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ORIGINAL ARTICLE

An autopsy study to clarify characteristics of local recurrence after extended pancreatectomy with intraoperative radiation therapy in patients with pancreatic cancer

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Abstract
Purpose Local relapses frequently occur even after curative resection of pancreatic cancer. To control local recurrence, we adopted extended radical resection combined with intraoperative radiation therapy.
Methods A retrospective review was conducted on 41 patients who underwent extended radical pancreatectomy combined with intraoperative radiation therapy for pancreatic cancer. Fourteen patients underwent autopsies. We took en bloc specimens of the abdominal aorta with surrounding connective tissue to evaluate histological characteristics of local status at autopsies.
Results Autopsies disclosed microscopic local recurrence in five (36%) of the 14 patients, although no evidence of local relapse was observed in either follow-up images or macroscopic findings at autopsy. Of the three patients with R1 resection, two had no local recurrence microscopically at autopsy. Histological features of local recurrence in autopsy samples showed small numbers of cancer cells surrounded by thick connective tissue without mass formation.
Conclusions The autopsy study revealed that a characteristic of local recurrence after this treatment was tiny cancer cells scattered in dense connective tissue; these cells were undetected by follow-up imaging.

Keywords Local recurrence · Extended pancreatectomy · Intraoperative radiation therapy · Pancreatic cancer · Autopsy study

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Introduction

Pancreatic cancer remains a lethal disease: The annual incidence has been shown revealed to be approximately equal to the annual deaths [1]. Surgical resection offers the only chance for cure, but even after curative resection, there is a high probability of systemic and/or local relapse [2]. Local recurrence occurs in 71.8–73% of the patients [3, 4]. Therefore, local control is one of the most crucial points of treatment for pancreatic cancer. We first applied intraoperative radiation therapy (IORT) for pancreatic cancer in 1969 [5] and first combined it with resection in such patients in 1976 [6, 7]. Moreover, we adopted extended radical resection combined with IORT for pancreatic cancer in 1984 in an attempt to control local recurrence. Local recurrence after surgery in patients with pancreatic cancer was usually evaluated by follow-up imaging including CT, MRI, and ultrasonography, but often could not be identified especially after radiation therapy.

The aim of this study was to clarify histological characteristics of local status after extended radical resection combined with IORT for pancreatic cancer in an autopsy study and to assess the ability of clinical images to detect local recurrence in relation to autopsy findings.

Methods

Patients and surgical technique

Between 1984 and 1999, we performed pancreatic surgery on 88 patients with pancreatic cancer at Kumamoto University Hospital. Of these 88 patients, 41 underwent extended radical pancreatectomy combined with IORT for invasive

ductal carcinoma of the pancreas. The indication for extended pancreatectomy with IORT for this patient group has been described [2]. Briefly, curative resection was required as assessed by physical examination and the following imaging criteria: (1) no evidence of distant metastases, (2) no evidence of involvement of the celiac axis or the superior mesenteric artery, and (3) the possibility of resecting and reconstructing the superior mesenteric vein and/or the portal vein. The extended radical pancreatectomy consisted of complete dissection of regional lymph nodes around the porta hepatis, the celiac axis, the mesenteric radix, and the aorta extending from the diaphragm above to the inferior mesenteric artery below. Following dissection, a dose of 30 Gy with a 9- to 12-Mev electron beam was intraoperatively administered to the dissection field using a special variable pentagon applicator, focusing on the route of the superior mesenteric artery, as described previously [6, 7]. No patients in this study received pre- or postoperative external radiation therapy, while 12 patients received pre- and/or postoperative 5-fluorouracil (5-FU)-based chemotherapy.

Histopathological examination and outcomes analyzed

We evaluated histological characteristics according to the classification of pancreatic cancer defined by the Japanese Pancreas Society [8]. All patients underwent chest and abdominal CT every 3 months for the first year, every 4 months the second year, and every 6 months subsequently to evaluate recurrences. The first site of disease recurrence was documented for outcome analyses. The Kaplan–Meier method was used to analyze survival.

Autopsy evaluation of local relapse

Of 41 patients, 14 patients underwent autopsies. An en bloc specimen of the abdominal aorta with surrounding connective tissue was taken at the autopsy to evaluate local findings (Fig. 1). These specimens were fixed in 20% formalin solution. The paraffin sections for histological examination were prepared and stained with hematoxylin and eosin.

Results

Characteristics of autopsy patients

The characteristics of the autopsy patients are outlined in Table 1. Study subjects included four women and ten men. The median age was 58 years (range, 40–76 years). Tumor location at the operation was nine in the pancreas head and five in the pancreas body. Three autopsy patients were classified as stage III, nine as stage IVa, and two as stage IVb. As to residual tumor (R), R0 resection was achieved in 11 (65%) patients, R1 resection in three, and no R2 resection was

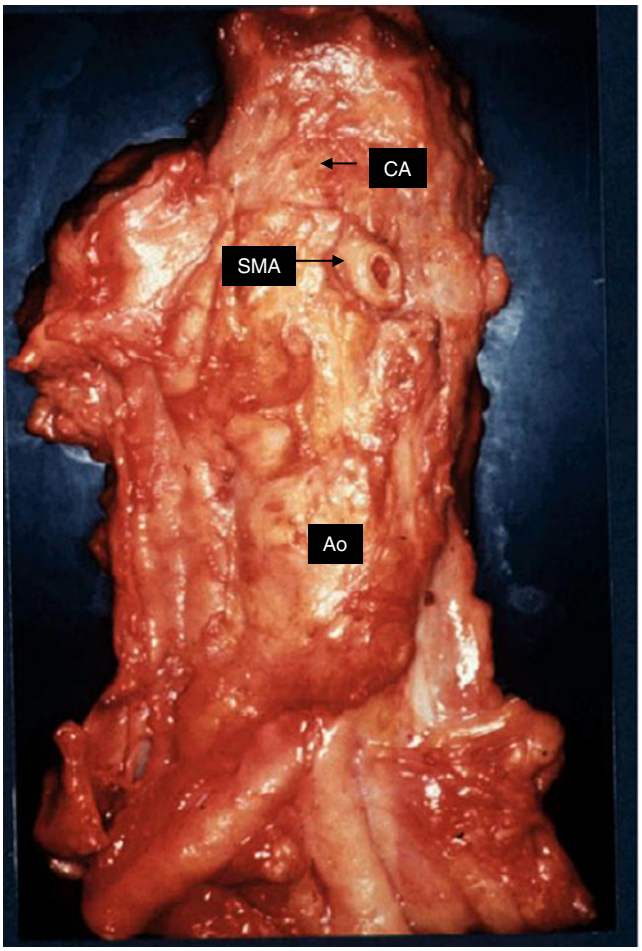

Fig. 1 **a** En bloc specimen of the abdominal aorta with surrounding connective tissue at autopsy to evaluate local recurrence. **b** The schema of en bloc specimen. *Ao* aorta, *CA* celiac axis, *SMA* superior mesenteric artery

Table 1 Patient characteristics

No. of patients	14
Age (years)	
Median	58 (range, 40–76)
Gender	
Male	10
Female	4
Stage	
III	3
IVa	9
IVb	2
Residual tumor	
R0	11
R1	3
R2	0

performed. Three patients received adjuvant 5-FU-based chemotherapy. The cumulative survival curve in these patients was determined using the Kaplan–Meier method and is shown in Fig. 2. The median survival time of these patients was 10.8 months (range from 1.6 to 60.6). Serum CA 19–9 levels were measured in 38 of the 41 patients. The mean CA 19–9 level was 190 U/ml in the seven patients who suffered from local recurrence, including those identified only by autopsy. There was no statistically significant difference in CA 19–9 levels between patients with local recurrence and those with other pattern of recurrence.

Autopsy findings

Autopsies disclosed microscopic local recurrence in five (36%) of the 14 patients, although these patients had no evidence of local relapse either in follow-up imaging or macroscopic findings at autopsy. Their survival periods ranged from 7.6 to 60.6 months. On the other hand, no local recurrence was observed microscopically at autopsy in two of the three patients with R1 resection (Table 2). Local recurrence sites are shown in Fig. 3. In two cases, widespread local recurrences were found on both sides of the aorta from the celiac axis above to the inferior mesenteric artery below (cases 1 and 2). In one case, we found cancer cells in the limited area between the aorta and the inferior vena cava (case 3). In the other two cases, local recurrence occurred in the small part surrounding the splenic artery and close to the superior mesenteric artery (case 4), and close to the celiac axis (case 5). In no case did local relapse appear as a mass formation macroscopically visible at autopsy. Histological features of local recurrence showed small numbers of cancer cells surrounded by a large quantity of thick connective tissue without mass formation (Fig. 4).

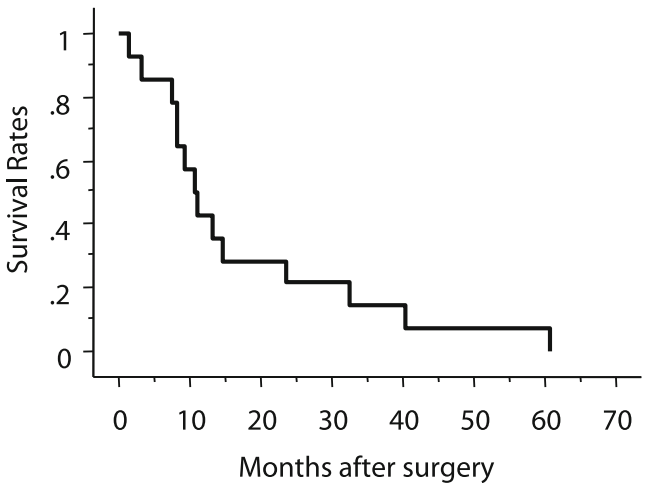

Fig. 2 The cumulative survival curve in this series was determined using a Kaplan–Meier method: the median survival time of these patients was 10.8 months

Table 2 Relation of clinical outcome to presence of local recurrence at autopsy

Clinical outcome	Number of patients	Local recurrence (+) at autopsy
R0 resection	11	4
Cancer-related death		
Liver metastasis	3	2
Lung metastasis	1	
Pleural dissemination	1	
Peritoneal dissemination	2	1
Multi-organ metastases	1	1
Other cause of death	3	
R1 resection	3	1
Cancer-related death		
Peritoneal dissemination	1	
Other cause of death	2	1

Discussion

Local recurrence initially occurs in about 72% of the patients with pancreatic cancer [3, 4]. Most patients who have local recurrence also have systemic recurrences, often resulting in death. Among the 41 patients in this study, imaging showed only two patients with isolated local recurrence. Once the local recurrence occurs, its behavior might be similar to that of locally advanced pancreatic cancer, that is to say, rapid, systemic spread of cancer cells. Several reports have revealed that a negative margin of resection (R0 resection) is one of the most significant prognostic factors [9–11]. This suggests that local control is required to prolong survival in patients with pancreatic cancer. Our combined treatment of extended radical resection and IORT therapy might contribute to local control. Autopsies disclosed microscopic local recurrence in five (36%) of the 14 patients, in whom follow-up imaging had revealed no local recurrence after surgery. This implicates that imaging might be of limited use in diagnosing local relapse after this combined therapy for pancreatic cancer. Hishinuma et al. [12] also reported local recurrence, not demonstrated by CT, but found by histological examination at autopsy in three (33%) of nine patients who underwent pancreatectomy for pancreatic cancer. As far as we know, our study is the first report of precise evaluation by autopsy of local recurrence after extended radical resection combined with IORT in patients with pancreatic cancer.

It is noteworthy that of three patients with R1 resection, two patients proved not to have local recurrence even at histological evaluation at autopsy. This suggests that IORT after radical resection could contribute to local control. Several reports have revealed that IORT results in an excellent

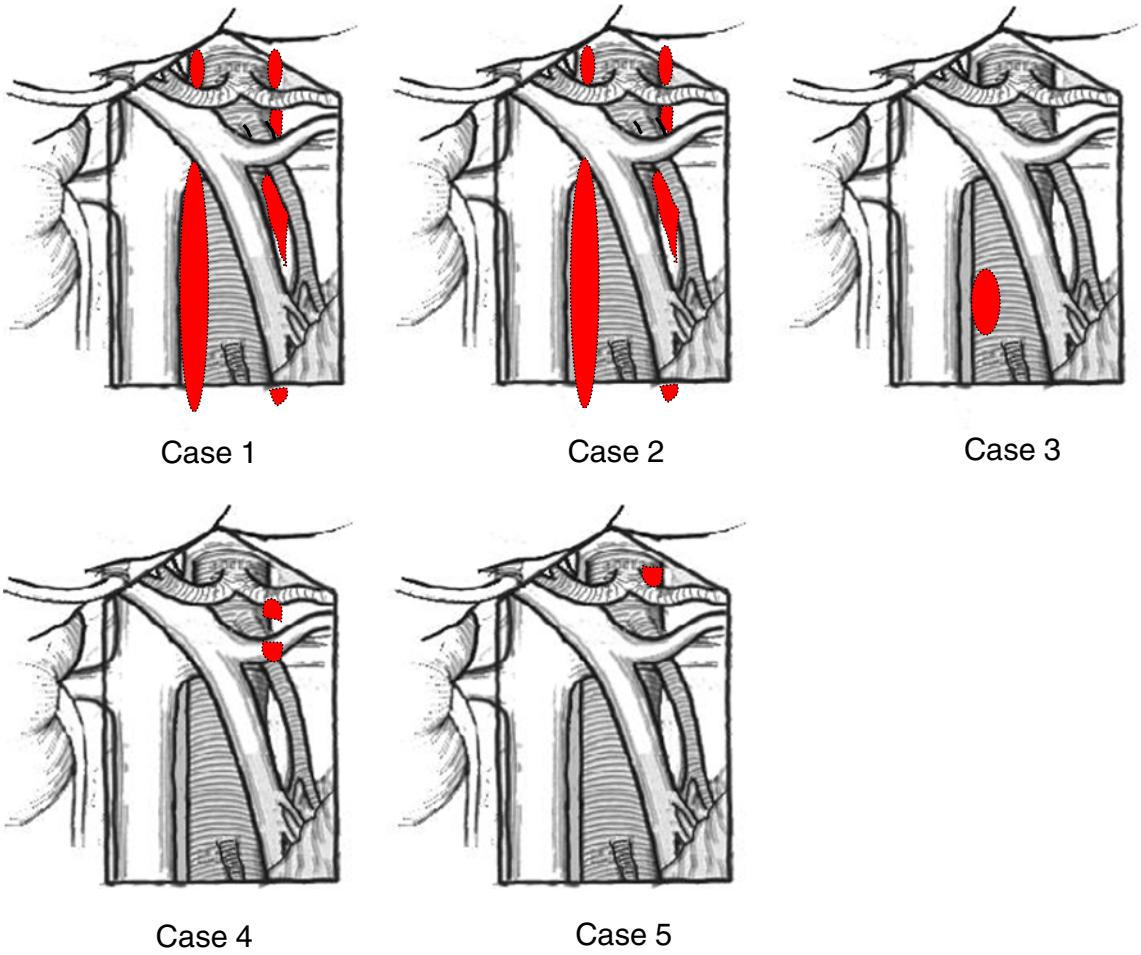

Fig. 3 These schemas indicate sites of local recurrence (*red color*), detected microscopically by autopsy specimens. The *pentagon* denotes the intraoperative radiation field. Original tumor in the pancreas located in Pb in cases 1 and 4 and in Ph in case 2, 3, and 5. *Pb* pancreatic body, *Ph* pancreatic head

local control rate for resectable pancreatic cancer, although it has little impact on survival [13–17].

Five patients were found to be suffering from local recurrence at autopsy. The survival time of these patients

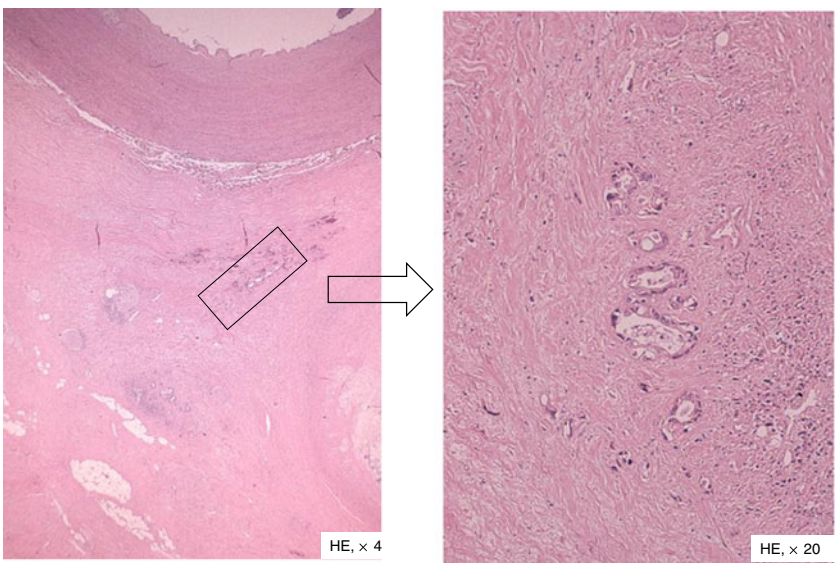

Fig. 4 Microscopic features of local recurrence after extended resection combined with IORT

ranged from 7.6 to 60.6 months. The key histological findings of local recurrence at autopsy were small cancer nests surrounded by dense connective tissue. This finding suggested that local recurrence itself might not be the direct cause of death, as shown in Table 2. In fact, one patient survived for over 5 years. We have already reported that the actual 5-year survival rate in all the 41 patients who underwent extended radical pancreatectomy combined with IORT was 14.6% with a median survival time of 17.6 months [18]. Cancer-related death occurred in 32 patients, 18 of whom had liver metastases, and local recurrence was observed in only two patients by imaging [18]. We also reported that an elevated serum CA 19–9 level was associated with hepatic metastases of pancreatic cancer in clinical and experimental studies [19] but that no significant correlation was observed between serum CA 19–9 level and local recurrence.

In our study, CT and/or MRI imaging showed limited ability to detect local recurrence after this combined therapy because the characteristic of this relapse pattern was for cancer nests to infiltrate the dense retroperitoneal connective tissue without tumor formation. Recently, the value of fluorine-18-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) for the detection of recurrence after surgery for pancreatic cancer was reported [20]. In that study, FDG-PET detected local recurrence at a rate of 96%, compared to 39% for CT/MRI. In fact, FDG-PET has better detection potential of local recurrence than CT/MRI, but local relapse after this combined therapy still might not be detected by FDG-PET because cancer nests in the connective tissue are small volume and scattered.

There were several limitations of this study. First, we could not clarify the influence of chemotherapy on local control because we did not define criteria or a regimen for adjuvant chemotherapy. Second, this is a single-institution retrospective study with a small sample size; a larger population study is required to assess the precise rate of local recurrence after this combined treatment.

Conclusion

Microscopic evaluation in autopsy specimens after combined therapy of extended radical pancreatectomy and IORT for pancreatic cancer revealed local recurrence in 36% of patients undergoing autopsy, none of whom showed evidence of recurrence on clinical imaging. This implies that clinical imaging might be limited in diagnosing local recurrence. The histological features of local recurrence were small-size cancer nests surrounded by dense connective tissue.

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Conflicts of interest None.

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