Surgical outcome of adenosquamous carcinoma of the pancreas

Takehiro Okabayashi, Kazuhiro Hanazaki

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

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. 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.

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].

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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  |     | 4.2 | - | - | | | | | | |
|           | 61  |     | Head | PD | 4.5 | - | - | | | | |
| Wilczynski | 8   | 1984 | 68 | M | Head, body | PD | 4.5 | - | - | | 20 d |
| Yamaguchi | 9   | 1991 | 60 | M | Head | PD | ND | - | - | Location | 3 mo |
|           | 52  |     | Head | PD | ND | - | - | | | | |
|           | 44  |     | Head | PD | ND | - | - | | | | |
|           | 56  |     | Head | PD | ND | - | - | | | | |
|           | 56  |     | Head | PD | ND | - | - | | | | |
|           | 49  |     | Body | PD | ND | - | - | | | | |
|           | 61  |     | Tail | PD | ND | - | - | | | | |
| Motojima  | 10  | 1992 | 52 | M | Body, tail | PD | 7.0 | ND | ND | Systemic metastasis | 3 mo |
| Tanaka    | 11  | 1994 | 48 | F | Head | PD | 4.2 | + | - | | 7 mo |
| Makihara  | 12  | 1995 | 58 | M | Head | PD | 5.0 | - | - | Peritoneum | 18 mo |
| Onoda     | 13  | 1995 | 64 | M | Body, tail | PD | 7.0 | + | - | Liver, peritoneum | 3 mo |
| Campman   | 14  | 1997 | 65 | F | Body, tail | DP | 7.5 | ND | ND | | |
| Kuji      | 15  | 1997 | 73 | M | Body, tail | TP | 6.0 | - | - | | |
| Nabe     | 16  | 1998 | 60 | M | Body | PD | 6.0 | - | - | IOR | ND | 4 mo |
| Myung     | 17  | 1998 | 64 | M | Head | PD | 3.5 | - | - | | |
| Lozano    | 18  | 1998 | 75 | M | Head, body | PD | 4.5 | + | + | ND | ND |
| Aranha    | 19  | 1999 | 52 | M | Head | PD | 3.2 | + | + | Systemic metastasis | 13 mo |
| Komatsuda | 20  | 2000 | 67 | M | Body | DP | 5.0 | - | - | Peritoneum | 6 mo |
| Yauvus    | 21  | 2000 | 51 | M | Head | PD | 4.0 | ND | ND | - | 36 mo |
| Yamaue    | 22  | 2001 | 63 | M | Head | PD | 2.0 | ND | ND | ND | |
| Kardon    | 23  | 2001 | ND | ND | Head | PD | 4.5 | + | + | - | 40 mo |
| Murakami  | 24  | 2003 | 41 | M | Head | PD | 3.0 | - | + | Peritoneum | 5 mo |
| Rahmentullah | 25  | 2003 | ND | ND | Head | PD | ND | ND | ND | ND | 13 mo |
| Alwaheeb  | 26  | 2005 | 45 | M | Head | PD | 6.0 | - | - | ND | ND |
| Hsu       | 27  | 2005 | 66 | M | Head | PD | 3.5 | - | - | | 2.5 mo |
| Jamali    | 28  | 2007 | 75 | M | Head | PD | 3.0 | + | + | - | |

Cx: Chemotherapy; RT: Radiotherapy; Rec site: Recurrence site; ND: Not described; PD: Pancreaticoduodenectomy; DP: Distal pancreatectomy; TP: Total pancreatectomy. †Surviving 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 ± 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[25,30]. 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[38]. However, more detailed
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[15,16,18,21,23,26,30]. However, the two malignant cellular components of adenosquamous carcinoma can be recognized in aspirated smears[17,19,24]. 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[12,14]. 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[16,22,23]. 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[2,34]. 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-fluorouracil[30]. 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 = 0.564). Almost all of the patients in the adjuvant chemotherapy group were treated with a 5-fluouracil-based regimen. Recently, adjuvant chemotherapy using new drug agents has been considered as the standard therapeutic option following resection for pancreatic adenosquamous carcinoma, 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...
losses, acute renal failure and eventually congestive heart failure 20 d after undergoing PD. 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. 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. Therefore, once an adenocarcinoma has transformed into an adenosquamous carcinoma, the carcinoma may exhibit a higher degree of malignancy.

**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 postoperative 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. Consensus of opinion regarding the surgical indication required for this type of tumor has not been reached yet. Elucidating

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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 |
|-----------------|-----------------|------------------|----------------------------------|--------------|
| 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) |
| > 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) |
| Female          | 11              | 12.0             | 12.0                             | 12.0         | 6.8 (5.0-6.6) |
| Tumor location  |                 |                  |                                  |              |
| Head            | 30              | 34.8             | 17.9                             | 17.9         | 8.0 (5.3-10.7) |
| 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) |
| DP or TP        | 9               | 12.5             | -                                | -            | 4.0 (2.7-5.3) |
| LN metastasis   |                 |                  |                                  |              |
| Present         | 14              | 20.0             | -                                | -            | 5.0 (2.0-8.0) |
| Absent          | 8               | 50.0             | 50.0                             | 50.0         | 5.0 (3.0-7.0) |
| Chemotherapy    |                 |                  |                                  |              |
| Yes             | 8               | 50.0             | 16.7                             | 16.7         | 7.0 (0.0-35.4) |
| 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) |
| No              | 23              | 18.0             | 9.0                              | -            | 6.0 (4.0-8.0) |

PD: Pancreatocoduodenectomy; 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).
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