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ORIGINAL ARTICLE

Factors affecting long-term survival after surgical resection of pancreatic ductal adenocarcinoma

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Purpose: Some patients who undergo surgical resection of pancreatic cancer survive longer than other patients. The purpose of this study was to identify the factors that affect long-term survival after resection of histopathologically confirmed pancreatic ductal adenocarcinoma. **Methods:** A single-center, retrospective study was conducted among 164 patients who underwent surgical resection of pancreatic cancer, between May 1995 and December 2004. The patient follow-up process was conducted via telephone survey and review of electronic medical records for at least 5 years or until death. **Results:** We compared patients with long-term (≥60 months, n = 19) and short-term survival (<60 months, n = 145). Resection margin status, differentiation of the tumor, tumor stage, pre-operative serum level of albumin, total bilirubin and carbohydrate antigen (CA) 19-9 level are related with survival difference (all factors, $P < 0.05$). Multivariate analysis revealed that a pre-operative serum total bilirubin level <7 mg/dL and a pre-operative serum CA19-9 level <37 U/mL is a statistically significant prognostic factor for long-term survival. **Conclusion:** The preoperative serum total bilirubin and serum CA19-9 levels are associated with long-term survival after surgical resection of pancreatic cancer.

Key Words: Pancreatic neoplasms, Bilirubin, CA19-9 antigen

INTRODUCTION

The 5-year survival rate of patients with pancreatic cancer in Korea was 8.0% between 2001 and 2005, 7.7% between 2003 and 2007 [1]. Although the death rates of most malignancies have declined, the poor prognosis of pancreatic cancer has not improved with advances in proper curative surgical resection [2,3].

Nevertheless, some patients who underwent surgical resection of pancreatic cancer survive longer than other patients [4]. It is important to predict the prognosis of patients with pancreatic cancer after surgical resection to provide proper surgical and adjuvant management, which may thus improve the survival of patients with pancreatic cancer [5,6].

In previous studies, clinical factors associated with survival after surgical resection have not been thoroughly studied. Some histopathologic findings of long-term survivors have been shown to resemble the findings of other kinds of neoplasm by the review of slides in a previous study. In other previous studies, follow-up period data have usually been <5 years because of the poor prognosis

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of pancreatic cancer [7,8].

The purpose of this study was to identify the clinical factors that affect long-term survival after resection of histopathologically confirmed pancreatic ductal adenocarcinoma.

METHODS

A retrospective study was conducted among 176 patients who underwent surgical resection of pancreatic cancer at Samsung Medical Center between May 1995 and December 2004. The demographic, clinical data and lab findings based on electronic medical records at this center were reviewed. The body mass index (BMI) data were based on the anesthesia records maintained during surgery. The serum levels of albumin, hemoglobin, total bilirubin, and carbohydrate antigen (CA) 19-9 were based on data from the day of admission. The slides of cancer specimen were re-evaluated by pathologists to confirm the diagnosis. Eleven patients were excluded because the final diagnoses were mucinous cystic neoplasms, intraductal papillary mucinous neoplasms, squamous cell carcinomas, and leiomyosarcomas. One patient was lost to follow-up and excluded. One hundred sixty-four patients were thus enrolled.

Patient follow-up was conducted through telephone survey. The duration of the follow-up period was at least 60 months or until the patient's death. The records of death were based on data from the National Statistical Office of Korea. Patients who survived ≥60 months after surgical resection were considered long-term survivors.

All of the long-term survivors after surgical resection of pancreatic cancer who were included in this study were finally re-confirmed to have ductal adenocarcinoma of the pancreas by histopathologic review. The stage was classified according to the cancer staging system published by the American Joint Committee on Cancer, 7th edition.

An independent t-test, Pearson's chi-square test, linear-by-linear association, and Fisher's exact test were used to analyze the factors. $P < 0.05$ were considered statistically significant. The variables that had prognostic potential, as suggested by univariate analysis, were subjected to multivariate analysis with a logistic regression model [9]. All statistical analyses were performed using SPSS ver. 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Nineteen of 164 patients (11.6%) of the patients achieved 60-month long-term survival after surgical resection of pancreatic cancer. Among the long-term survival group, 15 patients were alive on 1 January 2010. The mean duration of survival of the 145 patients in the short-term survival group was 483 ± 348.7 days (range, 21 to 1,632 days) since the day of surgery. The mean age of all the patients (98 [59.8%] men and 66 [40.2%] women) included in this study was 59 ± 9.9 years (range, 32 to 80 years).

The majority of patients (92.7%) had one or more symptoms at the time of admission, including abdominal pain, jaundice, and dyspepsia. Ninety-one (55.5%) patients underwent pre-operative intervention for biliary drainage or decompression because obstructive jaundice developed secondary to the tumor located in the head or body of pancreas. Seventy-six patients (46.3%) had an American Society of Anesthesiologists (ASA) score of 1 and 88 patients (53.6%) had an ASA Score >1.

The following surgical procedures were performed: Whipple procedure, 66 patients (39.0%); pylorus-preserving pancreaticoduodenectomy, 42 patients (25.6%); distal pancreatectomy, 30 patients (18.3%); and total pancreatectomy, 26 patients (15.9%). The location of tumor in 130 patients (79.2%) was the head or neck of pancreas, including uncinate process of 2 patients; 23 patients (14.0%) was the body of pancreas; and 11 patients (6.7%) was the tail of pancreas.

A transfusion of packed red blood cells (pRBCs) was required in 68 patients (41.5%) intra-operatively. Nine of the 68 patients required massive transfusions, (>10 units of pRBCs). The mean operative time was 340 ± 102 minutes (range, 110 to 700 minutes). In 126 patients (76.8%), including all of the patients who achieved long-term survival, R0 resections were performed. Negative margins could not be obtained (R1 and R2) in 38 patients (23.2%). Portal vein resections were performed in 3 patients in the long-term

Table 1. Demographic, clinical, and pathologic factors affecting survival after surgical resection of pancreatic cancer

	Long-term survival (n = 19)	Short-term survival (n = 145)	P-value
Age (yr)	56.26 ± 9.03[a]	59.22 ± 10.03[a]	0.224
Gender			0.748[d]
Male	12	86	
Female	7	59	
ASA Score			0.559[d]
1	10	66	
>1	9	79	
BMI (kg/m^2)			0.994[d]
Normal BMI (<25)	16	122	
Overweight/obese	3	23	
Hospital days (day)	19.95 ± 8.52[a]	23.02 ± 19.66[a]	0.503
Albumin (g/dL)	4.06 ± 0.49[a]	3.80 ± 0.55[a]	0.050
Hemoglobin (g/dL)	12.90 ± 1.79[a]	12.63 ± 1.85[a]	0.563
CA 19-9 (U/mL)			0.001[d]
<37	10	26	
≥37	9	119	
Total bilirubin (mg/dL)			0.010[c]
<7	18	82	
≥7	1	63	
Preoperative intervention			0.082[d]
No intervention	12	61	
Intervention performed	7	84	
Operation			0.535[d]
PPPD	7	35	
Whipple operation	5	61	
Total pancreatectomy	3	23	
Distal pancreatectomy	4	26	
Operative time (min)	312.63 ± 101.75[a]	344.62 ± 101.70[a]	0.199
Resection of SMV or PV			0.723[c]
No resection	16	126	
Resection performed	3	19	
Transfusion			0.236[b]
No transfusion	13	83	
0 to 9 units	6	53	
≥10 units	0	9	
Resection status			0.008[c]
R0	19	107	
R1 or R2	0	38	
Tumor location			0.523[d]
Head	14	116	
Body and tail	5	29	
Differentiation			0.033[b]
Well	5	17	
Moderate	13	99	
Poor	1	29	
T stage			0.010[b]
T1	1	1	
T2	3	3	
T3	15	130	
T4	0	11	
N stage			0.309[d]
N0	11	66	
N1	8	79	
TNM Stage			0.021[b]
Ia	1	1	
Ib	2	3	
IIa	8	58	
IIb	8	71	
III	0	11	
IV	0	1	
Adjuvant treatment			0.125[d]
No adjuvant treatment	5	65	
Treatment performed	14	80	

CA19-9, carbohydrate antigen 19-9.

PPPD, pylorus preserving pancreaticoduodenectomy; SMV, superior mesenteric vein; PV, portal vein; TNM, tumor, node, metastasis.
[a]Mean ± standard deviation. [b]Linear-by-linear association. [c]Fisher's exact test. [d]Pearson's chi-square test.

survival group and confirmed to be invasive pancreatic adenocarcinoma. In short-term survival group, 19 patients were required resection of the portal vein or superior mesenteric vein and 9 patients had confirmed invasive malignancies.

The mean length of hospital day was 22 ± 18.7 days (range, 7 to 215 days), because some patients underwent adjuvant treatment subsequently after surgical treatment.

Ninety-four patients received post-operative adjuvant treatment; specifically, 69 patients (42.1%) received chemotherapy and radiation therapy and 25 patients (15.2%) received chemotherapy alone. Whether or not adjuvant therapy was administered, recurrence of pancreatic cancer occurred in 99 patients (60.4%) after surgical resection.

All cases were confirmed to be ductal adenocarcinoma of the pancreas and classified with differentiation by histopathologic review. The demographic, clinical, and pathologic factors of the long-term and short-term survival groups are listed in Table 1.

At the time of admission, the albumin level (P = 0.05), pre-operative serum total bilirubin level (3.14 ± 4.46 mg/dL in the long-term survival group and 7.39 ± 7.97 mg/dL in the short-term survival group, P = 0.01), pre-operative serum CA19-9 level (194.74 ± 383.55 U/mL in the

long-term survival group and 1,526.19 ± 3,756.46 U/mL in the short-term survival group, P < 0.01), resection status (P < 0.01), T stage (P = 0.01), and overall stage (P = 0.02) are factors affecting the survival of patient with surgically treated pancreatic cancer. Pre-operative total bilirubin level <3 mg/dL in 13 patients of long-term survival group and 66 patients in short-term survival group, and failed to show statistical significance for this level of total bilirubin (P = 0.06). Whereas age, gender, ASA score, BMI, length of hospital stay, hemoglobin concentration at the time of admission, pre-operative interventions, symptoms at the time of admission, operative time, intra-operative transfusion of pRBCs, and adjuvant treatments did not correlate with long-term survival (all P > 0.05).

Table 2. Multivariate analysis of factors that show statistical significance of relationship with long-term survival after surgical resection of pancreatic cancer, based on the result of univariate analysis

	Odds ratio	Confidence interval	P-value
Pre-operative serum total bilirubin (<7 mg/dL)	10.57	1.193-93.689	0.034
Pre-operative serum CA19-9 (<37 U/mL)	4.21	1.187-14.945	0.026

The statistically significant variables (P < 0.05) based on univariate analysis were included in a multivariate logistic regression model. Multivariate analysis identified a pre-operative serum total bilirubin <7 mg/dL and a pre-operative serum CA19-9 level <37 U/mL was a prognostic factor for long-term survival (Table 2). Pre-operative serum total bilirubin <7 mg/dL and pre-operative serum CA19-9 level <37 U/mL were associated with better survival outcome (Fig. 1). Mean overall survival was 30 ± 3.4 months (median 14 months). The mean survival in patients with pre-operative serum total bilirubin level <7 mg/dL (100 of 164 patients) was 38.1 months (median 14.9 months) compared with 16.6 months (median 11.4 months) in those patients with pre-operative serum total bilirubin level ≥7 mg/dL (64 of 164 patients, log-rank test P = 0.002). The mean survival in patient with pre-operative se-

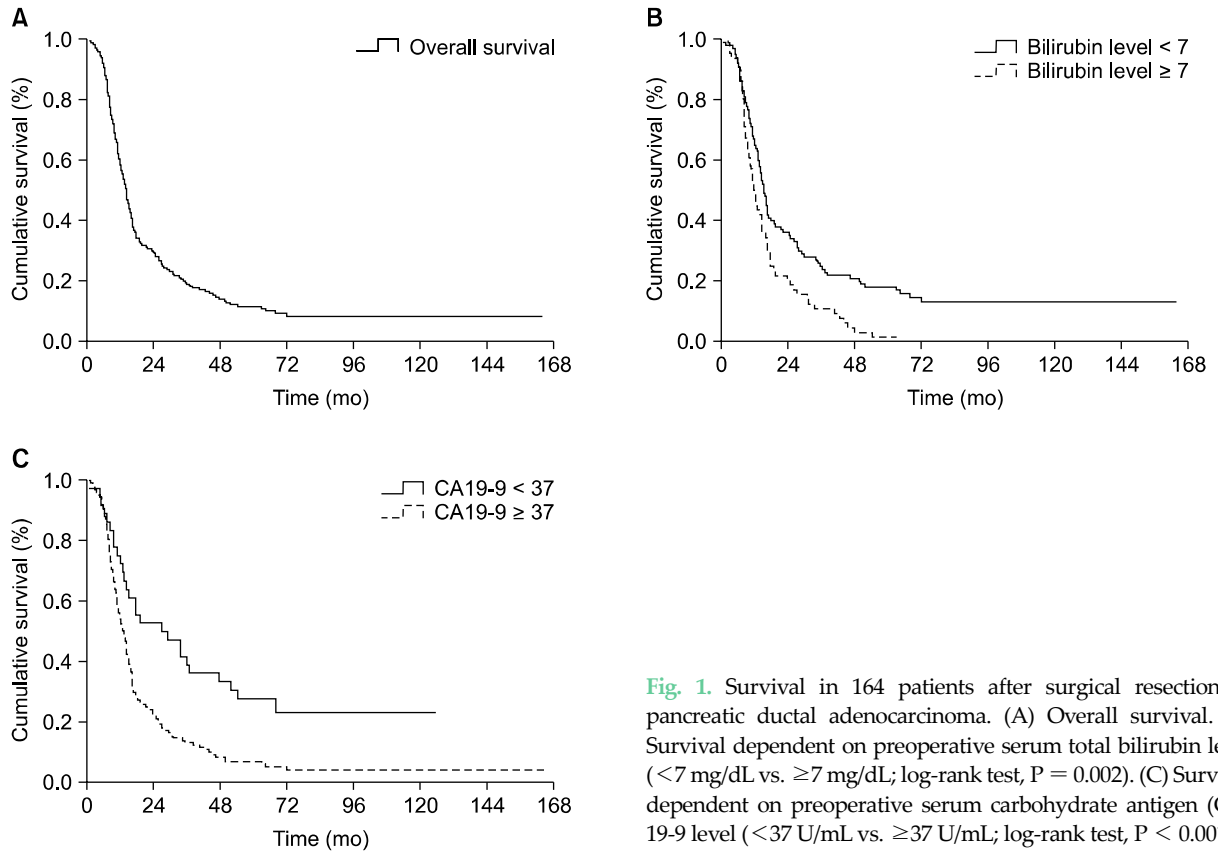

Fig. 1. Survival in 164 patients after surgical resection of pancreatic ductal adenocarcinoma. (A) Overall survival. (B) Survival dependent on preoperative serum total bilirubin level (<7 mg/dL vs. ≥7 mg/dL; log-rank test, P = 0.002). (C) Survival dependent on preoperative serum carbohydrate antigen (CA) 19-9 level (<37 U/mL vs. ≥37 U/mL; log-rank test, P < 0.001).

rum CA19-9 level <37 U/mL (128 of 164 patients) was 46.6 months (median 27 months) compared with 23 months (median 13 months) in those patient with pre-operative serum CA19-9 level ≥37 U/mL (36 of 164 patients, log-rank test, $P < 0.001$).

DISCUSSION

Because pancreatic cancer is fatal, there are few 5-year survivors, even after surgical and adjuvant treatment, or using early detection by screening strategies. The factors affecting survival of pancreatic cancer have been studied by many investigators.

Cleary et al. [10] conducted a study in patients with resected pancreatic adenocarcinomas and reported that early-stage disease is a prognostic factor for long-term survival. Cameron et al. [11] identified that the most important determinant of survival in patients with pancreatic cancer after surgical resection is the biologic properties of the tumor. Other studies have shown that age, symptoms, performance of a resection, tumor differentiation, resection margin, BMI, adjuvant treatment, tumor markers, and other co-morbidities are prognostic factors [2,4-7,12-25]. Some of the studies were limited by few survivors. The differences in treatment, heterogeneous diagnosis of initial and secondary histopathologic review, and limited follow-up were also shortcomings of previous studies. Further investigation is still needed to identify factors related to long-term survival after surgical resection of pancreatic cancer.

Ouaissi et al. [24] reported increased mortality in patient >70 years of age. In the current study, age did not influence survival of patients with pancreatic cancer. Other factors, including gender, length of hospital stay, and ASA score had no statistical significance.

Michaud et al. [15] conducted studies and reported that obesity significantly increased the risk of pancreatic cancer and decreased survival in compared with a normal BMI. The mean BMI of the patients in the current study was 22.65 ± 2.83 kg/m^2; only 1 patient had a BMI >30 kg/m^2. There was no statistically significant difference in BMI between the long-term and the short-term survival groups.

Smith et al. [26] suggested that the presence of jaundice at the time of resection had an adverse impact on early post-operative survival in pancreatic cancer patients undergoing pre-operative biliary drainage. Ninety-one of the patients in the current study underwent pre-operative intervention for biliary drainage; however, this procedure did not affect long-term survival. Tumor-related biliary obstruction most often occurs when the tumor is located in the head or neck of the pancreas, rather than the body or tail. None of the patients who underwent distal pancreatectomy received pre-operative intervention for biliary drainage. Additionally, there was no significance in the tumor locations between the long-term and short-term survival groups. This finding might account for the differing results of our study and other studies.

There was no significant difference in the operative time between the long-term and short-term survival groups. Also, there was no significant transfusion-related decrease in survival. In other studies, performing surgery appears to be an important factor influencing survival [11].

Surgical margin status is thought to affect the survival of patients after surgical resection of pancreatic cancer [2,12,23]. We found that when R0 resection was not achieved, long-term survival was not guaranteed. Also, we found a statistically significant difference in surgical margin status after surgical resection between the long-term and short-term survival groups.

Portal vein and/or superior mesenteric vein resections appear to decrease survival compared to cases in which vein resections are not performed [27]. Compared with R1/R2 resections, vein resections increase survival. Vein resections do not necessarily indicate a negative possibility of long-term survival after surgical resection of pancreatic cancer, as previous studies have showed [6]. In the current study, 19 patients in the short-term survival group underwent vein resections; 9 of the 19 patients had invasive pancreas adenocarcinoma, and 2 patients did not achieve R0 resection. It is not clear whether or not resection of cancer-invaded veins have a survival benefit. Because resection status was different in some cases, the analysis might have been biased.

There was statistical significance based on linear-by-lin-

ear association in tumor differentiation and the survival group. In agreement with previous studies, histologic differentiation could be a reliable factor affecting survival of pancreatic cancer [18].

We observed that cancer stage was associated with survival after surgical resection of pancreatic cancer. All patients who achieved long-term survival had early-stage disease (stages I and II) and the T stage was statistically significant, as reported in previous studies [10]. But in the current study, nodal status did not have a statistically significant effect on survival of patient with pancreatic cancer. According to other investigators, T stage and regional lymph node spreading of cancer has been suggested to be an important prognostic factor of survival in patients with pancreatic cancer [5,17,20]. In contrast, some investigators have suggested that patients with lymph node metastasis also have a chance for long-term survival [16]. Mukaiya et al. [28] suggested that the extent of lymph node dissection does not affect the prognosis of pancreatic cancer in advanced cases.

Like other studies [6,22,27], the effect of adjuvant treatment showed no increase in survival in patient with pancreatic cancer in the current study. Furthermore, some of patients dropped out during adjuvant treatment because of intolerable side effects of the chemotherapy. These problems make further statistical evaluation difficult to progress. A number of other investigators [5,14,19,20,23,29] suggested that adjuvant treatment is effective for increasing survival in patients with pancreatic cancer after surgical resection, and studies for proper regimen are ongoing.

We demonstrated that the pre-operative lab findings, with the exception of the hemoglobin level at the time of admission, had a statistically significant difference between the long-term and short-term survival groups. Efforts for developing the screening strategies discovered that the pre-operative serum CA19-9 level is related to survival after resection of pancreatic cancer. An elevated serum bilirubin level and decreased serum albumin level pre-operatively had an unfavorable impact on prognosis [6,12,13,21,26]. The pre-operative serum levels of albumin, total bilirubin, and CA19-9 had a significant effect on survival.

A multivariate logistic regression model identified a pre-operative serum total bilirubin <7 mg/dL and a pre-operative serum CA19-9 level <37 U/mL as statistically significant prognostic factors for long-term survival. Indeed, these factors were associated with long-term survival after surgical resection in patient with pancreatic cancer. Tempero et al. [30] examined that only three of whom were Lewis antigen A and B negative in twenty patients of study and none of these three patients had elevated CA19-9 levels yet had detectable level of CA19-9 (they were not 0, but 4, 10, and 14). Lack of Lewis antigen A and B does not mean complete lack the ability to secrete CA19-9. Due to the restriction of retrospective study, the data related to Lewis antigen A and B was unable to include additionally in this study. As result, careful interpretations and additional investigations are needed.

The limitations of our study are as follow: First, co-morbidities which may affect survival, such as diabetes, hypertension, and chronic obstructive pulmonary disease, were not considered in the patients in the current study. Second, the regimen of adjuvant chemotherapy and dose of radiation therapy in this study was not specified, and some of patients dropped out during adjuvant treatment because of intolerable side effects of the chemotherapy or recurrence of cancer. Third, the causes of death of patients who had no radiologic evidence of recurrence were not clear. Disease-free survival was difficult to investigate in the current study. Fourth, we observed a patient with liver metastasis and a resection was performed during the surgical procedure. The patient with pancreatic cancer and distant metastases were not included in the current study. Finally, there were no differences between the surgical stapler and the hand-sewing method with respect to operative time, blood loss, and post-operative complications.

The pre-operative serum total bilirubin and pre-operative serum CA 19-9 levels were associated with long-term survival of patients with pancreatic cancer who underwent surgical resection. The serum albumin level at the time of admission, resection status, tumor differentiation, and cancer stage also affected survival of patients with pancreatic cancer.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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