

Surgical outcome of adenosquamous carcinoma of the pancreas

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Received: April 12, 2008 Revised: July 20, 2008

Accepted: July 27, 2008

Published online: November 28, 2008

Key words: Adenosquamous carcinoma of the pancreas; Pancreatectomy; Surgical outcome; Survival after pancreatic resection

Peer reviewer: Salvatore Gruttadauria, Professor, Department of Abdominal Transplant Surgery, Mediterranean Institute for Transplantation and Advanced Specialized Therapies (IsMeTT), Via E. Tricomi, Palermo 90127, Italy

Okabayashi T, Hanazaki K. Surgical outcome of adenosquamous carcinoma of the pancreas. *World J Gastroenterol* 2008; 14(44): 6765-6770 Available from: URL: <http://www.wjgnet.com/1007-9327/14/6765.asp> DOI: <http://dx.doi.org/10.3748/wjg.14.6765>

Abstract

Adenosquamous carcinoma is rare, accounting for 3%-4% of all pancreatic carcinoma cases. These tumors are characterized by the presence of variable proportions of mucin-producing glandular elements and squamous components, the latter of which should account for at least 30% of the tumor tissue. Recently, several reports have described cases of adenosquamous carcinoma of the pancreas. However, as the number of patients who undergo resection at a single institute is limited, large studies describing the clinicopathological features, therapeutic management, and surgical outcome for adenosquamous carcinoma of the pancreas are lacking. We performed a literature review of English articles retrieved from Medline using the keywords 'pancreas' and 'adenosquamous carcinoma'. Additional articles were obtained from references within the papers identified by the Medline search. Our subsequent review of the literature revealed that optimal adjuvant chemotherapy and/or radiotherapy regimens for adenosquamous carcinoma of the pancreas have not been established, and that curative surgical resection offers the only chance for long-term survival. Unfortunately, the prognosis of the 39 patients who underwent pancreatic resection for adenosquamous carcinoma was very poor, with a 3-year overall survival rate of 14.0% and a median survival time of 6.8 mo. Since the postoperative prognosis of adenosquamous carcinoma of the pancreas is currently worse than that of pancreatic adenocarcinoma, new adjuvant chemotherapies and/or radiation techniques should be investigated as they may prove indispensable to the improvement of surgical outcomes.

INTRODUCTION

The majority of malignant tumors in the pancreas are adenocarcinomas. Adenosquamous carcinoma of the pancreas occurs less frequently with an incidence of 3%-4%^[1]. These tumors are a malignant epithelial carcinoma of the pancreas and are characterized by the presence of variable proportions of both glandular and squamous components. At least 30% of the neoplasm should be comprised of the squamous component^[1,2]. Recently, several reports have described cases of adenosquamous carcinoma of the pancreas^[3-6]. However, as the number of patients who undergo resection at a single institute is limited, large studies describing the clinicopathological features, therapeutic management and surgical outcome for adenosquamous carcinoma of the pancreas are lacking.

To the best of our knowledge, our survey of the English literature reporting on adenosquamous carcinoma of the pancreas, which was found on Medline, revealed that only 39 intent-to-cure surgical resections had been performed and had clearly presented data (Table 1)^[7-28]. The purpose of this study was to clarify the surgical outcome including survival rates after surgery, and to determine the prognostic factors of adenosquamous carcinoma of the pancreas by conducting a retrospective analysis of the 39 patients.

PATIENTS

Our survey of the literature from 1980 to the end of 2007 revealed that 45 patients underwent surgical resection for adenosquamous carcinoma of the pancreas^[7-28].

Table 1 Clinical and pathological data for the 39 cases that underwent surgical resection for adenosquamous carcinoma of the pancreas

Author	Ref	Yr	Age	Sex	Location	Surgery	Size (cm)	Cx	RT	Rec site	Survival
Ishikawa	7	1980	67	M	Body	DP	10.0	-	-	Widespread metastasis	4 mo
			53	F	Head	PD	4.2	-	-		2 d
			61	M	Head	PD	4.5	-	-		12 mo
Wilczynski	8	1984	68	M	Head, body	PD	4.5	-	-		20 d
Yamaguchi	9	1991	60	M	Head	PD	ND	-	-	ND	3 mo
			52	F	Head	PD	ND	-	-	ND	7 mo
			44	F	Head	PD	ND	-	-	ND	5 mo
			56	F	Head	PD	ND	-	-	ND	4 mo
			56	M	Head	PD	ND	-	-	ND	5 mo ¹
			68	F	Head	PD	ND	-	-	ND	5 mo ¹
			49	F	Body	DP	ND	-	-	ND	5 mo
Motojima	10	1992	61	M	Tail	DP	ND	-	-	ND	14 mo ¹
			52	M	Body, tail	DP	7.0	ND	ND	Systemic metastasis	3 mo
			75	M	Head	PD	3.0	ND	ND	Liver	10 mo
			75	F	Head	PD	6.0	ND	ND	Liver	8 mo
Tanaka	11	1994	48	F	Head	PD	4.2	+	-	ND	7 mo
Makiyama	12	1995	58	M	Head	PD	5.0	-	-	Peritoneum	18 mo
Onoda	13	1995	64	M	Body, tail	DP	7.0	+	-	Liver, peritoneum	3 mo
Campman	14	1997	65	F	Body, tail	DP	7.5	ND	ND	ND	ND
Kuji	15	1997	73	M	Body, tail	TP	6.0	-	-	ND	2 mo
			60	M	Body	DP	6.0	-	IOR	ND	4 mo
Nabae	16	1998	73	M	Head	PD	ND	-	-	Liver	10 mo
			64	M	Head	PD	3.5	-	-	ND	4 mo ¹
Myung	17	1998	64	M	Head	PD	3.5	-	-	ND	4 mo ¹
Lozano	18	1998	75	M	Head, body	PD	4.5	+	+	ND	ND ¹
			42	M	Head	PD	3.5	+	+	ND	ND ¹
Aranha	19	1999	52	M	Head	PD	3.2	+	+	Systemic metastasis	13 mo
			62	M	Head	PD	3.0	+	+	Systemic metastasis	14 mo
Komatsuda	20	2000	67	M	Body	DP	5.0	-	-	Peritoneum	6 mo
Yavus	21	2000	51	M	Head	PD	4.0	ND	ND	-	36 mo ¹
			48	M	Head	PD	2.0	ND	ND	ND	ND
Yamaue	22	2001	63	F	Head	PD	4.5	+	+	-	40 mo ¹
Kardon	23	2001	ND	ND	Head	PD	ND	-	-	ND	33 mo ¹
Murakami	24	2003	41	M	Head	PD	3.0	-	+	Peritoneum	5 mo
Rahemtullah	25	2003	ND	ND	Head	PD	ND	ND	ND	ND	13 mo ¹
			ND	ND	Head	PD	ND	ND	ND	ND	ND
Alwaheeb	26	2005	45	M	Head	PD	6.0	-	-	ND	ND
Hsu	27	2005	66	M	Head	PD	3.5	-	-	ND	2.5 mo
			38	F	Head	PD	3.8	-	+	ND	6.8 mo
Jamali	28	2007	75	M	Head	PD	3.0	+	-	Liver	6 mo

Cx: Chemotherapy; RT: Radiotherapy; Rec site: Recurrence site; ND: Not described; PD: Pancreaticoduodenectomy; DP: Distal pancreatectomy; TP: Total pancreatectomy. ¹Surviving patients.

Of these, six patients were excluded due to a lack of clear data. The remaining 39 patients were analyzed in this study (Table 1) and included 25 men, 11 women, and three patients of unknown sex with a mean age of 59.0 years (range, 38-75 years). The prognosis outcome of each case was obtained from the published data. The clinicopathological data associated with the pancreatic adenosquamous carcinomas described in these case reports were evaluated, and included tumor location, type of operation, tumor size, whether chemotherapy and radiotherapy had been administered, recurrence sites, and survival times. All of the patients had undergone surgery involving an attempted curative resection. Survival rates were generated using the Kaplan-Meier method and compared using the log-rank test^[29]. Values were expressed appropriately as the mean \pm SD. Differences in proportions were evaluated by the Pearson chi-square test. A value of $P < 0.05$ was considered to be statistically significant.

DIAGNOSIS OF ADENOSQUAMOUS CARCINOMA OF THE PANCREAS

Table 1 lists 39 patients who had undergone surgical resection for adenosquamous carcinoma of the pancreas. Adenosquamous carcinomas have not been associated with any specific clinical syndromes^[2,30]. Each of the 39 patients presented clinical symptoms such as abdominal pain, back pain, painless jaundice, anorexia, and/or body weight loss (data not shown). Accurate preoperative diagnosis of adenosquamous carcinoma of the pancreas is very difficult, because imaging studies have revealed no characteristic features that can facilitate the differentiation of this tumor type from ordinary invasive ductal carcinoma. One study reported that intense Gallium-67 citrate uptake was observed in adenosquamous carcinoma of the pancreas, indicating that Gallium-67 citrate scintigraphy might be useful in detecting these carcinomas^[15]. However, more detailed

imaging data are required to improve the ability to diagnose this rare disease.

Adenosquamous carcinoma of the pancreas appears to be larger than ordinary pancreatic adenocarcinoma. The tumors in the 27 cases for which the relevant data was available had a mean size of 4.8 ± 1.8 cm (range, 2-10 cm; Table 1). Preoperative cytological or pathological diagnosis of adenosquamous carcinoma of the pancreas is reportedly rare^[12,16-18,21,24,26,30]. However, the two malignant cellular components of adenosquamous carcinoma can be recognized in aspirated smears^[17,18,24]. A careful search for glandular differentiation is warranted when the squamous component predominates, particularly if squamous carcinoma specimens only are obtained by biopsy or fine needle aspiration biopsy^[12,16]. Adenosquamous carcinoma of the pancreas has no specific radiological findings or serum data, including tumor markers such as carcinoembryonic antigen, carbohydrate antigen 19-9, or squamous cell carcinoma antigen^[12,22]. Physicians should try to remember to consider adenosquamous carcinoma of the pancreas in the differential diagnosis of ordinary pancreatic adenocarcinoma, especially if the patient has severe abdominal symptoms and/or a large tumor size^[2,30]. Recently, preoperative and intraoperative cytological examinations have been diagnostically correct, however these findings did not alter treatment decisions or survival^[30].

MANAGEMENT FOR RESECTABLE ADENOSQUAMOUS CARCINOMA OF THE PANCREAS

Since adenosquamous carcinomas are uncommon tumors with a poor prognosis, the outcomes associated with various therapeutic interventions are not well defined.

Table 1 lists the tumor location and operative method used in the 39 cases analyzed here. Three main operative methods were performed: pancreaticoduodenectomy (PD) including pylorus-preserving PD (PPPD) in 30 cases (76.9%); distal pancreatectomy (DP) in eight cases (20.5%); and total pancreatectomy (TP) in one case (2.6%). Tumors were located in the head alone in 28 cases (76.9%), in the head and body in two cases, and in the body and/or tail of the pancreas in nine cases (23.1%). Although adenosquamous carcinoma of the pancreas has different clinicopathological features to pancreatic adenocarcinoma, the treatment strategy of patients with adenosquamous carcinoma is dealt with in the same manner as patients with adenocarcinoma. Surgical treatment remains the only curative management option that is seriously considered for adenosquamous carcinoma of the pancreas.

To date, only eight patients have received adjuvant chemotherapy, indicating that postoperative adjuvant chemotherapy is not usually administered to patients with adenosquamous carcinoma of the pancreas (Table 1). Tanaka *et al.* reported that the size of an unresectable adenosquamous carcinoma of the pancreas was reduced by neo-adjuvant chemotherapy consisting of a combination of interferon- α , tumor necrosis factor- α , and 5-fluoroura-

cil^[11]. However, the patient only survived 7 mo after surgery^[11]. In this case, although neo-adjuvant chemotherapy might not have contributed to prolonging the patient's survival, the ability of the chemotherapy to reduce the size of the tumor from one that was unresectable to one that could be resected was confirmed. In the current study, the adjuvant chemotherapy group had a 2- or 3-year cumulative survival rate of 16.7% and a median survival period of 7 mo (Table 2). In comparison, the group who did not receive adjuvant chemotherapy had a 2-year cumulative survival rate of 9.2% and a median survival period of 5 mo ($P = 0.364$). Almost all of the patients in the adjuvant chemotherapy group were treated with a 5-fluorouracil-based regimen. Recently, adjuvant chemotherapy using new drug agents has been considered as the standard therapeutic option following resection for pancreatic adenocarcinoma, and several reports suggest that adjuvant chemotherapy with gemcitabine is responsible for a significant increase in patient survival^[31-33]. Postoperative administration of gemcitabine also significantly delayed the development of recurrent disease after complete resection of pancreatic cancer compared with observation alone^[34]. However, information regarding gemcitabine use in cases with adenosquamous carcinoma of the pancreas is not available as previous reports lack such data. Further investigations examining whether adjuvant chemotherapy using gemcitabine will improve surgical outcome in patients with adenosquamous carcinoma of the pancreas are therefore warranted.

There are no published prospective randomized controlled trials investigating radiotherapy treatment of pancreatic adenosquamous carcinoma following curative resection, only retrospective studies. Limitations of the present study include the errors and biases inherent in a small retrospective study design. Two retrospective studies investigating the benefit of radiotherapy following curative resection for pancreatic carcinoma showed no significant difference in the overall survival between patients who were or were not treated with radiotherapy^[35,36]. In the current study, patients who had received intra- and/or postoperative radiotherapy had a 2- or 3-year cumulative survival rate of 20.0% and a median survival period of 13 mo (Table 2). By comparison, the non radiotherapy group had a 2-year cumulative survival rate of 9.0% and a median survival period of 6 mo ($P = 0.284$). There was no significant difference in survival between patients who did and did not receive radiotherapy.

PROGNOSIS AFTER PANCREATIC RESECTION

The overall 1-, 2-, and 3-year survival rates after pancreatic resection were 25.5%, 14.0%, and 14.0%, respectively (Figure 1). Table 1 shows operative mortality occurred in two patients during the early 1980s^[7,8]. One patient died of myocardial infarction 2 d after undergoing PD and another died of numerous postoperative complications including electrolyte disturbance from massive abdominal fluid

Table 2 Clinical characteristics after surgical resection for adenosquamous carcinoma of the pancreas

Characteristics	No. of patients	Survival rate (%)			Median survival in months (range)	P value
		1 yr	2 yr	3 yr		
Overall	39	25.5	14.0	14.0	6.8 (4.6-9.0)	
Age (yr)						
< 60	16	26.9	9.0	9.0	6.8 (4.4-9.2)	0.975
> 60	20	20.4	13.6	13.6	6.0 (1.3-10.7)	
Gender						
Male	25	28.4	8.5	8.5	6.0 (1.1-10.9)	0.842
Female	11	12.0	12.0	12.0	6.8 (5.0-8.6)	
Tumor location						
Head	30	34.8	17.9	17.9	8.0 (5.3-10.7)	0.017
Body or tail	9	11.1	-	-	4.0 (2.6-5.4)	
Operation type						
PD	30	33.4	17.2	17.2	8.0 (5.2-10.8)	0.063
DP or TP	9	12.5	-	-	4.0 (2.7-5.3)	
LN metastasis						
Present	14	20.0	-	-	5.0 (2.0-8.0)	0.134
Absent	8	50.0	50.0	50.0	5	
Chemotherapy						
Yes	8	50.0	16.7	16.7	7.0 (0.0-15.4)	0.364
No	23	18.4	9.2	-	5.0 (3.0-7.0)	
Radiotherapy						
Yes	7	60.0	20.0	20.0	13.0 (0.0-26.3)	0.284
No	23	18.0	9.0	-	6.0 (4.0-8.0)	

PD: Pancreaticoduodenectomy; DP: Distal pancreatectomy; TP: Total pancreatectomy; LN metastasis: Lymph node metastasis.

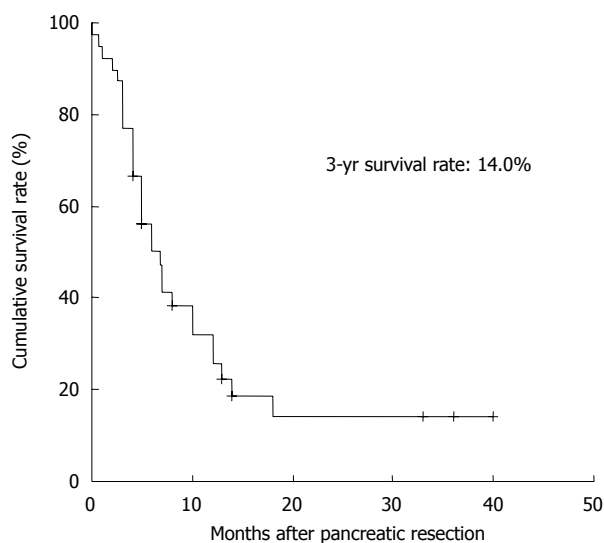


Figure 1 Survival after surgical resection for adenosquamous carcinoma of the pancreas ($n = 39$).

losses, acute renal failure and eventually congestive heart failure 20 d after undergoing PD^[7,8]. Univariate analysis of the different prognostic factors predicted to contribute to patient prognosis showed that tumor location was the only unfavorable prognostic factor. Median survival of patients with a tumor located in the body and/or tail (4 mo) was significantly worse than those with tumors located in the head (8 mo) (Table 2). Prognostic differences based on tumor location may relate to tumor size, as the size of a distal pancreatic tumor (7.3 ± 1.8 cm) was significantly larger than that of a proximal pancreatic tumor (4.7 ± 1.9 cm, $P = 0.002$). Age, gender, type of operative procedure, and

lymph node metastasis were not significant prognostic factors.

Recently, long-term survival after PD for pancreatic adenocarcinoma has improved, and the number of patients surviving for five or 10 years has increased^[37-39]. On the other hand, the prognosis for the 39 patients with adenosquamous carcinoma in this study was poor, with a 3-year overall survival rate of only 14.0%, and includes two patients with hospital mortality. A patient surviving for five years post-resection has not been reported yet (Table 1). This suggests that adenosquamous carcinoma of the pancreas has greater malignant potential than adenocarcinoma of the pancreas. A previous report also found that squamous cell carcinomas grow at twice the speed of adenocarcinomas^[31]. Therefore, once an adenocarcinoma has transformed into an adenosquamous carcinoma, the carcinoma may exhibit a higher degree of malignancy^[40].

CONCLUSION

Even though curative resection for adenosquamous carcinoma of the pancreas was performed in the 39 patients, prognosis remained poor because systemic metastases in the liver and peritoneal dissemination were the major sites of recurrence (Table 1). In addition, tumor recurrence occurred during the early stages of the post-operative period in a large number of patients. Yamaue et al. reported that it might be preferable not to perform a pancreatic resection if a pancreatic tumor is diagnosed as an adenosquamous carcinoma^[22]. Consensus of opinion regarding the surgical indication required for this type of tumor has not been reached yet. Elucidating

a surgical treatment strategy based on the appropriate surgical indication is essential for improving the surgical outcome of adenosquamous carcinoma of the pancreas.

The results of this current study indicate that tumor location may be an important factor in determining the appropriate surgical indication. Namely, surgical resection may be better suited for proximal pancreatic tumors than for distal tumors because the proximal location of tumors was the only significant favorable prognostic factor found in this study. Furthermore, exploration of new radiation techniques and chemotherapeutic regimens using new drug agents such as gemcitabine may be required because conventional chemotherapy and radiotherapy treatments did not contribute to survival benefit. The incorporation of novel 'molecularly targeted' agents into therapy will also be required to improve surgical outcome.

Although adenosquamous carcinoma of the pancreas has a poor prognosis even after curative resection, we must continue to endeavor to improve the surgical outcome of this tumor, because despite its rarity, it occurs worldwide. More data, including epidemiological and pathological findings, will be required to determine the appropriate surgical indication for this tumor.

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S- Editor Zhong XY L- Editor Logan S E- Editor Ma WH