

## Retrospective Study

# Long-term survival after resection of pancreatic cancer: A single-center retrospective analysis

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**METHODS:** From January 2000 to December 2011, 195 patients underwent pancreatic resection in our hospital. The prognostic factors after pancreatic resection were analyzed in all 195 patients. After excluding the censored cases within an observational period, the clinicopathological characteristics of 20 patients who survived  $\geq 5$  ( $n = 20$ ) and  $< 5$  ( $n = 76$ ) years were compared. For this comparison, we analyzed the patients who underwent surgery before June 2008 and were observed for more than 5 years. For statistical analyses, the log-rank test was used to compare the cumulative survival rates, and the  $\chi^2$  and Mann-Whitney tests were used to compare the two groups. The Cox-Hazard model was used for a multivariate analysis, and  $P$  values less than 0.05 were considered significant. A multivariate analysis was conducted on the factors that were significant in the univariate analysis.

**RESULTS:** The median survival for all patients was 27.1 months, and the 5-year actuarial survival rate was 34.5%. The median observational period was 595 d. With the univariate analysis, the UICC stage was significantly associated with survival time, and the CA19-9  $\leq 200$  U/mL, DUPAN-2  $\leq 180$  U/mL, tumor size  $\leq 20$  mm, R0 resection, absence of lymph node metastasis, absence of extrapancreatic neural invasion, and absence of portal invasion were favorable prognostic factors. The multivariate analysis showed that tumor size  $\leq 20$  mm (HR = 0.40; 95%CI: 0.17-0.83,  $P = 0.012$ ) and negative surgical margins (R0 resection) (HR = 0.48; 95%CI: 0.30-0.77,  $P = 0.003$ ) were independent favorable prognostic factors. Among the 96 patients, 20 patients survived for 5 years or more, and 76 patients died within 5 years after operation. Comparison of the 20 5-year survivors with the 76 non-survivors showed that lower concentrations of DUPAN-2 (79.5 vs 312.5 U/mL,  $P = 0.032$ ), tumor size  $\leq 20$  mm (35% vs 8%,  $P = 0.008$ ), R0 resection (95% vs 61%,  $P = 0.004$ ), and absence of lymph node

## Abstract

**AIM:** To retrospectively analyze factors affecting the long-term survival of patients with pancreatic cancer who underwent pancreatic resection.

metastases (60% *vs* 18%,  $P = 0.036$ ) were significantly associated with the 5-year survival.

**CONCLUSION:** Negative surgical margins and a tumor size  $\leq 20$  mm were independent favorable prognostic factors. Histologically curative resection and early tumor detection are important factors in achieving long-term survival.

**Key words:** Pancreatic cancer; Long-term survival; Long-term survivor; Prognostic factor; R0 resection

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**Core tip:** The prognosis of pancreatic cancer patients remains quite poor. In this study, however, the 5-year actuarial survival rate was much higher (34.5%) than normal. Histologically curative resection and early tumor detection were important factors in achieving long-term survival.

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## INTRODUCTION

Pancreatic cancer is the fourth leading cause of death among all types of cancer, accounting for 6% of men and 7% of women who died of cancer in the United States in 2010. The prognosis of patients with pancreatic cancer remains quite poor, with a 5-year survival rate of only 6%<sup>[1]</sup>. Surgery remains the only curative treatment for pancreatic cancer. Only 10%-20% of the patients with pancreatic cancer could be candidates for surgical resection in previous reports<sup>[2,3]</sup>. In 1984, the 5-year survival rate after surgery was only 3%. However, patient prognosis has been improving, and the 5-year survival rate after surgery has been approximately 11%-25% in the last decade<sup>[4-7]</sup>. This improvement may be attributable to the increased experience of surgeons performing pancreatic resection and possibly to the effects of adjuvant chemotherapy.

Several studies have reported prognostic factors after surgical resection of pancreatic cancer. The significant prognostic factors identified are tumor size, lymph node metastasis, surgical margin status, tumor markers, and adjuvant chemotherapy<sup>[5,8-10]</sup>. This study was designed to analyze the factors prognostic of survival in patients with pancreatic cancer and the characteristics of long-term survivors.

## MATERIALS AND METHODS

From January 2000 to December 2011, 195 patients with pancreatic cancer in our hospital underwent pancreatic resection, consisting of a standard operation without extended lymphadenectomy<sup>[11]</sup>. We first analyzed the prognostic factors after pancreatic resection for all 195 patients. We then assessed the clinicopathological characteristics of the 96 patients who underwent surgery on or before June 2008 and who were followed-up for  $> 5$  years. Of these 96 patients, 20 patients survived  $\geq 5$  years, and 76 patients died within 5 years. The clinicopathological characteristics of these two subgroups were analyzed. The analysis of extrapancreatic neural invasion and portal invasion followed the Japan Pancreas Society (JPS) classification<sup>[12]</sup>.

The protocol for the present study was approved by the Institutional Review Board of our hospital. The informed consents were waived because the study consisted of a historical cohort.

### Statistical analysis

The values are presented as the mean  $\pm$  SD, medians (interquartile range), or numbers and percentages. The log-rank test was used to compare the cumulative survival rates, and the  $\chi^2$  and Mann-Whitney tests were used to compare the two groups. The Cox-Hazard model was used for the multivariate analysis, and  $P$  values less than 0.05 were considered significant. A multivariate analysis was conducted using the factors that were significant in the univariate analysis. Cutoff values were determined using receiver operating characteristic curves, except that for carcinoembryonic antigen (CEA), which was determined to be the upper limit of normal. The normal ranges of tumor markers in our hospital are CEA  $\leq 5.0$  ng/mL, CA19-9  $\leq 37.0$  U/mL and DUPAN-2  $\leq 150$  U/mL. CEA and CA19-9 were measured by chemiluminescence enzyme immunoassay, and DUPAN-2 was by enzyme-linked immunosorbent assay.

## RESULTS

### Patient characteristics

The 195 patients consisted of 108 males and 87 females (mean age  $68 \pm 8.1$  years at the time of pancreatic resection) (Table 1). Median and interquartile range of tumor marker concentrations were carcinoembryonic antigen (CEA) 2.8 (1.7-4.8) ng/mL, carbohydrate antigen 19-9 (CA19-9) 143.5 (29.3-435.3) U/mL, and pancreatic cancer-associated antigen (DUPAN-2) 182 (31.0-739.3) U/mL. There were a few patients who didn't undergo examination of tumor marker, and their data of tumor markers were missing. Of the 195 patients, 145 (74%) had lymph node metastases, 108 (55%) had extrapancreatic neural invasion, and 63 (32%) had portal invasion.

**Table 1** Clinicopathological characteristics of all patients

Variables	Value ( <i>n</i> = 195)
Age, mean ± SD	67.6 ± 8.1
Gender	
Male	108
Female	87
Tumor marker, median (IQR)	
CEA (ng/mL)	2.8 (1.7-4.8)
CA19-9 (U/mL)	143.5 (29.3-435.3)
DUPAN-2 (U/mL)	182 (31.0-739.3)
Operative procedures, <i>n</i>	
Pancreaticoduodenectomy	123
Distal pancreatectomy	61
Total pancreatectomy	11
UICC T classification, <i>n</i>	
T1	10
T2	6
T3	168
T4	11
Surgical margin status, <i>n</i>	
R0	138
R1	50
R2	7
Lymph node metastasis, <i>n</i>	
Negative	50
Positive	145
Extrapancreatic neural invasion, <i>n</i>	
Positive	108
Negative	87
Portal invasion, <i>n</i>	
Positive	63
Negative	132
UICC stage, <i>n</i>	
I A	9
I B	1
II A	38
II B	110
III	9
IV	28
Adjuvant chemotherapy, <i>n</i>	
GEM	142
S1	6
GEM+S1 or others	2
None	45
Time to initiation of adjuvant chemotherapy (mean days)	54.9

CEA: Carcinoembryonic antigen; UICC: Union for international cancer control; GEM: Gemcitabine; IQR: Interquartile range.

The union for International Cancer Control (UICC) pathological stage<sup>[13]</sup> was I A in nine patients (4.6%); I B in one patient (0.5%); II A in 38 patients (19.5%); II B in 110 patients (56.4%); III in nine patients (4.6%); and IV in 28 patients (14.4%). Of the 195 patients, 123 patients (63%) underwent pancreaticoduodenectomy; 61 patients (31%) underwent distal pancreatectomy; and 11 patients (6%) underwent total pancreatectomy. The surgical margin status was negative (R0) in 138 patients (71%); microscopically positive (R1) in 50 patients (26%); and grossly positive (R2) in 7 patients (4%). One hundred fifty patients (77%) received postoperative chemotherapy for an average of 208 d. During chemotherapy, 142 patients received gemcitabine; six patients received tegafur-gimeracil-oteracil potassium (S1); and two patients

**Table 2** Univariate analysis of factors prognostic for survival in patients undergoing pancreatic resection for pancreatic cancer

Variables	<i>n</i>	MST (mo)	5-yr survival (%)	<i>P</i> value
Age				0.071
> 65	130	22.1	31.3	
≤ 65	65	47.3	40.5	
Gender				0.060
Male	108	17.5	31.6	
Female	87	23.9	38.6	
CEA (ng/mL)				0.082
> 5	42	18.5	33.1	
≤ 5	138	35.2	38.4	
CA19-9 (U/mL)				0.006 <sup>b</sup>
> 200	80	20.7	22.6	
≤ 200	104	47.4	47.2	
DUPAN-2 (U/mL)				0.003 <sup>b</sup>
> 180	69	24.2	22.7	
≤ 180	101	30.8	51.0	
Tumor size				< 0.001 <sup>b</sup>
> 20 mm	156	21.7	25.9	
≤ 20 mm	39	29.4	69.9	
Surgical margin status				< 0.001 <sup>b</sup>
R0	138	47.3	45.2	
R1-2	57	16.0	5.6	
Lymph node metastasis				< 0.001 <sup>b</sup>
Positive	145	21.8	26.4	
Negative	50	28.8	55.8	
Extrapancreatic neural invasion				0.00 <sup>b</sup>
Positive	108	22.0	23.9	
Negative	87	47.4	47.9	
Portal invasion				0.006 <sup>b</sup>
Positive	63	21.1	15.0	
Negative	132	35.4	42.7	
UICC Stage				< 0.001 <sup>b</sup>
I A	9	34.9	87.5	
I B	1	27.1	0	
II A	38	28.2	51.3	
II B	110	20.2	29.0	
III	9	16.3	0	
IV	28	10.4	14.4	
Adjuvant chemotherapy				0.301
Yes	150	21.1	40.5	
No	45	27.1	32.5	
Time to initiation of adjuvant chemotherapy				0.985
> 40 d	66	27.1	31.1	
≤ 40 d	84	30.8	34.0	

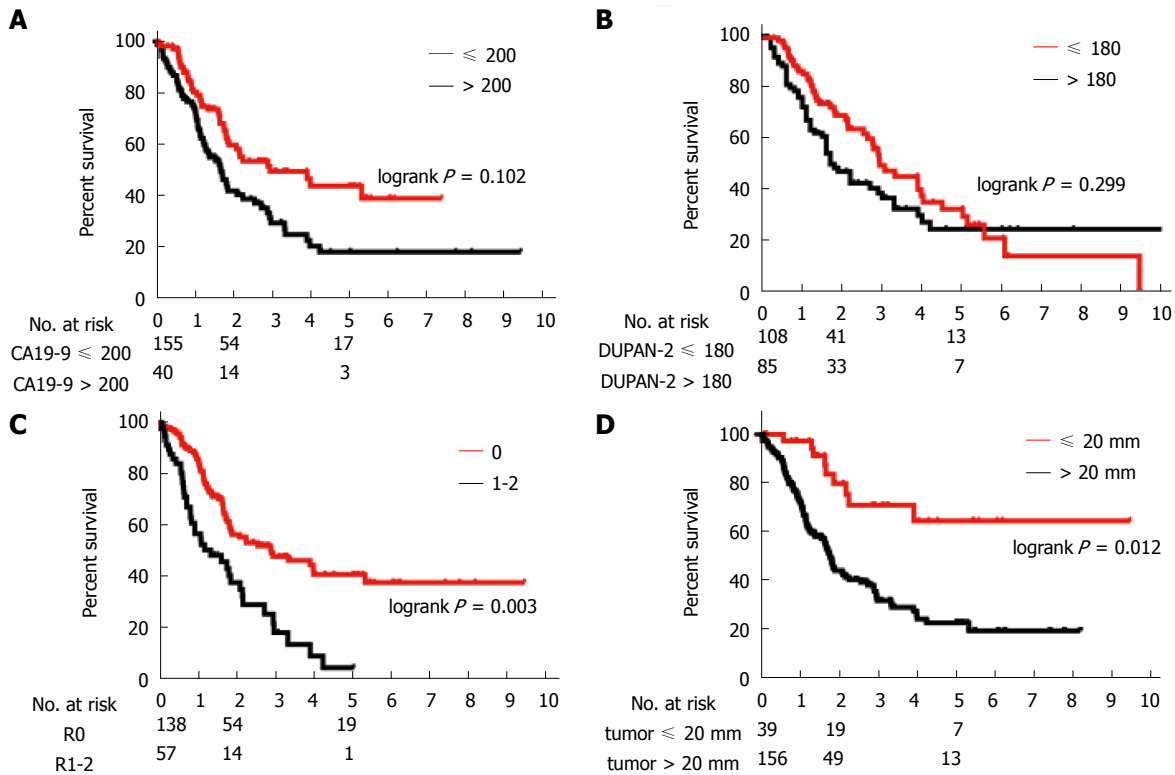
<sup>b</sup>*P* < 0.01 vs control. MST: Mean survival time.

received other regimens. The average time from operation to the initiation of adjuvant chemotherapy was 54.9 d. Adjuvant radiation therapy was not used for any patient.

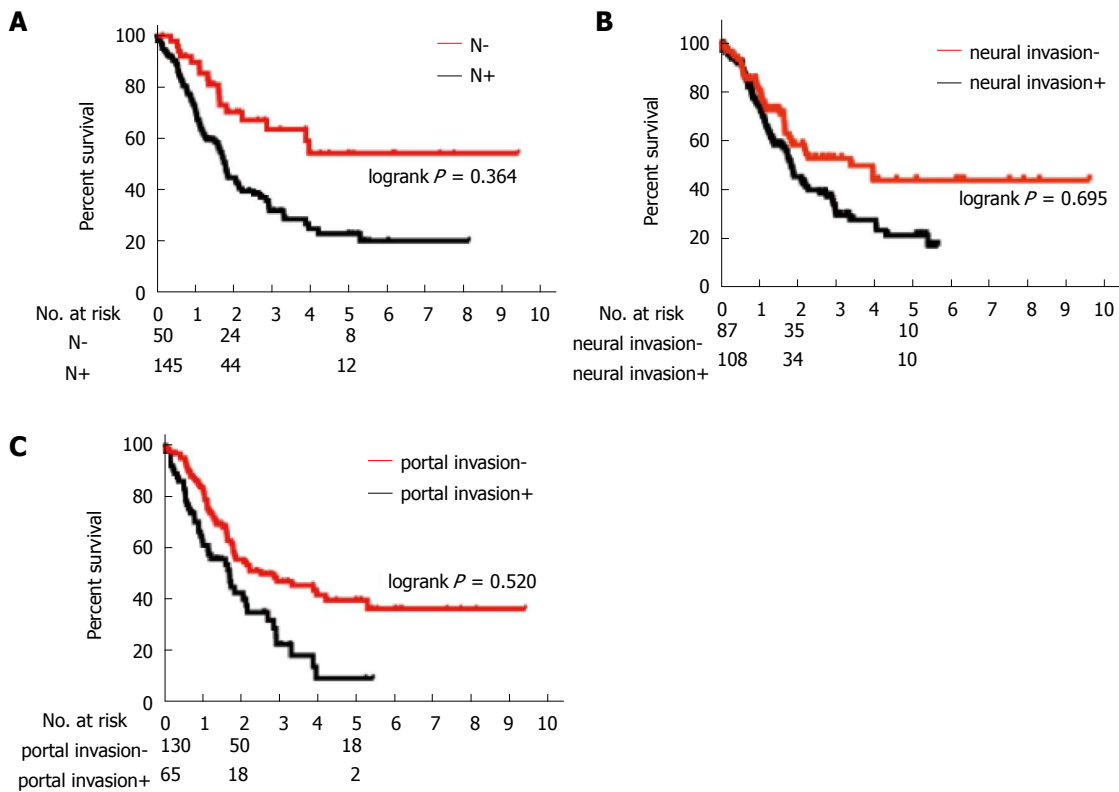
### Prognostic factors for all patients

The median observational period for all patients was 595 d. The median survival was 27.1 mo, and the 5-year actuarial survival rate was 34.5%.

Table 2 shows the prognostic factors analyzed. The univariate analysis showed that UICC stage, CA19-9 ≤ 200 U/mL, DUPAN-2 ≤ 180 U/mL, tumor size ≤ 20 mm, R0 resection, absence of lymph node metastasis, absence of extrapancreatic neural invasion, and absence



**Figure 1** Survival curves in the multivariate analysis for CA19-9, DUPAN-2, surgical margin, and tumor size. A: CA19-9 ( $\leq$ / $>$ 200); B: DUPAN-2 ( $\leq$ / $>$  180); C: Surgical margin (R0/R1-2); D: tumor size  $\leq$ / $>$  20 mm.



**Figure 2** Survival curves in the multivariate analysis for lymph node metastasis, extrapancreatic neural invasion, and portal invasion. A: Lymph node metastasis (+/-); B: Extrapancreatic neural invasion (+/-); C: Portal invasion.

**Table 3** Multivariate analysis of factors prognostic for survival in patients undergoing pancreatic resection for pancreatic cancer

Variables	HR	95%CI	P value
CA19-9 ( $\leq 200$ )	0.668	0.410-1.084	0.102
DUPAN-2 ( $\leq 180$ )	0.767	0.461-1.264	0.299
Negative surgical margin (R0)	0.478	0.296-0.770	0.003
Tumor size $\leq 20$ mm	0.399	0.171-0.825	0.012
No lymph node metastasis	0.764	0.413-1.355	0.364
No extrapancreatic neural invasion	0.906	0.548-1.477	0.695
No portal invasion	0.859	0.541-1.370	0.520

of portal invasion were all associated with a greater overall survival. Table 3 and Figures 1 and 2 show the results of from the multivariate analysis. Tumor size  $\leq 20$  mm (HR = 0.40; 95%CI: 0.17-0.83) and R0 resection (HR = 0.48; 95%CI: 0.30-0.77) were the only independent favorable prognostic factors.

### Comparison between 5-year survivors and non-survivors

Table 4 compares the 20 patients who survived  $\geq 5$ -year and the 76 patients who died within 5 years after surgery. Comparison of these two groups showed that lower concentrations of DUPAN-2, tumor size  $\leq 20$  mm, R0 resection, absence of lymph node metastases and portal invasion were significantly associated with 5-year survival. Even among the 20 patients who survived  $\geq 5$ -years, 13 (65%) had tumors  $> 20$  mm, eight (40%) had lymph node metastases, 10 (50%) had extrapancreatic invasion, and two (10%) had portal invasion.

## DISCUSSION

This study retrospectively analyzed patients who underwent resection for pancreatic cancer at a single center. An analysis of factors prognostic for survival showed that tumor size  $\leq 20$  mm and R0 resection were independently associated with long-term survival, indicating that early tumor detection and histologically curative resection were important to achieve long-term survival. A comparison of 5-year survivors with non-survivors revealed that a significantly higher percentage of survivors had low DUPAN-2 concentrations, tumor sizes  $\leq 2$  cm, negative surgical margins, no lymph node metastasis, and no portal invasion. Among the 20 patients who survived  $\geq 5$ -years, 13 had tumors larger than 20 mm; eight patients had lymph node metastases; 10 patients had extrapancreatic neural invasion; and two patients had portal invasion. An analysis of the 19 patients who survived more than 3 years revealed that seven patients (36.8%) had lymph node metastasis and 16 patients (84.2%) had tumors larger than 20 mm<sup>[14]</sup>. Thus, even in patients with advanced pancreatic cancer, radical resection can increase the long-term survival.

Several studies have also shown that surgical margin status and/or tumor size was associated with survival rate<sup>[5,6,10,14,15]</sup>. For example, a retrospective study of 194

**Table 4** Clinicopathological characteristics of 5-year survivors and non-survivors

Variables	5-yr survivors (n = 20)	Non-survivors (n = 76)	P value
Age (mean $\pm$ SD)	65.5 $\pm$ 9.4	67.2 $\pm$ 7.9	0.393
Gender			0.398
Male	10	46	
Female	10	30	
Tumor marker, median (IQR)			
CEA (ng/mL)	2.0 (1.3-2.7)	3.0 (1.6-5.4)	0.536
CA19-9 (U/mL)	57.0 (35.0-378.0)	213.5 (48.0-594.5)	0.071
DUPAN-2 (U/mL)	79.5 (25.0-508.0)	312.5 (55.8-965.3)	0.032 <sup>a</sup>
Tumor size			0.008 <sup>a</sup>
$> 20$ mm, n	13	70	
$\leq 20$ mm, n	7	6	
UICC T classification			0.161
T1, n	1	1	
T2, n	0	3	
T3, n	19	66	
T4, n	0	6	
Surgical margin status			0.004 <sup>a</sup>
R0, n	19	46	
R1, n	1	26	
R2, n	0	4	
Lymph node metastasis			0.036 <sup>a</sup>
Positive, n	8	62	
Negative, n	12	14	
Extrapancreatic neural invasion			0.200
Positive	10	50	
Negative	10	26	
Portal invasion			0.005 <sup>a</sup>
Positive	2	31	
Negative	18	45	
UICC stage			0.184
I A, n	1	1	
I B, n	0	1	
II A, n	7	11	
II B, n	10	43	
III, n	0	4	
IV, n	2	16	
Adjuvant chemotherapy			0.707
Yes	15	60	
No	5	16	
Time to initiation of adjuvant chemotherapy (d)	36.0 $\pm$ 24.0	64.5 $\pm$ 83.1	0.107

CEA: Carcinoembryonic antigen; UICC: Union for international cancer control. <sup>a</sup>*P* < 0.05.

pancreatic cancer patients found that negative surgical margin was the sole independent postoperative prognostic factor<sup>[10]</sup>. A more detailed evaluation of the histological margin status of the specimens found that tumors  $> 1.5$  mm from the closest margin were significantly associated with longer survival<sup>[15]</sup>. Furthermore, analyses of 396<sup>[5]</sup> and 185<sup>[16]</sup> patients with pancreatic cancer showed that tumor size  $\leq 2$  cm was a significant prognostic factor. Collectively, these findings indicate that earlier detection and histologically curative resection can achieve longer survivals in pancreatic cancer patients.

The procedure required for histologically curative resection remains unclear. The methods suggested include

“regional pancreatectomy”, *i.e.*, extended pancreatic resection together with vascular resection and retroperitoneal lymphadenectomy. The rationale for an extended operation is based on the high rates of intra- and extrapancreatic neural invasion and lymph node metastasis. An extended operation is thought to be essential for histologically curative resection<sup>[14]</sup>. Moreover, a study of 74 patients with pancreatic cancer found that the survival rate was significantly higher in patients who underwent an extended than a standard operation<sup>[17]</sup>. However, many recent prospective studies have shown that extended operations tend to increase morbidity and mortality rates without having a survival benefit<sup>[18-20]</sup>. A systematic review and meta-analysis showed no significant differences in the survival rate between standard and extended operations, with a trend towards increased morbidity in patients undergoing extended operations<sup>[21]</sup>. Indeed, a review of 424 patients in four prospective randomized controlled trials found that extended operation was not associated with a survival benefit but tended to increase the rates of postoperative morbidity, such as diarrhea, in the early months after surgery<sup>[22]</sup>. Thus, because a standard operation results in longer survival and avoids postoperative morbidity, extended operations are not performed at our facility.

The necessity and efficacy of adjuvant chemotherapy for pancreatic cancer also remains unclear. A multicenter, randomized, controlled phase III trial found that postoperative gemcitabine increased survival compared with observation alone<sup>[23]</sup>. Since then, gemcitabine has been the standard adjuvant chemotherapy for pancreatic cancer (also in Japan)<sup>[24]</sup>. Of our 195 patients, 150 patients (76.9%) received chemotherapy after operation. However, we were unable to show that either adjuvant chemotherapy or its early initiation significantly enhanced patient survival. A previous report indicated that survival was also significantly longer in patients who started adjuvant chemotherapy within 20 d after surgery than those patients who started chemotherapy more than 20 d after the operation<sup>[25]</sup>, indicating that earlier initiation of adjuvant chemotherapy may contribute to a longer survival. In our study, 142 patients received gemcitabine and only six patients received S1; therefore, we were not able to compare survival in these two groups. Future assessments of the efficacy of S1 require a greater number of patients receiving this agent.

This study was limited by its retrospective design; its performance at a single center; and the small number of patients. Therefore, a large-scale multicenter study should be planned to confirm our findings.

We found that the combination of negative surgical margins and tumor size  $\leq 20$  mm independently reduced the mortality rate to less than half, indicating that earlier tumor detection and histologically curative resection are important factors contributing to long-term survival.

## COMMENTS

### Background

The prognosis of patients with pancreatic cancer remains quite poor, and surgery remains the only curative treatment for pancreatic cancer. However, the 5-year survival rate after surgery has been reported to be less than 25%. This study was designed to analyze the factors prognostic of survival in pancreatic cancer patients and the characteristics of long-term survivors.

### Research frontiers

Several studies have reported prognostic factors after surgical resection of pancreatic cancer. This research aims to determine which factors are associated with long-term survival, *i.e.*, tumor size, lymph node metastasis, surgical margin status, tumor markers, and adjuvant chemotherapy, to improve the prognosis of pancreatic cancer patients.

### Innovations and breakthroughs

In previous reports, the 5-year survival rate after surgery was less than 25%. The 5-year actuarial survival rate in the present study was 34.5%, and this rate is much higher than other reports. The Japan Pancreas Society (JPS) classification of pancreatic cancer includes many pathological factors that make it possible to perform a detailed study. In the present study, we performed further analyses about extraneural invasion and portal invasion according to the JPS classification.

### Applications

The outcome of our study indicates that surgeons should make every effort to detect pancreatic cancer in an early stage and to perform histologically curative resection during surgery.

### Terminology

*Adjuvant chemotherapy* is chemotherapy used after a curative operation to prevent recurrence or metastasis.

### Peer review

This is a retrospective clinical investigation providing interesting information on the experience of a single center with pancreatic surgery outcomes. The study does not provide any new data but contributes additional data on a subject with significant available amount of data.

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