepatic artery and celiac axis, as well as the portal vein, and adjacent organs, including the transverse colon, adrenal grand and kidney. Combined vascular resection and other types of organ resection are often necessary to achieve a curative surgical resection. In the present study, portal vein resection was the most frequent type of vascular resection ($n=7$, 41.2%), followed by celiac axis resection ($n=3$, 17.6%). There was no significant difference between AC and ASC in the rate of combined vascular resection (AC 39.4% vs. ASC 52.9%, $P=0.264$). The R0 resection rates for AC and ASC did not differ significantly (87.7% vs. 94.1%, respectively; $P=0.707$), but combined organ resection was performed more frequently for ASC than for AC (8.9% vs. ASC 41.2%, respectively; $P<0.001$). To achieve a high rate

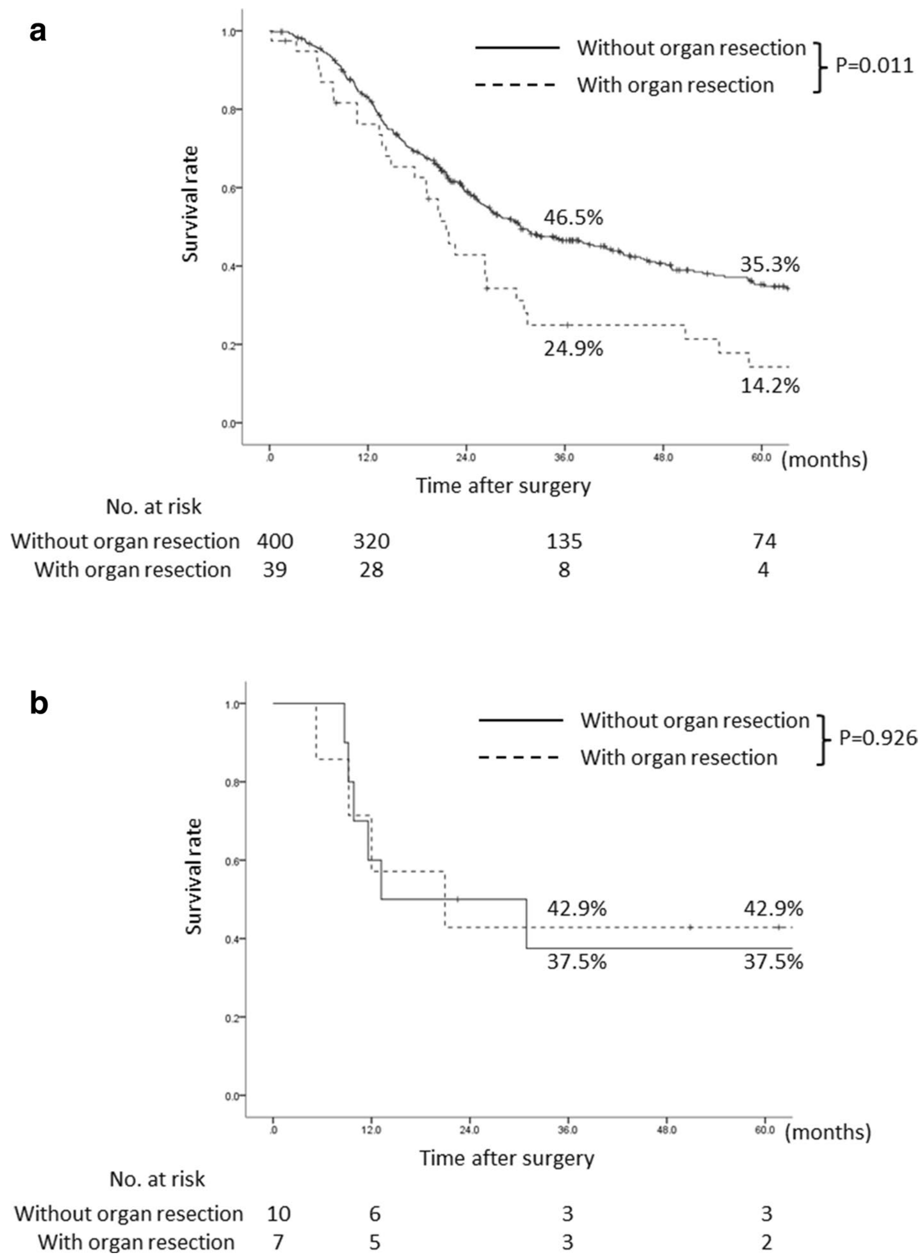

Fig. 3 The overall survival curve according to combined organ resection in the adenocarcinoma patients (**a**) and the adenosquamous carcinoma patients (**b**). *AC* adenocarcinoma of pancreas, *ASC* adenosquamous carcinoma of the pancreas. The AC patients who underwent combined organ resection had a poorer 5-year OS rate than those who did not (14.2% vs. 35.3%, $P=0.011$). The ASC patients who underwent combined organ resection had a similar 5-year OS rate to those who did not (42.9% vs. 37.5%, $P=0.926$)

of R0 resection, aggressive surgical treatment, such as combined vascular and other types of organ resection, is necessary for patients with ASC.

The survival outcome of the patients with surgically treated ASC in the present study was better than that reported previously (Table 5) [4, 5, 8, 9, 12, 18]. In the current California Cancer Registry study (a large study reporting the survival outcomes of patients with ASC), the outcomes after surgical resection for ASC were comparable to those after surgical resection for AC [5]. Hoshimoto et al. also reported that ASC patients had an MST of 17 months after surgical resection, which was similar to that of AC patients [18]. In the largest study, Hester reported that the survival of patients with ASC was worse than that of patients with AC, but the hazard ratio was only 1.11 (1.01–1.24) [12]. Previous reports described a low R0 resection rate of < 70% for ASC associated with poor survival outcomes, whereas current reports describe relatively high R0 resection rates (> 85%) associated with survival outcomes similar to those of AC.

Although R1 resection was achieved in only one of our ASC patients, this patient had a significantly poorer OS than the AC patients for whom R1 resection was achieved. Furthermore, univariate analysis of the OS for ASC patients revealed that R1 resection was significantly associated with poor OS. Hester et al. reported that R0 resection was independently associated with better OS. After considering the relationship between the survival outcomes and R1 resection

Table 2 Background characteristics of patients with pancreatic adenocarcinoma vs. those with adenosquamous carcinoma of the pancreas

	Adenocarcinoma (n = 439)	Adenosquamous carcinoma (n = 17)	P
Age[a]	68.0 (38–88)	69.0 (32–82)	0.951
Sex			
Male	258 (58.7%)	8 (47.0%)	0.337
Female	181 (41.3%)	9 (53.0%)	
Tumor location			
Head	327 (74.5%)	5 (29.4%)	< 0.001
Body	86 (19.6%)	8 (47.1%)	
Tail	26 (5.9%)	4 (23.5%)	
Tumor size (mm)[a]	35 (6–130)	50 (19–96)	0.003
Primary tumor status[b]			
T1	8 (1.8%)	0	0.001
T2	15 (3.4%)	0	
T3	401 (91.4%)	13 (76.5%)	
T4	15 (3.4%)	4 (23.5%)	
Resection type			
Pancreatoduodenectomy	328 (74.7%)	6 (35.3%)	0.001
Distal pancreatectomy	103 (23.5%)	11 (64.7%)	
Total pancreatectomy	8 (1.8%)	0	
Combined vascular resection			
Absent	266 (60.6%)	8 (47.1%)	0.264
Present	173 (39.4%)	9 (52.9%)	
Combined organ resection			
Absent	400 (91.1%)	10 (58.8%)	< 0.001
Present	39 (8.9%)	7 (41.2%)	
Lymph node metastasis			
Absent	129 (29.4%)	6 (35.3%)	0.601
Present	310 (70.6%)	11 (64.7%)	
Microscopic venous invasion			
Absent	164 (37.4%)	3 (17.6%)	0.125
Present	275 (62.6%)	14 (82.4%)	
Lymphatic invasion			
Absent	75 (17.1%)	3 (17.6%)	1.000
Present	364 (82.9%)	14 (82.4%)	
Perineural invasion			
Absent	32 (7.3%)	1 (5.9%)	1.000
Present	407 (92.7%)	16 (94.1%)	
R status			
R0	385 (87.7%)	16 (94.1%)	0.707
R1	54 (12.3%)	1 (5.9%)	
CEA	3.2 (0.5–662)	4.5 (0.5–135.0)	0.006
CA 19-9	95 (2–17324)	64 (4–9771)	0.788
Adjuvant chemotherapy			
None	177 (40.3%)	6 (35.3%)	0.871
S-1	144 (32.8%)	7 (41.2%)	
Gemcitabine	113 (25.8%)	4 (23.5%)	
Others	5 (1.1%)	0	

CEA carcinoembryonic antigen, *CA19-9* carbohydrate antigen19-9

[a]Median (range)

[b]UICC 7th edition

Table 3 Univariate analysis of the overall survival of patients with adenocarcinoma vs. adenosquamous carcinoma of the pancreas

	Adenocarcinoma		Adenosquamous carcinoma		P
	n	5-year survival (%)	n	5-year survival (%)	
Tumor location					
Head	327	32.2	5	60.0	0.393
Body	86	37.4	8	37.5	0.645
Tail	26	30.6	4	25.0	0.287
Resection type					
Pancreatoduodenectomy	328	31.5	6	50.0	0.633
Distal pancreatectomy	103	35.9	11	36.4	0.499
Total pancreatectomy	8	75.0	0	N.A.	N.A.
Combined organ resection					
Absent	400	35.3	10	37.5	0.966
Present	39	14.2	7	42.9	0.402
Combined vascular resection					
Absent	266	40.1	8	50.0	0.956
Present	173	21.8	9	33.3	0.675
CEA					
< 15 ng/mL	414	34.9	11	45.5	0.566
≥ 15 ng/mL	25	6.1	6	33.3	0.940
CA 19-9					
< 100 U/mL	221	45.4	9	55.6	0.561
> 100 U/mL	218	21.0	8	25.0	0.269
Tumor size (mm)					
< 30 mm	139	45.2	3	66.7	0.363
≥ 30 mm	300	27.5	14	34.3	0.868
Primary tumor status[a]					
T1	8	62.5	0	N.A.	N.A.
T2	15	61.5	0	N.A.	N.A.
T3	401	32.5	14	53.8	0.273
T4	15	10.8	3	0	0.071
Lymph node metastasis					
Absent	129	55.9	6	50.0	0.498
Present	310	23.2	11	34.1	0.662
Microscopic vascular invasion					
Absent	164	50.0	3	100.0	0.126
Present	275	23.2	14	26.8	0.669
Lymphatic invasion					
Absent	75	57.7	3	66.7	0.787
Present	364	28.2	14	34.3	0.908
Perinerural invasion					
Absent	32	36.1	1	100.0	0.322
Present	407	33.0	16	36.5	0.822
R status					
R0	385	35.1	16	42.9	0.842
R1	54	21.3	1	0	< 0.001
Adjuvant chemotherapy					
Absent	177	24.6	6	50.0	0.287
S-1	144	50.5	7	42.9	0.173
Gemcitabine	113	27.0	4	25.0	0.706
Others	5	60.0	0	N.A.	N.A.

Table 3 (continued)

CEA carcinoembryonic antigen, *CA19-9* carbohydrate antigen19-9, *N.A.* not assessed

[a]UICC 7th edition

rates in the present and previous studies, residual tumor factors, such as R0 or R1/2 resection, may have a more important prognostic impact in surgically treated ASC than AC. Although the AC patients who required combined organ resection had a poorer survival outcome than those who did not, ASC patients who required combined organ resection had a similar survival outcome to those who did not (Fig. 3). Thus, to achieve R0 resection, local control with combined resection, if macroscopic organ invasion is identified, may have a positive influence on the survival of ASC patients.

Combined other organ resection may also increase the risk of post-operative complications. Solaini et al. reported that combined colon resection was associated with increased post-operative morbidity and mortality [19]. Adrenal gland and kidney resection can lead to adrenal and renal dysfunction, and patients with renal dysfunction may not be able to receive adjuvant chemotherapy or chemotherapy after recurrence at a sufficient dose intensity, with consequently poorer survival outcomes than those without renal dysfunction. In the present study, patient no. 11, who underwent combined stomach, left diaphragm, and left kidney resection (Fig. 1), survived for more than 5 years without any symptoms or recurrence, but had mild renal dysfunction. In terms of renal function, combined renal resection should not be indicated as prophylactic resection, but rather, it should be performed when macroscopic invasion is detected intra-operatively.

The degree of squamous component was a prognostic factor for OS in the present study. Hong et al. reported that the survival time of patients with ASC of the extrahepatic bile duct decreased as the squamous component increased [20]. In contrast, Voong et al. reported that the squamous component in pancreatic cancer did not influence survival when using the current cut-off of 30% squamous differentiation for the definition of ASC or when analyzing it as a continuous variable [9]. In the present study, no association was noted between ASC and microscopic venous invasion. Komatsu et al. reported that venous invasion was more marked in ASC than in AC [21]. In the present study, a marginal correlation was noted between a poorer OS rate and microscopic venous invasion. However, few studies have explored this, so further investigations are necessary to establish the associations among pathological characteristics, including the degree of squamous component, and lymphovascular and perineural invasion.

Pre-operatively, ring enhancement or a round-lobulated lesion on imaging are characteristically associated with ASC [22, 23]. However, more detailed imaging data are

Table 4 Univariate analyses of the factors associated with the overall survival of patients with adenosquamous carcinoma

	n	5-year overall survival (%)	Median survival time (months)	Univariate *P*
Tumor location				
Head	5	60.0	N.R.	0.499
Body/tail	12	33.3	13.2	
Tumor size				
< 30 mm	3	66.7	N.R.	0.432
≥ 30 mm	14	34.3	13.2	
Primary tumor status[a]				
T1/2/3	13	53.8	N.R.	0.055
T4	4	0.0	9.1	
Combined vascular resection				
Absent	8	50.0	20.9	0.489
Present	9	33.3	13.2	
Combined organ resection				
Absent	10	37.5	13.2	0.926
Present	7	42.9	20.9	
Squamous component rate				
< 60%	11	63.6	N.R.	0.001
≥ 60%	6	0	9.1	
Lymph node metastasis				
Absent	6	50.0	20.9	0.455
Present	11	34.1	13.2	
Microscopic venous invasion				
Absent	3	100.0	N.R.	0.058
Present	14	26.8	12.0	
Lymphatic invasion				
Absent	3	66.7	N.R.	0.345
Present	14	34.3	13.2	
Perineural invasion				
Absent	1	100.0	N.R.	0.329
Present	16	36.5	13.2	
R status				
R0	16	42.9	20.9	< 0.001
R1	1	0.0	5.2	
CEA				
< 15 ng/mL	11	45.5	30.9	0.575
≥ 15 ng/mL	6	33.3	12.0	
CA 19-9				
< 100 U/mL	9	55.6	N.R.	0.137
≥ 100 U/mL	8	25.0	9.8	
SCC-Ag[b]				
< 8.5 ng/mL	2	0	11.6	0.695
≥ 8.5 ng/mL	2	N.R.	5.2	
Adjuvant chemotherapy				
Absent	6	50.0	13.2	0.692
Present	11	34.1	20.9	

CEA carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9, *SCC-Ag* squamous cell cancer antigen, *N.R.* not reached

[a]UICC 7th edition

[b]Including four patients

Table 5 Recent reports analyzing more than ten cases of resected adenosquamous carcinoma of the pancreas

Author	Year	*n*	Procedure PD/DP/TP	Diameter	Vascular resection	Organ resection	Lymph node metastasis	v	ly	pn	Squamous component[a]	R0 rate	Adjuvant therapy	Survival rate (%)					MST
														1-year	2-year	3-year	4-year	5-year	
Smoot [8]	2008	12	7/5/0	45 mm	0%	–	33.3%	–	–	100.0%	(5%-80%)	66.7%	41.6%	–	–	–	–	–	13.1 months
Voong [9]	2010	38	23/10/5	50 mm	–	–	76.3%	81.5%	–	86.8%	(10%-90%)	63.1%	57.9%	34	11	–	–	5	10.9 months
Katz [4]	2011	26	18/5/3	–	–	–	57.7%	–	–	–	–[b]	–	52.0%	–	–	–	–	–	12 months
Boyd [5]	2012	99	–	–	–	–	–	–	–	–	–	–	–	54.1	31.2	–	–	–	13 months
Hoshimoto [18]	2017	12	9/2/1	45 mm	58.3%	–	83.3%	100.0%	83.3%	83.3%	60%	91.6%	50.0%	55.6	–	33.3	–	–	17 months
Hester [12]	2018	503[c]	53%/27%/–	–	–	–	56.5%	53.5%[d]		–	–	86.6%	66.8%	59.2	–	–	–	18.2	14.2 months
Present report		17	6/11/0	50 mm	52.9%	41.2%	64.7%	82.4%	82.4%	94.1%	50%	94.1%	64.7%	64.7	47.1	40.3	40.3	40.3	20.9 months

PD/DP/TP pancreatoduodenectomy/distal pancreatectomy/total pancreatectomy, *LN* lymph node metastasis, *v* microscopic venous invasion, *ly* lymphatic invasion, *pn* perineural invasion, *MST* median survival time

[a]Median (range)

[b]Including squamous proportion < 30%

[c]For stage I/II

[d]Including microscopic venous and lymphatic invasion

required to improve the ability to diagnose ASC pre-operatively [24]. In the present study, pre-operative pancreatic biopsy was performed in four patients and three of the four biopsies (75.0%) revealed a squamous component, while one revealed adenocarcinoma alone. Recent advances in endoscopic techniques, such as the advent of the endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNAB), will increase the pre-operative diagnostic accuracy of pancreatic cancer. Subsequently, aggressive surgical resection may also be acceptable for patients with ASC.

Surgical resection followed by adjuvant chemotherapy is considered a standard strategy for resectable pancreatic cancer [25–27]. However, no standard peri-operative strategy has yet been established for resectable ASC. At our institution, adjuvant chemotherapy is given to patients with ASC and to those with AC. Adjuvant S-1 therapy is the standard strategy for pancreatic cancer only in Japan [27, 28]. S-1 was administered as adjuvant chemotherapy to 4 (33.3%) of 12 patients, with an MST of 17 months, in the study of Hoshino et al. and to 7 (41.1%) of our 17 patients, with an MST of 20.9 months, respectively [18]. It is difficult to discuss the advantages of adjuvant S-1 therapy based on this small difference; therefore, whether adjuvant S-1 therapy can improve the prognosis remains a topic for investigation. Retrospective studies demonstrated that adjuvant chemoradiation or the addition of a platinum agent to adjuvant regimens improves the survival of patients after resection for ASC [9, 29]. Furthermore, no standard therapy for unresectable and recurrent ASC has been established, making it difficult to recommend neoadjuvant therapy for ASC.

The limitations of this study include its retrospective nature and single-institution setting with a limited number of patients, especially in the ASC group. The number of subjects was inadequate for drawing broad interpretations.

In conclusion, ASC was able to be diagnosed by EUS-FNAB, but not by MDCT alone, and local control may play an important and positive role in extending the survival of patients with resectable ASC.

Compliance with ethical standards

Conflict of interest Takaaki Ito and his co-authors have no conflicts of interest to declare.

References

1. Capussotti L, Massucco P, Ribero D, Vigano L, Muratore A, Calgaro M (2003) Extended lymphadenectomy and vein resection for pancreatic head cancer: outcomes and implications for therapy. Arch Surg 138:1316–1322
2. Wray CJ, Ahmad SA, Matthews JB, Lowy AM. Surgery for pancreatic cancer: recent controversies and current practice. Gastroenterology. 2005;128:1626–41.
3. Yamada S, Fujii T, Sugimoto H, Nomoto S, Takeda S, Kodera Y, et al. Aggressive surgery for borderline resectable pancreatic cancer: evaluation of National Comprehensive Cancer Network guidelines. Pancreas. 2013;42:1004–100.
4. Katz MH, Taylor TH, Al-Refaie WB, Hanna MH, Imagawa DK, Anton-Culver H, et al. Adenosquamous versus adenocarcinoma of the pancreas: a population-based outcomes analysis. J Gastrointest Surg. 2011;15:165–74.
5. Boyd CA, Benarroch-Gampel J, Sheffield KM, Cooksley CD, Riall TS. 415 patients with adenosquamous carcinoma of the pancreas: a population-based analysis of prognosis and survival. J Surg Res. 2012;174:12–9.
6. Madura JA, Jarman BT, Doherty MG, Yum MN, Howard TJ (1999) Adenosquamous carcinoma of the pancreas. Arch Surg. 134:599–603
7. Hsu JT, Chen HM, Wu RC, Yeh CN, Yeh TS, Hwang TL, et al. Clinicopathologic features and outcomes following surgery for pancreatic adenosquamous carcinoma. World J Surg Oncol. 2008;6:95.
8. Smoot RL, Zhang L, Sebo TJ, Que FG. Adenosquamous carcinoma of the pancreas: a single-institution experience comparing resection and palliative care. J Am Coll Surg. 2008;207:368–70.
9. Voong KR, Davison J, Pawlik TM, Uy MO, Hsu CC, Winter J, et al. Resected pancreatic adenosquamous carcinoma: clinicopathologic review and evaluation of adjuvant chemotherapy and radiation in 38 patients. Hum Pathol. 2010;41:113–22.
10. Simone CG, Zuluaga Toro T, Chan E, Feely MM, Trevino JG, George TJ Jr. Characteristics and outcomes of adenosquamous carcinoma of the pancreas. Gastrointestinal cancer research : GCR. 2013;6:75–9.
11. Kardon DE, Thompson LD, Przygodzki RM, Heffess CS. Adenosquamous carcinoma of the pancreas: a clinicopathologic series of 25 cases. Gastrointest Cancer Res GCR. 2001; 14:443-51.
12. Hester CA, Augustine MM, Choti MA, Mansour JC, Minter RM, Polanco PM, et al. Comparative outcomes of adenosquamous carcinoma of the pancreas: an analysis of the National Cancer Database. J Surg Oncol. 2018;118:21–30.
13. Yamamoto T, Sugiura T, Mizuno T, Okamura Y, Aramaki T, Endo M, et al. Preoperative FDG-PET predicts early recurrence and a poor prognosis after resection of pancreatic adenocarcinoma. Ann Surg Oncol. 2015;22:677–84.
14. Ito T, Sugiura T, Okamura Y, Yamamoto Y, Ashida R, Aramaki T et al (2017) The diagnostic advantage of EOB-MR imaging over CT in the detection of liver metastasis in patients with potentially resectable pancreatic cancer. Pancreatology. 17:451–456
15. Sugiura T, Okamura Y, Ito T, Yamamoto Y, Uesaka K. Surgical indications of distal pancreatectomy with celiac axis resection for pancreatic body/tail cancer. World J Surg. 2017;41:258–66.
16. Sugiura T, Uesaka K, Mihara K, Sasaki K, Kanemoto H, Mizuno T, et al. Margin status, recurrence pattern, and prognosis after resection of pancreatic cancer. Surgery. 2013;154:1078–86.
17. Sobin L, Gospodarowicz M, Wittekind C (2009) TNM classification of malignant tumors, 7th edn. Wiley, New York
18. Hoshimoto S, Hoshi N, Hishinuma S, Shirakawa H, Tomikawa M, Ozawa I et al (2017) Clinical implications of the proliferative ability of the squamous component regarding tumor progression of adenosquamous carcinoma of the pancreas: a preliminary report. Pancreatology. 17:788–794
19. Solaini L, de Rooij T, Marsman EM, Te Riele WW, Tanis PJ, van Gulik TM, et al. Pancreatoduodenectomy with colon resection for pancreatic cancer: a systematic review. HPB. 2018;20:881–7.
20. Hong SM, Kim MJ, Jang KT, Yoon GS, Cho H, Frierson HF, et al. Adenosquamous carcinoma of extrahepatic bile duct:

clinicopathologic study of 12 cases. Int J Clin Exp Pathol. 2008;1:147–56.
21. Komatsu H, Egawa S, Motoi F, Morikawa T, Sakata N, Naitoh T, et al. Clinicopathological features and surgical outcomes of adenosquamous carcinoma of the pancreas: a retrospective analysis of patients with resectable stage tumors. Surg Today. 2015;45:297–304.
22. Imaoka H, Shimizu Y, Mizuno N, Hara K, Hijioka S, Tajika M et al (2014) Ring-enhancement pattern on contrast-enhanced CT predicts adenosquamous carcinoma of the pancreas: a matched case–control study. Pancreatology. 14:221–226
23. Toshima F, Inoue D, Yoshida K, Yoneda N, Minami T, Kobayashi S, et al. Adenosquamous carcinoma of pancreas: CT and MR imaging features in eight patients, with pathologic correlations and comparison with adenocarcinoma of pancreas. Abdom Radiol (New York). 2016;41:508–20.
24. Okabayashi T, Hanazaki K. Surgical outcome of adenosquamous carcinoma of the pancreas. World J Gastroenterol. 2008;14:6765–70.
25. Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K et al (2007) Adjuvant chemotherapy with gemcitabine vs. observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. Jama. 297:267–277
26. Oettle H, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, Ridwelski K, 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.
27. Uesaka K, Boku N, Fukutomi A, Okamura Y, Konishi M, Matsumoto I, 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 (London, England). 2016;388:248–57.
28. Yamaguchi K, Okusaka T, Shimizu K, Furuse J, Ito Y, Hanada K, et al. Clinical practice guidelines for pancreatic cancer 2016 from the Japan Pancreas Society: a synopsis. Pancreas. 2017;46:595–604.
29. Wild AT, Dholakia AS, Fan KY, Kumar R, Moningi S, Rosati LM, et al. Efficacy of platinum chemotherapy agents in the adjuvant setting for adenosquamous carcinoma of the pancreas. J Gastrointest Oncol. 2015;6:115–25.