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Analysis of long-term survivors after surgical resection for invasive pancreatic cancer

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Abstract

Pancreatic cancer remains a lethal disease. Although there are many reports on the survival rates of pancreatic cancer patients after surgical resection, the clinicopathological characteristics that influence long-term survival over 5 years remain controversial. Here, we clarify the favourable prognostic factors for long-term survival. One hundred and eighty-two patients with pancreatic cancer underwent surgical resections from 1981 to 1997 in our department. Among them, eight patients survived for at least 5 years after the surgery. The clinicopathological characteristics of the eight long-term survivors who underwent radical resections were studied retrospectively. R0 surgical resections, including five combined with portal vein resections (62.5%), were achieved in these eight patients. Negative invasions of the major regional artery (seven of eight, 87.5%) and to the extrapancreatic nerve plexus (seven of eight, 87.5%), and N0 or N1 lymph node metastasis (7 of 8, 87.5%) were detected as clinicopathological features of long-term survivors in our study. No exposure of carcinoma at the dissected surface and cut end (seven of eight, 87.5%) was characteristically confirmed by pathology. Portal vein invasion was seen in three of the eight patients (37.5%). For long-term survival in cases of pancreatic cancer, complete R0 resections should be performed and negative invasions in the major regional arteries and to the extrapancreatic plexus of the nerve were necessary. No invasion to the portal vein was not necessarily required if R0 was achieved by combined resection of the portal vein.

Key Words: *Pancreatic cancer, long-term survival, clinicopathological factors*

Introduction

Today, pancreatic cancer remains a highly lethal disease, and not many patients are able to live for more than 5 years after pancreatic resection. Recently, new technologies (computed tomography, ultrasonography, digital subtraction angiography, etc.) have enabled us to detect the degree of tumour invasions more accurately and to determine operability more easily [1–3]. In addition, recent improvements in surgical technologies have enabled us to better perform extended radical resections in selected cases. However, there are some scientists who maintain that the surgery is not beneficial to patients in the advanced stage of disease [4]. In our department, we have successfully and safely performed pancreatectomies combined with portal vein resections using antithrombogenic catheters for bypasses of the portal veins [5,6]. Apparent superior mesenteric arterial invasions and/or complete encasements of the portal vein were not detected during resections in the portal veins [7].

Many authors have reported prognostic factors that affect the long-term survival of pancreatic cancer patients based on macroscopic and histological findings and surgical factors [8–30]. However, most of these authors regarded 3-year survivors as long-term survivors because the prognosis of pancreatic cancer is usually very poor. In actuality, many patients who live for over 3 years after surgery still have recurrent disease.

The aim of this study was to clarify the favourable prognostic factors for long-term survival after curative resection by studying the clinical data of several patients who have survived after surgery for over 5 years, and investigating the criteria for patient selection for radical surgery. The clinicopathological factors of long-term survivors were thoroughly evaluated, and the important factors contributing to long-term survival were also investigated.

Methods

Patients

One hundred and eighty-two patients with pancreatic cancer underwent surgical resections in our department from 1981 to 1997. All the patients' medical records were retrospectively reviewed. After excluding

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the patients with intraductal papillary mucinous neoplasms (IPMNs), the long-term survivors who lived for >5 years after the surgery were studied on the bases of surgical factors and clinicopathological findings. These were used to identify the factors that seemed to contribute to their long-term survival.

Surgical factors

Following the general rules of the Japan Pancreas Society [30], the tumour location; tumour size (TS); invasion to adjacent structures, e.g. common bile duct (CH); duodenum (DU); pancreatic serosa (S); retroperitoneum (RP); portal vein (PV); major regional artery, including the common hepatic artery, the superior mesenteric artery, the splenic artery, and the coeliac artery (A); and extrapancreatic nerve plexus (PL) were all examined. Tumour nodal metastasis (TNM) staging is determined by operative findings. The T factor is defined as follows: T1, tumour size 2 cm and the tumour is limited to the pancreas; T2, tumour size >2 cm and the tumour is limited to the pancreas; T3, tumour is extended into CH, DU, S, or RP; and T4, the tumour is extended into PV, A, PL, or other organs. As for the severity of lymph node metastasis, N0 indicates no nodal metastasis, N1 indicates positive metastasis in the region of the tumour, N2 indicates positive metastasis in an extensive region around the N1 region, and the positive N3 node means systemic disease and is equal to M1. The degree of radicality, including the combined resection of adjacent structures, was also studied.

Pathological factors

Microscopic findings, such as the histological grade, invasion of the lymphatic duct (LY) and vessels (V), and perineural invasion (NE) were studied. In order to compare them with the operative findings, we also pathologically examined the nodal status and local invasions of adjacent structures, followed by the bile duct (CH), duodenum (DU), pancreatic serosa (S), retroperitoneum (RP), portal vein (PV), major regional artery (A), and plexus of the nerve (PL). These were studied together with the exposure of carcinoma on the pancreatic cut end margin (PCM), the cut edge of the bile duct (BCM), and the dissected peripancreatic tissue margin (DPM). The term LY0 is used to indicate that no invasion was microscopically detected in the lymphatic duct around the tumour; LY1 indicates mild invasion, LY2 indicates moderate invasion, and LY3 indicates severe invasion. The factors V and NE are also classified by the degree of invasion from V0 to V3 and from NE0 to NE3, respectively, like the factor LY. Final TNM staging and curability were determined by all of the pathological findings following the general rules for the study of pancreatic cancer, which were set by the Japan Pancreas Society [30].

Table I. Characteristics of patients.

Patient no.	Age/ sex	Survival period (years)	Outcome	Tumour site	Adjuvant therapy	Operation
1	64/M	9.5	Dead	Head	None	PD
2	68/F	8	Dead	Body	IR+FU	PD
3	46/M	5	Dead	Head, body	None	PD
4	62/M	8.9	Dead	Head	FU	PD
5	54/M	5	Dead	Head	IR+FU	PPPD
6	62/M	5.3	Alive	Head	IR+FU	PPPD
7	51/F	5	Alive	Head	None	PPPD
8	60/M	5	Alive	Head	IR+FU	PD

M, male; F, female; None, adjuvant therapy not given; PD, pancreatoduodenectomy; PPPD, pylorus-preserving pancreatoduodenectomy; IR, irradiation; FU, 5-fluorouracil administration.

Adjuvant therapy

In this study, we confirmed whether or not some adjuvant therapies, such as intraoperative radiotherapy (IORT) of 30 Gy using a linear accelerator (Linac) and/or intraportal administration of 5-fluorouracil (5-FU), were used.

Results

Twelve of the 182 pancreatic cancer patients (6.6%) survived for >5 years after surgical resection. There were 4 IPMN patients among the 12, and they were excluded from our study. The characteristics of the remaining eight patients with invasive pancreatic cancer are shown in Table I.

There were six males and two females among the eight patients, and their mean age was 58.3 years at the time of operation (range 46–68); their mean survival period was 6.4 years after the surgery (range 5–9.5). Three of the eight patients survived without recurrence into the year 2002, three died from the recurrent disease, and two succumbed to another disease. Tumour sites were located on the pancreatic head in seven cases, and in the body in one case. Among the eight patients, one underwent a distal pancreatectomy, four received pancreatoduodenectomies (PD), and three had pylorus-preserving pancreatoduodenectomies (PPPD). Five pancreatic head cancer patients underwent combined resections of the PV, which were successfully performed without residual cancer. All eight patients underwent regional lymph node dissections that included the para-aortic region.

We performed radical resections including wide dissections of the regional lymph nodes, retroperitoneal tissues and extrapancreatic nerve plexuses for those with advanced pancreatic cancer. All eight patients macroscopically underwent *en bloc* resections without cancer exposure at the sites of the cut ends and dissected edges. The pancreatic cut end margin (PCM factor), bile duct cut end margin (BCM factor), and dissected peripancreatic tissue margin (DPM factor)

Table II. Surgical factors.

Patient no.	TS	CH	DU	S	RP	PV	A	PL	T	N	JPS stage	UICC stage	PCM BCM DPM	Combined resection
1	2	−	−	−	+	−	−	−	3	1	III	III	−	−
2	2	−	−	+	−	−	−	−	3	0	III	II	−	−
3	3	+	+	+	+	+	−	−	4	2	IVb	1V A	−	Portal vein
4	2	+	+	+	+	+	−	−	4	0	IVa	IV A	−	Portal vein
5	2	+	−	−	+	+	+	+	4	0	IVa	IV A	−	Portal vein
6	1	+	−	−	−	+	−	−	3	0	III	II	−	Portal vein
7	1	+	−	−	−	−	−	−	3	0	III	II	−	−
8	3	−	+	+	+	+	−	−	4	1	IVa	IV A	−	Portal vein

CH, choleduct; DU, duodenum; S, serosa; RP, retroperitoneum; PV, portal vein; A, major regional artery; PL, peripancreatic nerve plexus; PCM, pancreatic cut end margin; BCM, bile duct end margin; DPM, dissected peripancreatic tissue margin. The JPS stage is the TNM stage determined by the Japan Pancreas Society. The UICC stage is the TNM stage determined by UICC.

were found to be macroscopically negative for all eight patients and were microscopically proven as cancer-negative for seven of eight patients.

The operative findings are listed in Table II. The tumour size (TS) factors are classified into four degrees. TS1 means a tumour size within 2.0 cm, TS2 means that it is between 2.0 cm and 4.0 cm, TS3 means that it is between 4.0 cm and 6.0 cm, and TS4 means that it is larger than 6.0 cm. These eight patients were macroscopically classified as follows: TS1, 25%; TS2, 50%; TS3, 25%; and TS4, 0%.

Five patients (62.5%) were observed with invasion to the intrapancreatic bile duct (positive CH factor), three (37.5%) with invasion to the duodenum (positive DU factor), four (50%) with invasion to the pancreatic serosa (positive S factor), four (50%) with invasion to the retroperitoneum (positive RP factor), five (62.5%) with invasion to the portal vein (positive PV factor), and one (12.5%) with invasion to a major regional artery at the splenic artery, as well as the extra-pancreatic nerve plexus (positive PL factor). The severity of lymph node metastases in the eight cases was: N0, five cases (62.5%); N1, two cases (25%); and N2, one case (12.5%).

The surgical T factors of TNM classification were found as follows: T1, no cases (0%); T2, no cases (0%); T3, four cases (50%); and T4, four cases (50%). The surgical stages of the eight patients were: stage I, no cases (0%); II, no cases (0%); III, four cases (50%); and IV, four cases (50%). All five patients with suspected PV invasion underwent combined resections of the PV. PCM, BCM, and DPM were concluded to be surgically negative in all eight cases (100%).

The pathological findings are shown in Table III. Invasive cancer was detected in all eight cases (100%). The histological types of the tumours were as follows: well differentiated tubular carcinoma was detected in one case (12.5%), moderately differentiated tubular adenocarcinoma in six cases (75%), and mucinous carcinoma in one case (12.5%). The pathological factors of the DU, A, PL, BCM and PCM were consistent with the macroscopic findings. The CH, PV, S and RP factors were not consistent with the surgical diagnoses in one case (no. 7), two cases (nos 4 and. 8), two cases (nos 2 and 8) and two cases (nos 1 and 8), respectively. The DPM was also not consistent with the macroscopic diagnosis in one case (no. 5). The factors of LY and NE were confirmed as follows: LY0,

Table III. Pathological findings.

Patient no.	Histology	CH	DU	S	RP	PV	A	PL	pT	pN	JPS f-stage	UICC f-stage	LY	V	NE	PCM BCM DCM	pR
1	Muc	−	−	−	+	−	−	−	3	1	III	III	2	0	0	−	0
2	Tub mod	−	−	−	−	−	−	−	1	0	I	I	1	1	2	−	0
3	Tub mod	+	+	+	+	+	−	−	4	2	IVb	IV A	3	1	2	−	0
4	Tub mod	+	+	+	+	+	−	−	4	0	IVa	IV A	1	1	1	−	0
5	Tub mod	+	−	−	+	+	+	+	4	0	IVa	IV A	1	0	3	+	1
6	Tub mod	+	−	−	−	−	−	−	3	0	III	II	1	0	1	−	0
7	Tub well	−	−	−	−	−	−	−	1	0	I	I	0	0	3	−	0
8	Tub mod	−	+	−	−	−	−	−	3	1	III	III	1	1	1	−	0

Muc, mucinous carcinoma; Tub mod, tubular adenocarcinoma, moderately differentiated type; Tub well, tubular adenocarcinoma, well differentiated type; CH, choleduct; DU, duodenum; S, serosa; RP, retroperitoneum; PV, portal vein; A, major regional artery; PL, peri-pancreatic nerve plexus; PCM, pancreatic cut end margin; BCM, bile duct end margin; DPM, dissected peripancreatic tissue margin; R, residual tumour; P, pathological diagnosis; F, final diagnosis. The JPS f-stage is the final confirmed TNM stage determined by the Japan Pancreas Society. The UICC f-stage is the TNM stage determined by UICC.

12.5%; LY1, 62.5%; LY2, 12.5%; LY3, 12.5%; NE0 12.5%; NE1, 37.5%; NE2, 25%; and NE3, 25%. Regarding the V factor, all cases were distinctively categorized within V0 (50%) and V1 (50%), whereas V2 and V3 were both 0%. The final confirmed T factors were: T1 in two cases (25%), T2 in no cases (0%), T3 in three cases (37.5%), and T4 in three cases (37.5%). Final staging confirmed by the pathological findings was as follows: stage I, two cases (25%); II, no cases (0%); III, three cases (37.5%); and IV, three cases (37.5%).

Adjuvant therapy of intraportal 5-FU infusion was given in one case (no. 4). Combined therapies consisting of intraoperative irradiation using Linac and intraportal 5-FU infusion chemotherapy were performed in the four cases (nos 2, 5, 6 and 8) who underwent radical resection. R0 was achieved in all five cases.

Discussion

Many authors have used the statistical analysis method to discuss the prognostic factors that influenced long-term survival after surgical resection for pancreatic cancer [8–30]. They presented us with several beneficial factors, as follows: radical resection *en bloc* without residual cancer [12,16], a smaller tumour size [13,17,25], an operator or institutional factor [19], a histological differentiation [25,26], no frontal invasion of the pancreatic capsule, no retroperitoneal invasion [27], negative resection margins [27–29], a negative lymph node, a positive lymph node within the limited nodal status [8–10,17,18,22–25,27,30], negative invasion of blood vessels [24], negative perineural invasion [8,11,22], and the tumour location [12,17]. However, most authors regarded patients who survived for >3 years as long-term survivors, and only a few studied and evaluated these prognostic factors in patients who survived for >5 years.

Based on our study, four of these factors were considered important for long-term survival. They are: 1) resection without residual cancer; 2) no lymph node metastasis, or if present, limited within the N1 level; 3) no invasion of major regional arteries, including the superior mesenteric artery, common hepatic artery, splenic artery, and coeliac artery; and 4) no invasion of the extrapancreatic nerve plexus. As for the portal vein, Nakao et al. reported that if it is invaded, and if R0 resection is completed by portal vein resection, the survival rate is still more favourable than in the case of negative portal invasion with positive margin invasion [28]. In the eight patients that we studied, portal invasion was histologically confirmed in three (37.5%), and the percentage was surprisingly high.

There is no validity in the argument that the true curative resection is the R0 resection, and that R0 resection is identified as a valuable factor for long-term survival [28]. To achieve R0 resection, we usually perform a radical resection with the dissection of the regional lymph node and the retropancreatic tissue, including the extrapancreatic nerve plexus for invasive pancreatic cancer. For intraoperative diagnosis of the portal vein and PL invasion, intraportal endovascular ultrasonography (IPEUS) is helpful [2,32]. Portal vein resection is important in obtaining a carcinoma-free surgical margin in pancreatic cancer surgery [7]. If such a surgical margin cannot be obtained by extensive surgery, there is no indication for surgical resection in patients with pancreatic carcinoma.

Authors of some reports have claimed that stage III pancreatic cancer defined by the UICC rules should not be resected if neoadjuvant therapy is not effective [4]. However, we do not agree with this opinion, because in our study, five of the eight cases were classified as stages III or IV according to the UICC rules. The difference of these two opinions may be because of the difference in the extent of resection that could be performed safely.

If the extent of lymph node dissection is insufficient, we may misdiagnose cancer invasion. Therefore, it is not easy to predict long-term survival by TNM staging alone. Furthermore, as demonstrated in this study, a diagnostic discrepancy between macroscopic and microscopic findings may occur, so it is important to investigate the resected specimen carefully to correctly determine the final staging and whether or not R0 resection has been achieved. As the advanced stage in TNM classification was seen in most of our eight long-term survivors, consideration of those surgical and pathological factors, as well as TNM staging, is necessary to understand the tumour characteristics and to predict the prognosis. In general, there are many local factors as regards how the cancer invades around the pancreas. From the surgical standpoint, A0, PL(–), and R0 (DPM, PCM, BCM) were important factors affecting long-term survival. Furthermore, it was suggested that portal vein invasion does not exclude operative indication. T3 and T4 of the TNM classification were identified in 100% of the eight patients on surgical findings and 75% on pathology.

In the inconsistency between surgical and pathological diagnoses, a discrepancy seen in the CH factor in one case (no. 7) might be because of the existence of pancreatitis around the tumour. In five of the eight patients who underwent portal vein resections, portal invasion was pathologically positive only in three cases (nos 3, 4 and 5). This may have been caused by misdiagnosis due to compression of the portal vein, possibly because of a large tumour or accompanying pancreatitis. IPEUS can accurately differentiate between compression and a subtle portal venous invasion and reduce this discrepancy [3]. However, portal vein resection was considered to be necessary to obtain cancer-free margins in those cases.

Some authors have explained the benefits of using adjuvant therapies, including chemotherapy and radiotherapy [18,34,35]. As already shown, we also consider radiotherapy to be an effective method to control the pain caused by the infiltration of carcinoma into the

extrapancreatic nerve plexus [36,37]. However, irradiation does not improve the prognosis. We employed intraoperative combined adjuvant therapies consisting of radiation and 5-FU chemotherapy in four of the eight patients. However, the true feasibility of adjuvant therapy for long-term survival was not clarified in this study. Protocols evaluating the efficacy of Gemcitabine (difluorodeoxycytidine; dFdC), a new chemotherapeutic agent for pancreatic cancer, are now underway in randomized controlled trials.

From this study, we conclude that in order to achieve a long-term survival goal, it is important to perform a complete R0 resection. When portal vein invasion is suspected without invasion to the major regional arteries and distant metastasis at the time of operation, a pancreatectomy with combined resection of the portal vein is to be performed to achieve a curative resection. Moreover, if PL(−), DPM, PCM and BCM(−) are microscopically confirmed in the resected specimen, a favourable outcome can be expected after the surgery.

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