

# Long-Term Survival Following Pancreatectomy and S-1 Chemotherapy for Pancreatic Acinar Cell Carcinoma With Peritoneal Dissemination

## *A Case Report and Literature Review*

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**Abstract:** Current case is the third report of S-1 chemotherapy against acinar cell carcinoma (ACC) of pancreas, and our patient has achieved the longest reported recurrence-free survival, longer than 6 years, despite the presence of disseminated nodules at laparotomy.

A 77-year-old man presented with abdominal discomfort. Computed tomography showed a low-density tumor in the pancreas tail and the patient was referred for surgery. A 3-cm sized pancreatic tumor, with localized disseminated nodules, was detected on laparotomy. Distal pancreatectomy with concomitant resection of disseminated nodules was performed, and histopathological examination revealed an ACC. Oral S-1 chemotherapy was administered postsurgery, and the patient showed no sign of recurrence during 73 months of follow-up. This is the first report of long-term survivor of pancreatic ACC with peritoneal dissemination, following pancreatectomy and S-1 chemotherapy.

Current case suggests a beneficial effect of S-1 chemotherapy in cases of ACC.

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**Abbreviations:** 5-FU = 5-fluorouracil, AC = adenocarcinoma, ACC = acinar cell carcinoma, CT = computed tomography, MST = median survival time, PR = partial response, SD = stable disease.

## INTRODUCTION

Pancreatic acinar cell carcinoma (ACC) is a rare malignant neoplasm that produces exocrine enzyme and accounts for approximately 1% of all pancreatic neoplasms.<sup>1</sup> Although radical surgery is the only treatment method resulting in long-term survival in ACC, its outcome is not always successful, and the development of effective chemotherapy is necessary.<sup>2,3</sup> However, because of the rarity of this disease, no chemotherapeutic

regimens have been established for pancreatic ACC. S-1, described in the current report, is an orally administered drug, comprising the 5-fluorouracil (5-FU) prodrug tegafur and 2 molecules, gimeracil and oteracil potassium, that increase the blood concentration, and enhance the antitumor effect of 5-FU.<sup>4</sup> Clinical studies have demonstrated a significant anticancer effect of S-1 in several types of malignant tumors, such as stomach cancer, colorectal cancer, head and neck cancer, nonsmall cell lung cancer, breast cancer, and pancreatic adenocarcinoma (AC).<sup>5,6</sup> Here, we report the case of a 6-year recurrence-free survivor of pancreatic ACC with peritoneal dissemination, treated with pancreatectomy and S-1 chemotherapy.

## CASE REPORT

A 77-year-old man with no previous history of disease presented with abdominal discomfort and was referred to the local hospital. Laboratory test results showed no abnormal findings. Tests for carcinoembryonic antigen, carbohydrate 19-9, DUPAN-2, and s-pancreas-1 antigen were all negative. Contrast-enhanced computed tomography (CT) showed a well-demarcated low-density tumor, 3.1 cm in size, located in the pancreas tail (Figure 1A). An area of lower density, suspected to be necrosis, was present in that tumor. Tumor invasion was suspected from the extrinsic compression of the posterior stomach wall, seen on gastrointestinal fiberoptic examination. The patient was referred to our hospital and surgery was planned. At laparotomy, a 3-cm tumor was located in the pancreatic tail. The tumor was visible on the surface of the pancreas and had invaded the posterior stomach wall. Localized disseminated nodules were also detected around the pancreatic tumor. Although surgery was unlikely to be curable, the disseminated nodules were localized, and distal pancreatectomy, concomitant with partial gastrectomy and resection of the disseminated nodules, was performed (Figure 1B). Macroscopically, the pancreatic tumor was yellowish-white and well demarcated (Figure 1C). Intratumoral necrosis was also found, as indicated on the preoperative CT. Microscopically, the tumor was characterized by extensive cellularity and minimal stroma, and the tumor cells were arranged in a solid pattern (Figure 1D). The nuclei showed only moderate atypia and eosinophilic granules were frequently seen in the cytoplasm. The pancreatic tumor was diagnosed as ACC. The patient recovered well, without any complications, and was discharged 11 days after surgery. S-1 chemotherapy was administered postsurgery, with palliative intent. The regimen consisted of 3-week cycles, in which 60 mg of oral S-1 per square meter of body surface area per day was administered for 2 weeks, and no chemotherapy

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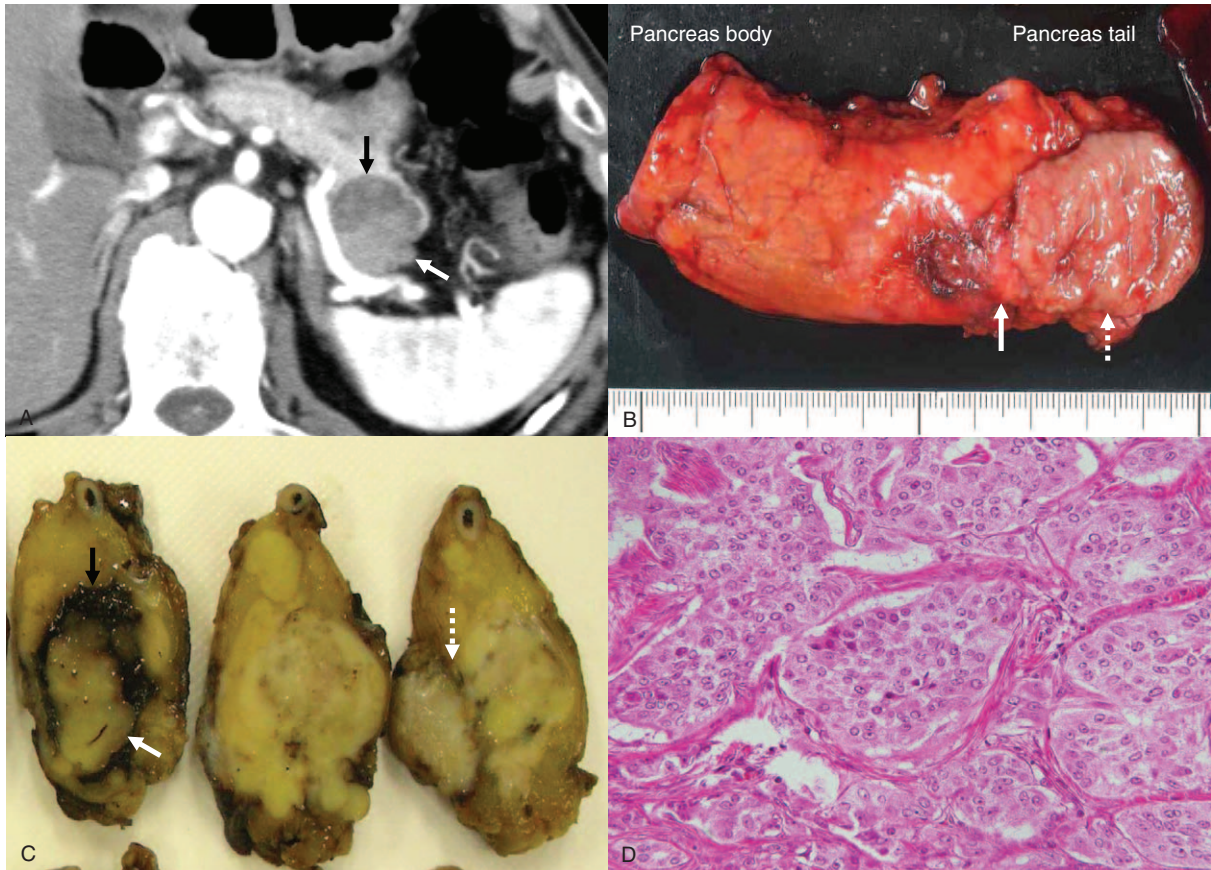
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**FIGURE 1.** Computed tomography (CT) findings. CT showed a low-density tumor, 3.1 cm in size, in the pancreatic tail (white arrow). An area of lower density, suspected to be necrosis, was seen in the tumor (black arrow) (A). Resected specimen. The tumor was visible on the surface of the pancreas (solid arrow), and had invaded the posterior stomach wall (dotted arrow) (B). Macroscopic findings of resected tumor. Macroscopically, the tumor was yellowish-white and well demarcated (white arrow), and intratumoral necrosis was present (black arrow). The tumor had invaded the stomach wall (dotted arrow) (C). Microscopically, the tumor was characterized by extensive cellularity and minimal desmoplastic stroma, and the tumor cells were arranged in a solid pattern. The nuclei showed only moderate atypia, and eosinophilic granules were frequently seen in the cytoplasm (hematoxylin and eosin; original magnification  $\times 40$ ) (D).

was given during the third week. S-1 chemotherapy was tolerated well, and no severe complications were observed. The patient continues to receive S-1 therapy, and has been regularly followed up using contrast-enhanced CT examination. The patient has shown no sign of recurrence and is in good health, 73 months after the surgery.

## DISCUSSION

Pancreatic ACC is a rare malignant epithelial neoplasm that exhibits exocrine enzyme production.<sup>1</sup> Several recent reports have described its specific morphological characteristics such as intratumoral necrosis, intraductal tumor growth, and venous tumor thrombus.<sup>7</sup> Although ACCs were regarded to be equally aggressive as pancreatic ACs in the past, it has been recently elucidated that ACCs show lower malignant potential and significantly better survival than ACs. In the largest series of ACC (865 patients), Schmidt et al<sup>3</sup> found that the stage-specific 5-year survival was significantly better for resected ACC than AC (stage I: 52.4% vs 28.4%; II: 40.2% vs 9.8%; III: 22.8% vs 6.8%; IV: 17.2% vs 2.8%).

Currently, surgical resection is the only curative approach to this disease.<sup>2,8</sup> Kitagami et al<sup>2</sup> reported that the 5-year

survival rate for patients with resected ACC was 43.9%, with a median survival time (MST) of 41 months. On the contrary, the 5-year survival rate for unresected cases was 0%, with a MST of 3 months. Holen et al<sup>9</sup> reported an MST of 36 months for patients initially treated by surgical resection. Although there is no doubt that surgery is the mainstay for the treatment of ACC, a high recurrence rate of 72% following surgical resection has been reported.<sup>9</sup> Therefore, effective chemotherapy is necessary to improve the clinical outcome. However, chemotherapy regimens have not been established due to the rarity of this disease.<sup>5,8,9</sup> No prospective clinical trials of chemotherapy have been published, and several chemotherapy regimens have been reported only as case reports.<sup>5,8-13</sup> Riechelmann et al<sup>11</sup> reported a case of ACC with a remarkable response to weekly paclitaxel. However, disease control was maintained for only 4 months in that case. A study carried out in the Memorial Sloan-Kettering Cancer Center of 18 ACC patients who received 22 inhomogeneous chemotherapy regimens, containing gemcitabine, 5-FU, leucovorin, mitomycin, cisplatin, cytarabine, irinotecan, caffeine, and doxorubicin, reported no complete responses, 2 partial responses (PRs) and 7 stable diseases.<sup>9</sup> The PRs were associated with treatment combinations of irinotecan, 5-FU, and leucovorin, and also cytarabine,

**TABLE 1.** Reported Cases of S-1 Chemotherapy for Pancreatic ACC

Author	TNM	Stage	Surgery	Chemotherapy	Response	Status	Survival, mo
Seki <sup>12</sup>	T3N0M0	II	PD*	GEM→S1	PD**	BSC	26
	T3N1M1 (HEP)	IV	—	GEM→S1	PR	BSC	13
	T4N0M0	III	—	GEM→S1	PD**	BSC	10
Yamamoto <sup>5</sup>	TxNxM1(PER)	IV	DP	S1*	PR	RFS	24
Our case	T4N1M1(PER)	IV	DP	S1**	—	RFS	73

BSC = best supportive care, DP = distal pancreatectomy, GEM = gemcitabine, HEP = hepatic, PD\* = pancreaticoduodenectomy, PD\*\* = progression disease, PER = peritoneum, PR = partial response, Response = response to S1 chemotherapy, RFS = relapse-free survival, S1\*\* = postsurgery S1 chemotherapy, S1\* = presurgery S1 chemotherapy, TNM = International Union Against Cancer Tumor–Node–Metastasis classification.

cisplatin, and caffeine. The most common chemotherapy associated with stable disease was 5-FU. Other reports have also described the positive effect of using regimens containing 5-FU or 5-FU prodrugs.<sup>5,8,10,12,13</sup> Lee et al<sup>10</sup> reported that locally advanced ACC was successfully treated with capecitabine and concurrent radiotherapy. Distler et al<sup>8</sup> reported a primarily unresectable ACC that was curatively resected following 5-FU monotherapy. On the contrary, gemcitabine, which is the standard chemotherapeutic agent used for treatment of pancreatic AC, has not been shown to be effective against ACC. Seki et al<sup>12</sup> reported that monotherapy with gemcitabine was ineffective in 4 cases of ACC. Various other studies have also concluded that 5-FU, rather than gemcitabine, might be more effective for the treatment of ACC, although the number of reported cases is small and true efficacy should be determined by randomized controlled trials.<sup>5,12,13</sup> Considering these previous reports, S-1 was chosen for treatment of the patient in the current case. Two reports, published in English, have described the efficacy of S-1 against ACC (Table 1). Seki et al<sup>12</sup> reported 3 patients who were successfully treated with S-1 following the failure of gemcitabine monotherapy. One of the 3 patients who received S-1 as second-line chemotherapy showed a PR. Yamamoto et al<sup>5</sup> reported a case of a patient with an initially unresectable ACC with peritoneal disseminations. Following S-1 chemotherapy, the main tumor had shrunk from 3.5 cm to 0.8 cm, and the peritoneal disseminations had disappeared. A pancreatectomy was then possible, and the patient remained relapse-free for 2 years. Our case is the third report of S-1 chemotherapy against ACC, and our patient has achieved the longest reported recurrence-free survival, longer than 6 years, despite the presence of disseminated nodules at laparotomy. Although the number of reported cases is small and further research is necessary to clarify its true effect, our case suggests a beneficial effect of S-1 chemotherapy in cases of ACC.

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