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Clinicopathological study on long-term survivors after resection of carcinoma of the head of the pancreas

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ABSTRACT

We gradually extended the surgical dissection area for pancreatic cancer after 1973 in order to improve the resection rate and prognosis. As a result, 18 patients survived for ≥ 3 years up to present, and the 5-year survival rate for carcinoma of the pancreatic head has increased to 21.0% for macroscopically curative resection and 30.6% for histologically curative resection.

In this paper, 18 patients who survived for > 3 years are introduced and the state of histological progression of the 18 patients and 41 who died of cancer after < 3 years are compared. The results in our patients with carcinoma of the head of the pancreas suggest the following conditions of long-term survival: (1) tumor diameter $\leq$ 3 cm, (2) either absence of lymph node metastasis or metastasis to the n1 group, (3) s0, and (4) either rp0 or rpe with ew (-). At present, since the rp (+) rate is more than 70%, resection of the pancreas including the retropancreatic fusion fascia by our TRA is indispensable, and active introduction of combined resection of the superior mesenteric artery and vein may further improve the results of resection for pancreatic cancer.

KEY WORDS

Carcinoma of the head of the pancreas, extended dissection by TRA, histological

Abbreviations

tub1, 2, types of tubular adenocarcinoma; pap, papillary adenocarcinoma; un, undifferenciated carcinoma; sq, squamous cell 1 carcinoma; ac, acinar cell carcinoma;stage I ~IV, comprehensive stage; ts 1~4, tumor size; n 0~4, groups of lymph node metastasis; s 0~3, degrees of invasion of the anterior pancreatic capsule; rp 0~3, degrees of retropancreatic invasion; rpe, exposed retropancreatic invasion; ew 0~3, degrees of cancer invasion to the dissected peripancreatic tissue; stage I ~IV, comprehensive stage; INF $\alpha \sim \gamma$, growth patterns of tumors infiltrating the surrounding tissue; TRA, translateral retroperitoneal approach.

Introduction

We gradually extended the surgical dissection area for cancer after 1973, and developed pancreatectomy with extended dissection by a translateral retroperitoneal approach (TRA)[1] in 1977 in order to improve not only the resection rate but also prognosis. As a result, 18 patients survived for $\geq$ 3 years up to present, and the 5-year survival rate for carcinoma of the pancreatic head has increased to 21.0% for macroscopically curative resection and 30.6% for histologically curative resection.

Therefore, we evaluated the 18 patients with carcinoma of the head of the pancreas who survived for $\geq$ 3 years, and the conditions of long-term survival in terms of the state of histopathological progression.

I. Subjects and methods

Between 1974 and 1999, we performed macroscopically curative resection of carcinoma of the head of

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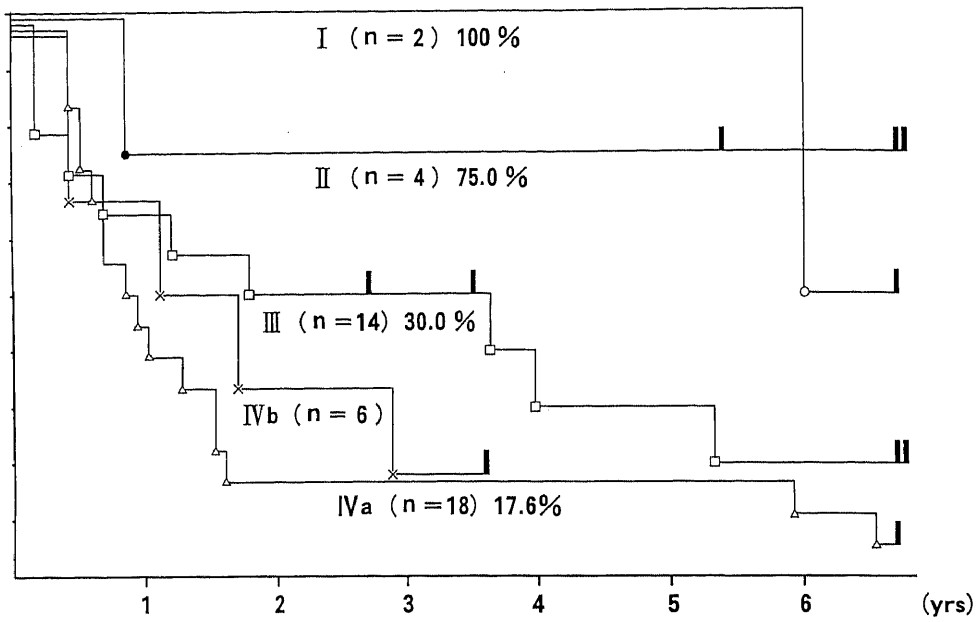

Fig. 1. Cumulative survival rate of carcinoma of the head of the pancreas

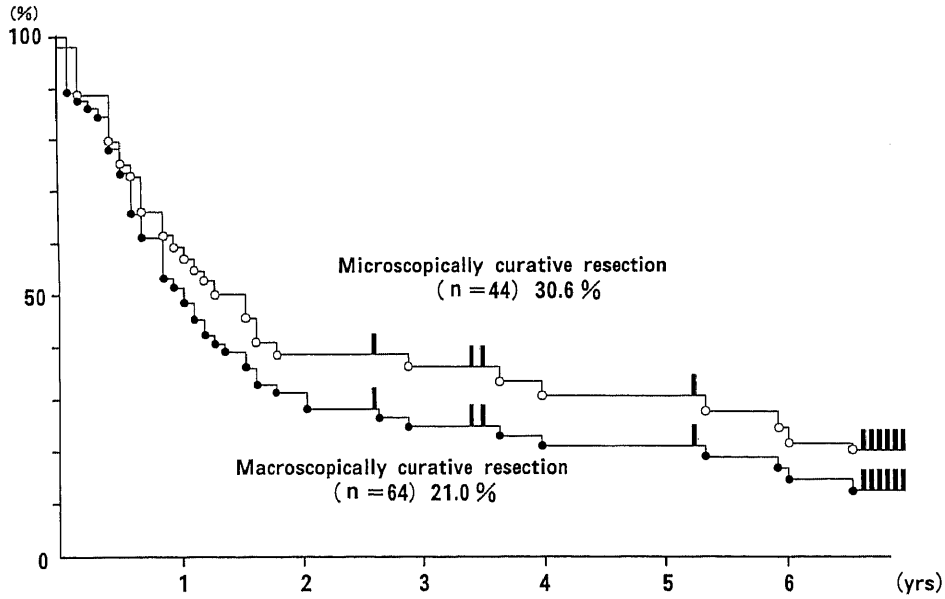

Fig. 2. Survival rates according to comprehensive stage

the pancreas in 64 patients, of whom 18 who survived for $\geq$ 3 years and 41 in whom death from cancer after < 3 years was confirmed were entered into this study. 5 patients who died during the opevation weve excluded from the study.

Dissection to the 1st group lymph nodes was regarded as standard dissection, complete dissection of the superior mesenteric plexus in addition to dissection to the 2nd/3rd group lymph nodes and retroperitoneal dissection as extended dissection, and dissection of the right 1/2 portion of this plexus or circumferential dissection of this plexus leaving a thin layer as quasi-extended dissection.

For histopathological examination, surgical specimens were fixed in formalin, cut into 3-5 mm sections (mean, 55 sections), embedded in paraffin, stained with hematoxylin and eosin (HE) and elastica von Gieson (EVG), and examined. The tumor

Table 1. Survival of more than 3 years in carcinoma of the head of the pancreas

		Histology	stage	ts	n	s	rp	ne	plx	ew	Prognosis
1	60♂	tub_1	IVb	ts_2	n_2	s_1	rp_2	ne_2	plx_1	ew_1	3y died (recurrence)
2	64♂	tub_2	IVb	ts_2	n_2	s_0	rp_2	ne_3	plx_1	ew_0	3y died (recurrence)
3	58♀	tub_1	II	ts_2	n_0	s_0	rp_0	ne_1	plx_0	ew_0	3y alive
4	54♂	tub_1	III	ts_2	n_1	s_0	rp_1	ne_2	plx_1	ew_0	3y8m died (recurrence)
5	45♂	tub_1	II	ts_3	n_0	s_0	rp_0	ne_2	plx_0	ew_0	4y alive
6	54♀	tub_2	IVa	ts_2	n_1	s_1	rp_2	ne_1	plx_0	ew_0	4y alive
7	72♀	pap	III	ts_2	n_0	s_1	rp_0	ne_1	plx_0	ew_0	4y4m alive
8	54♀	tub_2	I	ts_1a	n_0	s_0	rp_0	ne_1	plx_0	ew_0	5y alive
9	74♀	tub_2	III	ts_2	n_0	s_0	rp_1	ne_2	plx_1	ew_1	5y4m died (no recurrence)
10	58♂	pap	IVa	ts_2	n_1	s_0	rp_2	ne_0	plx_0	ew_0	6y died (recurrence)
11	80♂	pap	I	ts_1a	n_0	s_0	rp_0	ne_0	plx_0	ew_0	6y died (no recurrence)
12	69♀	tub_2	III	ts_2	n_1	s_0	rp_1	ne_1	plx_0	ew_0	6y alive
13	74♂	tub_2	IVa	ts_3	n_0	s_0	rp_2	ne_1	plx_0	ew_1	6y9m died (no recurrence)
14	33♂	un	IVa	ts_3	n_0	s_0	rp_2	ne_0	plx_0	ew_0	12y alive
15	53♀	pap	II	ts_1b	n_0	s_0	rp_0	ne_0	plx_0	ew_0	14y alive
16	59♂	tub_1	III	ts_2	n_0	s_0	rp_0	ne_1	plx_0	ew_0	15y alive
17	45♀	sq	III	ts_2	n_1	s_0	rp_0	ne_0	plx_0	ew_0	15y alive
18	68♀	ana	II	ts_1b	n_0	s_0	rp_0	ne_1	plx_0	ew_0	20y alive

diameter was histologically determined and expressed in terms of "ts". In "ts_2" in the General Rules for the Study of Pancreatic Cancer[2], 3.0 cm was used as the dividing point for discussion from our experience. For were followed other marks and classification of cancer spread. These Rules were followed for Rules[2].

II. Results

1. Outline

Of the 64 patients, 5 died due to the operation. Including these patients, the 5-year survival rate was 21.0% in 64 patients who underwent macroscopically curative resection and 30.6% in 44 patients who underwent histologically curative resection (Fig. 1).

In the patients who underwent histologically curative resection, the 5-year survival rate according to the stage was 100% for stage I, 75.0% for stage II, 30.0% for stage III, 17.6% for stage IVa, and 0% for stage IVb (Fig. 2).

2. Histopathological examination in patients who survived for ≥ 3 years

The profiles of the 18 patients who survived for ≥ 3 years are shown in Table 1. The age at the time of the first visit to our hospital was 33-74 years (mean, 56.6 years). There were 9 males and 9 females. Three patients were unicteric on admission. Extended pancreatoduodenectomy was performed in 12 patients, and quasi-extended operation in 4. According to the histological stage, stage I was observed in 2 patients, stage II in 4, stage III in 6, stage IVa in 4, and stage IVb in 2. The stage determinant factor was the tumor diameter in most patients, and lymph node metastasis or retropancreatic

Table 2. Comprehension of histological spreads between long and short survivals

	Survival more than 3 y (n=18)	Survival less than 3 y (n=41)
Tumor size (ts)		
• ts_1	4 (22.2%)	1 (2.4%)
• ts_2	5 (27.8%)	9 (22.0%)
• ts_3	4 (22.2%)	15 (36.6%)
• ts_4	5 (27.8%)	16 (16.7%)
Lymph node metastasis (n)		
• n_0	11 (61.1%)	7 (17.1%)
• n_1	5 (27.8%)	26 (63.4%)
• n_2	2 (11.1%)	8 (19.5%)
Invasion of the anterior pancreatic capsule (s)		
• s_0	15 (83.3%)	29 (70.7%)
• s_1	3 (16.7%)	2 (4.9%)
• s_2	0	10 (24.4%)
Reropancreatic invasion (rp)		
• rp_0	9 (50.0%)	2 (4.9%)
• rp_1	3 (16.7%)	7 (17.1%)
• rp_2	6 (33.3%)	32 (78.0%)
Dissected peripancreatic tissue (ew)		
• ew_0	15 (83.3%)	12 (29.3%)
• ew_1	3 (16.7%)	10 (24.4%)
• ew_2	0	19 (46.3%)
Comprehensive stage (stage)		
stage I	2 (11.1%)	0
II	4 (22.2%)	1 (2.4%)
III	6 (33.3%)	11 (26.8%)
IVa	4 (22.2%)	25 (61.0%)
IVb	2 (11.1%)	4 (9.8%)
Histological curative resection	18 (100%)	22 (53.6%)

tissue infiltration in some patients. Histologically, s_0 was found in most patients and s_1 in 2 patients. Lymph node metastasis was absent or when present, was limited to the n_1 group in most patients, and n_2 metastasis was observed in 2 patients. No patient showed macroscopic cancer infiltration to retropancreatic tissue. Histologically, rp_1 or rp_2 was noted in 9 (50.0%) of the 18 patients. However, after through dissection of retropancreatic tissue, ew (-) was achieved, and as a result, histologically curative resection was performed in all patients, of whom 2 showed carcinoma cells within 5 mm of the cut margin. According to the histological type, in 11 patients with tubular adenocarcinoma, though the tumor diameter was small ($\leq$ 3 cm in all patients excluding 1), the tumor was frequently the scirrhous type and INFγ. In 1 patient with papillary adenocarcinoma, 1 with squamous cell carcinoma, and 1 with undifferentiated carcinoma, the tumor diameter was $\geq$ 3.1 cm, and the tumor was often the medullary type and

INF α.

3. Comparison of histopathological progression between the group who survived for ≥ 3 years and the group who died of cancer after < 3 years

Table 2 shows the state of histopathological progression in 18 patients who survived for ≥ 3 years and 41 who died of cancer after < 3 years.

1) Tumor diameter (ts) and histological type

In the group who survived for ≥ 3 years, ts_1 was observed in 4 patients, ts_2 in 5, ts_3 in 4, and ts_4 in 4; the tumor diameter was ≤ 3 cm in 9 (50%) of the 18 patients. According to the histological type, 8 of the 9 patients with a tumor diameter of ≥ 3 cm had tubular adenocarcinoma. Of the 9 patients with a tumor diameter of ≥ 3.1 cm, 1 each had papillary adenocarcinoma, squamous cell carcinoma, undifferentiated carcinoma, and tubular adenocarcinoma.

In the group who died after < 3 years, ts_1 was observed in 1 patient, ts_2 in 9, ts_3 in 15, and ts_4 in 16; the tumor diameter was ≥ 3.1 cm in 90.2%. The histological type was tubular adenocarcinoma in most patients, but adenosquamous carcinoma was observed in 1.

2) Lymph node metastasis (n)

In the group who survived for ≥ 3 years, n_0 was observed in 11 patients (61.1%), n_1 in 5 (27.8%), and n_2 in 2 (11.1%); lymph node metastasis was absent or limited to the n_1 group in all patients excluding 1. In the group who died of cancer after < 3 years, n_0 was found in 7 patients (17.1%), n_1 in 26 (63.4%), and n_2 in 8 (19.5%); metastasis to the n1 group or more was observed in most patients.

3) Infiltration to the anterior capsule of the pancreas (s)

In the group who survived for ≥ 3 years, s_1 was observed in 3 patients but s_0 in the others. In the group who died of cancer after < 3 years, s_0 was noted in 29 patients (70.7%) and se in 12 (29.3%); the incidence of se was high. None of the patients with se survived for ≥ 2 years.

4) Infiltration to the retropancreatic tissue (rp) and residual cancer on the peripancreatic dissection surface (ew)

In the group who survived for ≥ 3 years, though rpe was found in 9 patients (50%), the ew factor was negative in all patients. In the group who died of cancer after < 3 years, rpe was observed in 95.1% and ew (+) in 46.3%. In about 50% of the patients who underwent macroscopically curative resection, histologically non-curative resection was performed.

5) Histological progression

In the group who survived for ≥ 3 years, stage I was observed in 2 patients, stage II in 4 (22.2%), stage III in 6 (33.3%), stage IVa in 4, and stage IVb in 2. Early stages were rarely noted even in the long-term survivors. In the group who died of cancer after < 3 years, stage I was not observed, but stage IV was observed in 29 patients (70.8%).

Ⅲ. Discussion

The treatment results for pancreatic cancer are much poorer than those for cancer in other gastrointestinal organs. To improve the treatment results for pancreatic cancer, great efforts have been made to detect early stage cancer that allows curative resection by tumor marker combination assay or various diagnostic imaging techniques[3]. Mainly in patients with advanced pancreatic cancer, extended operation that aims at radical treatment by extensive lymph node dissection, resection of the portal vein and adjacent organs, and total pancreatectomy has been performed[4-7]. We also gradually extended the dissection area for pancreatic cancer from 1973 and developed pancreatectomy with extended dissection by TRA in 1977 to improve not only the resection rate but also prognosis. As a result, good results have been gradually obtained in recent years, and there have been 18 patients with carcinoma of the head of the pancreas who survived for ≥ 3 years.

In all the 18 patients who survived for ≥ 3 years, histologically curative resection was performed. Though 9 (50.0%) of the 18 patients showed rpe, no cancer infiltration was observed on the peripancreatic dissection surface, and histologically curative resection was achieved. This may be because of extended surgery that places importance in extensive retrope-

ritoneal dissection and resection of the pancreatic head plexus. If these patients had undergone the standard operation, they could not have survived for a long period due to residual cancer on the peripancreatic dissection surface. In the group who died of cancer after < 3 years, the histologically curative resection rate was only 53.6%, and the determinant factor for histologically non-curative resection was residual cancer on the dissection surface of the retropancreatic tissue including the pancreatic head plexus in most patients. Therefore, in another evaluation of 33 patients with carcinoma of the head of the pancreas who underwent extensive retroperitoneal dissection, the ew (+) rate according to the tumor diameter was seen. The ew (+) rate acutely increased with a tumor diameter of ≥ 3.1 cm. When the tumor diameter exceeded 3 cm, histologically non-curative resection was performed in more than 50% of the patients who underwent macroscopically curative resection. The tumor diameter may be the main factor preventing improvement in surgical results in pancreatic cancer.

Recently, attention has been directed to mucus-producing carcinoma as pancreatic carcinoma with a good prognosis. Mucus-producing carcinoma, mainly originating in the main pancreatic duct, is papillary adenocarcinoma that actively produces mucus and shows extension in the pancreatic duct and expansive growth. Mucus-producing carcinoma has been reported to have a definitely better prognosis than solid carcinoma that is markedly infiltrative8). Of our patients, 1 with papillary adenocarcinoma survived for 5 years and 5 months. In addition, 1 with squamous cell carcinoma and 1 with undifferentiated carcinoma survived for ≥ 3 years. In these patients, though the tumor diameter was ≥ 3.1 cm, the tumor was of the medullary type and showed expansive growth and was limited to the pancreas without metastasis to other organs. These findings were in good contrast with those in the patients with tubular adenocarcinoma in whom the incidence of rpe markedly increased with a tumor diameter of ≥ 3 cm.

Though only carcinoma of the head of the pancreas was evaluated in this study, we have also performed the above-described surgical technique for carcinoma of the tail of the pancreas and observed survival for ≥ 3 years in 3 patients[9]. Out of a total of 10 patients.

The results in our patients with carcinoma of the head of the pancreas suggest the following conditions of long-term survival: (1) tumor diameter ≤ 3 cm, (2) either absence of lymph node metastasis or metastasis to the n1 group, (3) so, and (4) either rpo or rpe with ew (-). However, depending on the histological type, even when the tumor diameter is > 3 cm, adequate long-term survival can be expected if the other 3 conditions ware fulfilled in some patients.

In recent years, the limitations of extended operation for pancreatic cancer have been often reported[10),11)]. From our experience, efforts to achieve histologically curative resection appear to be inadequate. After our extended operation, long-term survival could not be also achieved in patients with metastasis to the superior mesenteric lymph nodes or para-aortic lymph nodes, but more rp (+) patients survived for a long period in our study than in previous studies. At present, since the rp (+) rate is more than 70%, resection of the pancreas including the retropancreatic fusion fascia by our TRA is indispensable, and active introduction of combined resection of the superior mesenteric artery and vein may further improve the results of resection for pancreatic cancer.

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膵頭部癌長期生存例の臨床病理学的検討

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要　　旨

著者らは，1973年以降癌に対し手術郭清範囲を次第に拡大し，その結果，３年以上生存例が18例得られ，膵頭部癌の５年生存率は肉眼的治癒切除で21.0%，組織学的治癒切除で30.6%となった。そこで，本稿では過去25年間に経験した膵頭部癌肉眼的治癒切除例64例のうち，３年以上生存し得た18例および３年未満に死亡が確認された41例を対象とし，病理組織学的進展状況からみた膵頭部癌長期生存の条件について考察を加え検討した。それをみると，現時点での膵頭部癌長期生存の条件としては，①腫瘍径が３cm以下であること，②リンパ節転移はないか，あってもn$_1$群までであること，③s0であること，④rp0またはrpeであってもew（－）であること，の４条件が必須である。即ち，rp陽性例が70%を超える現状では，著者が開発したtranslateral retroperitoneal approachによるretropancreatic fusion fasciaを含めた膵切除は必須のもので，rp陽性例に対する上腸間膜動静脈合併切除の積極的な導入によって膵癌の切除成績は一層向上するものと考えられた。