# Surgical Treatment of Periampullary Cancer

— Review of 766 surgical experiences of 8 hospitals —

Sae Min Kim, M.D., Seon Hahn Kim, M.D., Sang Yong Choi, M.D., and Young Chul Kim, M.D.

Department of Surgery, College of Medicine, Korea University, Seoul, Korea

The incidence of periampullary cancer has been steadily rising in Korea. In the present study, we have reviewed 766 cases of surgically treated periampullary cancers, including 122 cases of our own, which were published in the Korean literature from 1984 to 1992. The 6th decade was the most prevalent age group, occupying 38% of the patients. The ratio of male of female was 1.7 to 1. Approximately 60% of lesion located at the head of the pancreas. Computed tomography which had 85% sensitivity was the most commonly employed modality for a diagnosis. The diagnostic sensitivity of percutaneous transhepatic cholangiography was 72%, of endoscopic retrograde cholangiopancreatography was 71%, and of ultrasonography was 54% in order of frequency. Tumor markers such as CA-19, CEA, and CA-125 were also studied in pancreatic cancer. The combinations of these markers recorded a higher positivity than using solely. The resection rate for lesions at the head of the pancreas was 21%, and that of distal common bile duct, ampulla of vater, and duodenum were 37%, 85%, and 50%, respectively. The morbidity and mortality rates after pancreatoduodenectomy were 44% and 12%, respectively. TNM staging revealed 66% of patients were in stage III, 26% in stage I, and 8% in stage II. The actual 5-year survival rates for cancer of the head of the pancreas was 11%, and that of duodenal cancer, distal choledochal cancer, and ampullary cancer were 21%, 18%, and 15%, respectively. In nonresected group, none survived over 18 months after treatment. Relatively high portion of lymph node metastatic patients may explain the poor survival observed in our series.

Key Words: Periampullary cancer, Korea, Resection

#### INTRODUCTION

During the last 10 years, the reported cases of periampullary cancer has been steadily increasing in Korea. At the same time, diagnostic accuracy has been improving with a development in the diagnostic radiology and the endoscopy. An effort to make a diagnosis at the earlier stage of the disease has been emphasized to increase the chances of resectability.

Address for correspondence: Sae-Min Kim, Department of Surgery, Anam Hospital, Korea University Medical Center: 126-1, 5-Ka, Anam-Dong, Sungbuk-Ku, Seoul 136-705, Korea. Tel: 2-928-5782, Fax: 2-928-5781

Both early detection and improved operative techniques shoule be indispensable to increase the number of curative resection and to decrease morbidity and mortality associated with the extensive surgery. The purpose of this study was to review the surgical experiences with periampullary cancers in recent ten years of period in Korea, and to examine the result of curative resection concerning operative morbidity and survival.

### MATERIALS AND METHODS

A retrospective analysis of 766 cases, who were treated surgically throughout 1980's, was made from

the published data (Choo et al., 1984; Chung et al., 1987; Kim et al., 1989; Kim and Kim, 1992; Oh et al., 1986; Park et al., 1991; Son et al., 1985; Song et al., 1990) from 8 hospitals in Korea. We used our own data for analysis of operative procedure, early complication after resection, tumor staging, and survival rate because there were no adequately available data from the reviewed literature.

Survival analysis of our own patients was performed with Kaplan-Meier method using PROC LIFETEST of the SAS statistical software. The statistical differences were checked by generalized Wilcoxon test, and a pvalue of less than 0.05 was considered significant.

#### RESULTS

Among the age groups, the 6th decade was the most prevalent one with a mean age of 54.6 years, occupying 38% of the patients. There were 478 male and 288 female patients, and the ratio of male to female was 1.7 to 1. Four hundred fifty four cases (59.3%) were in the head of the pancreas, 182 cases (23.7%) in the distal portion of the common bile duct, 95 cases (12.4%) in the ampulla of Vater, and 35 cases (4.6%) in the duodenum (Table 1).

Pain was found in 66% of the patients, and jaundice in 65%. Other presenting symptoms and signs were anorexia and/or indigestion, weight loss, fever and/or chill, and palpable mass in descending order (Table 2).

Table 1. Age, sex, and anatomic location

l a a ati a a a	No. of Case	S	Sex		
Locations	(%)	Male	Female	Mean age	
Head of Pancreas	454(59.3)	296	158	54.5	
Distal CBD	182(23.7)	109	73	55.1	
Ampulla of Vater	95(12.4)	55	40	53.1	
Duodenum	35( 4.6)	18	17	54.0	
Total	766(100)	478	288	54.6	

CBD: common bile duct

Table 2. Clinical findings

	(n=766)		
Findings	% Positivity		
Pain	66		
Jaundice	65		
Indigestion, Anorexia	62		
Weight loss	42		
Fever, Chill	25		
Palpable mass	11		

The diagnostic serologic markers for pancreatic cancer have been studied by many authors. The results of Choi et al. (1990), Kwon et al. (1989), and Park et al. (1987) are documented in Table 3. Among the various combinations of these tumor markers, CA19-9 or CA 125 showed the highest positivity with an average rate of 89%. The accuracy of various diagnostic modalities is also shown in Table 4. Among these, computed tomography showed highest sensitivity (85%).

Among 766 cases collected from the literature review, 277 cases of periampullary tumors were resected with an overall resectability rate of 32%. The resection rate for lesion of the head of the pancreas was 21%, and that of distal common bile duct, ampulla of Vater, and duodenum were 37%, 85%, and 50%, respectively (Table 5). Among our own 122 cases from January, 1981 to June, 1991 (Kim and Kim, 1992), 65 cases (53%) were resected with a curative intent. Pancreatoduodenectomy was performed on 56 cases. Total and regional pancreatectomy were done on 7 and 2 cases, respectively. Among 57 cases of the non-

Table 3. Serologic markers in pancreatic cancer (% Positive)

			(70 1 0011110)
Author	Choi et al. (1990)	Kwon et al. (1989)	Park et al. (1987)
CEA	56	73.3	41.7
CA 19-9	67	86.7	66.7
CA 125	56	40.0	
CA 19-9/CEA	67	93.3	83.3
CA 125/CEA	78	86.7	
CA 19-9/CA 125	78	100	

Table 4. Diagnostic modalities

			(% Ser	ensitivity)	
Author (Year)	CT	US	ERCP	PTC	
Chung et al (1987)	89	57	90	78	
Kim and Kim (1992)	82	52	77	60	
Kim et al (1989)	89	46	92	85	
Oh et al (1986)	86	18	52	74	
Park et al (1991)	92	52	68	94	
Son et al (1985)	75	68	63	91	
Song et al (1990)	91	69	78	63	
Average*	85	54	71	72	

CT: computed tomography, US: ultrasonography, ERCP: endoscopic retrograde pancreaticoduodenography, PTC: percutaneous transhepatic cholangiography

<sup>\*</sup> Average value was calculated from sum of total examined number divided by sum of total positive findings in the reviewed literature.

resection group, bypass procedure (biliary and/or enteric) was done on 44 cases, and an external drainage on 9 cases. On 4 cases, only a biopsy after exploration was carried out (Table 6).

The postoperative complication rate of 270 cases after pancreatoduodenectomy ranged from 27% to 63%, with a mean of 44%. Postoperative mortality ranged from 7% to 25%, with a mean of 12% (Table 7). According to our own data, the common complications during early postoperative period were pulmonary complication, wound infection, and intraabdominal abscess. But fatal complications were pancreatic fistula and postoperative bleeding. Two out of 3 patients with leakage and 2 out of 3 patients with bleeding died of their complications (Table 8). TNM staging (UICC, 1987) of our own 65 resected specimens revealed 66% of patients were in stage III, 26% in stage I, and 8% in stage II. Especially, in case of cancer in the distal portion of the common bile duct, 16 out of 18 patients (89%) were in stage III (Table 9).

Among the resection group of our own 65 patients, 56 cases were followed. The actuarial survival rates at 1, 3, and 5 years were 68%, 25%, and 15%,

respectively. The actuarial survival rates at 1 and 3 years in the nonresection group were 7% and 0%, respectively. The difference in survival rate between resection group and nonresection group was statistically significant (p=0.0001) (Fig. 1). For duodenal cancer, the 5-year survival rate was 22%, whereas for cancer of common bile duct, ampulla of Vater, and pancreas, it was 18%, 15%, and 12%, respectively. But a survival difference according to tumor location was not statistically significant (p=0.513) (Fig. 2).

## DISCUSSION

In 1980, when the Central Cancer Registries started in Korea, pancreatic cancer was not one of ten most common cancers. After 1980, the incidence has risen steadily year by year. By 1983, pancreatic cancer recorded the 10th most common cancer in males. When the cancers of other periampullary areas are included, the incidence might be even higher (Central Cancer Registry, 1981-1990). According to the statistics of the year 1989 (National Bureau of Statistics, 1990), the death rate of pancreatic cancer in males

Table 5. Resectability rates of periampullary tumors

		Pancreas	Bile Duct	Ampulla	Duodenum	Total	
Author (Year)	Period -	Patient Resected/Patient Treated (% Resectability)					
Choo et al (1984)	1977-1982	7/41(17.1)	5/19(26.3)	5/5(100)	0/2(0)	17/67(25.4)	
Chung et al (1987)	1981-1982	9/31(29.0)	0/5(0)	3/5(60)		12/41(29.3)	
Kim and Kim (1992)	1981-1991	24/62(38.7)	18/29(62.1)	15/19(78.9)	8/12(66.7)	65/122(53.3)	
Kim et al (1989)	1977-1988	10/24(41.7)	11/15(73.3)	22/23(95.7)	2/3(66.7)	45/65(69.2)	
Oh et al (1986)	1972-1984	18/163(11.0)	20/84(23.8)	33/40(82.5)	6/16(37.5)	77/303(25.4)	
Park et al (1991)	1986-1990					36/62(58.1)	
Son et al (1985)	1979-1983	7/34(20.6)	4/6(66.7)	2/2(100)	1/1(100)	14/43(32.6)	
Song et al (1990)	1978-1988	11/63(17.5)				11/63(17.5)	
Average*		86/418(21)	58/158(37)	80/94(85)	17/34(50)	277/766(36)	

<sup>\*</sup> Average value was calculated from sum of total treated number divided by sum of total resected number.

Table 6. Operative procedures

(K.U.H.)

Locations	Resection			Rynass	External	EL
	PD	RP	TP	Bypass	drainage	only
Head of Pancreas (n=62)	16	2	6	29	7	2
Distal CBD (n=29)	17		1	8	2	1
Ampulla of Vater (n=19)	15			3		1
Duodenum (n=12)	8			4		
Total (n=122)	56	2	7	44	9	4

K.U.H.: Korea University Hospital, PD: pancreatoduodenectomy, RP: regional pancreatectomy, TP: total pancreatectomy, EL: explorative laparotomy, CBD: common bile duct

was 3.7 per 100,000, and it recorded the 5th most common lethal cancer in Korea. Whereas in females, the death rate was 2.3 per 100,000 and it recorded the 7th place. This trend has also been observed in other countries. In Japan, the incidence has almost

Table 7. Complication and mortality rates after resection

A () (	Total	Postoperative		
Authors (Year)	Cases	Complication (%)	Death (%)	
Choo et al (1984)	17	59	18	
Chung et al (1987)	12	50	25	
Kim and Kim (1992)	58#	41	7	
Kim et al (1989)	45	63	9	
Oh et al (1986)	77	42	9	
Park et al (1991)	36	36	*	
Son et al (1985)	14	36	7	
Song et al (1990)	11	27	12	

<sup>\*:</sup> no available data

**Table 8.** Early complication after pancreatoduodenectomy (K.U.H.)

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Complications	No. of Cases*
Pulmonary complication	7
Wound complication	6
Intraabdominal abscess	5
Pancreatic leakage	3#
Bleeding	3#
Stress ulcer bleeding	2
Diabetes mellitus	2
Biliary fistula	1
Cholangitis	1
Renal failure	1

K.U.H.: Korea University Hospital

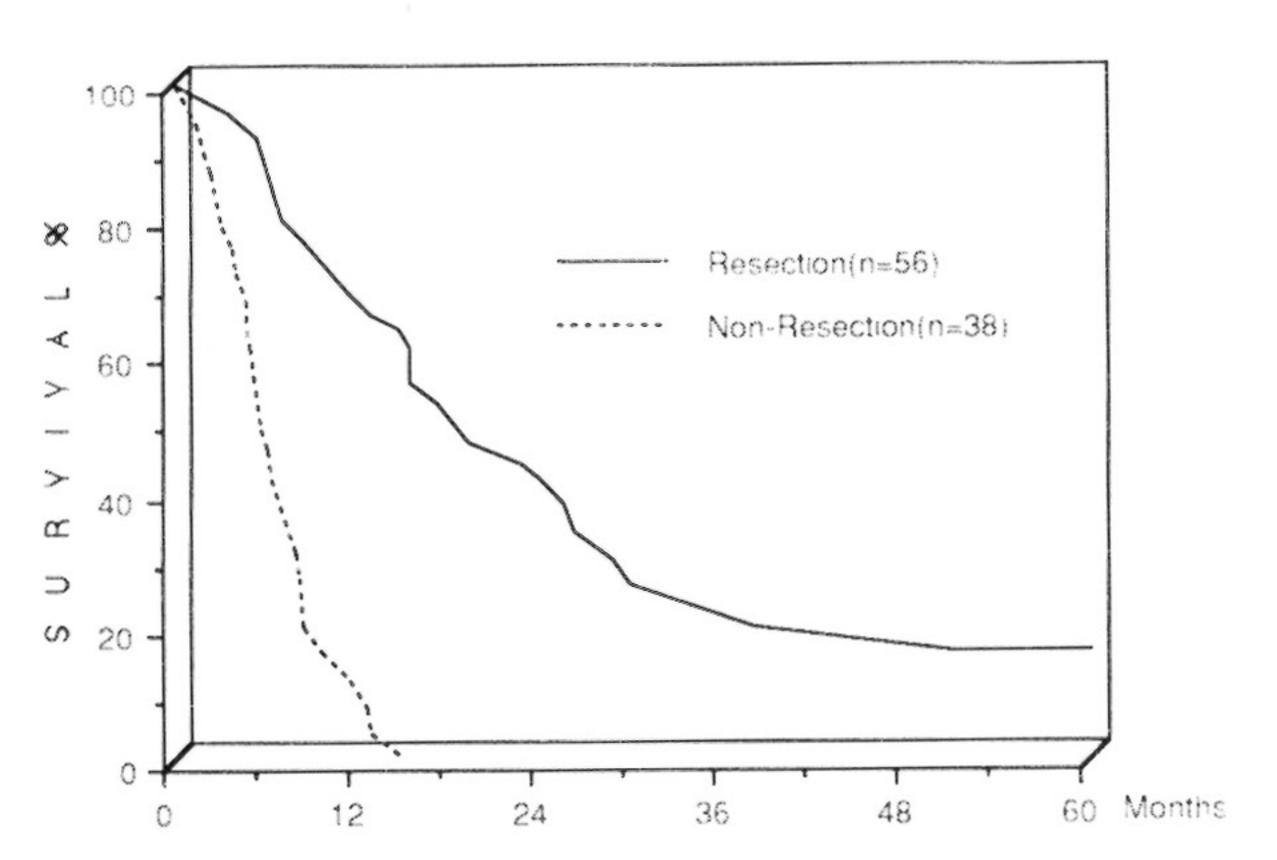
Table 9. Staging of resected tumors (TNM Classification, UICC)

		(N.U.H.)
Stage I	Stage II	Stage III
8	2	14
2	0	16
4	3	8
3	0	5
17(26%)	5(8%)	43(66%)
	8 2 4 3	8 2 2 0 4 3 3 0

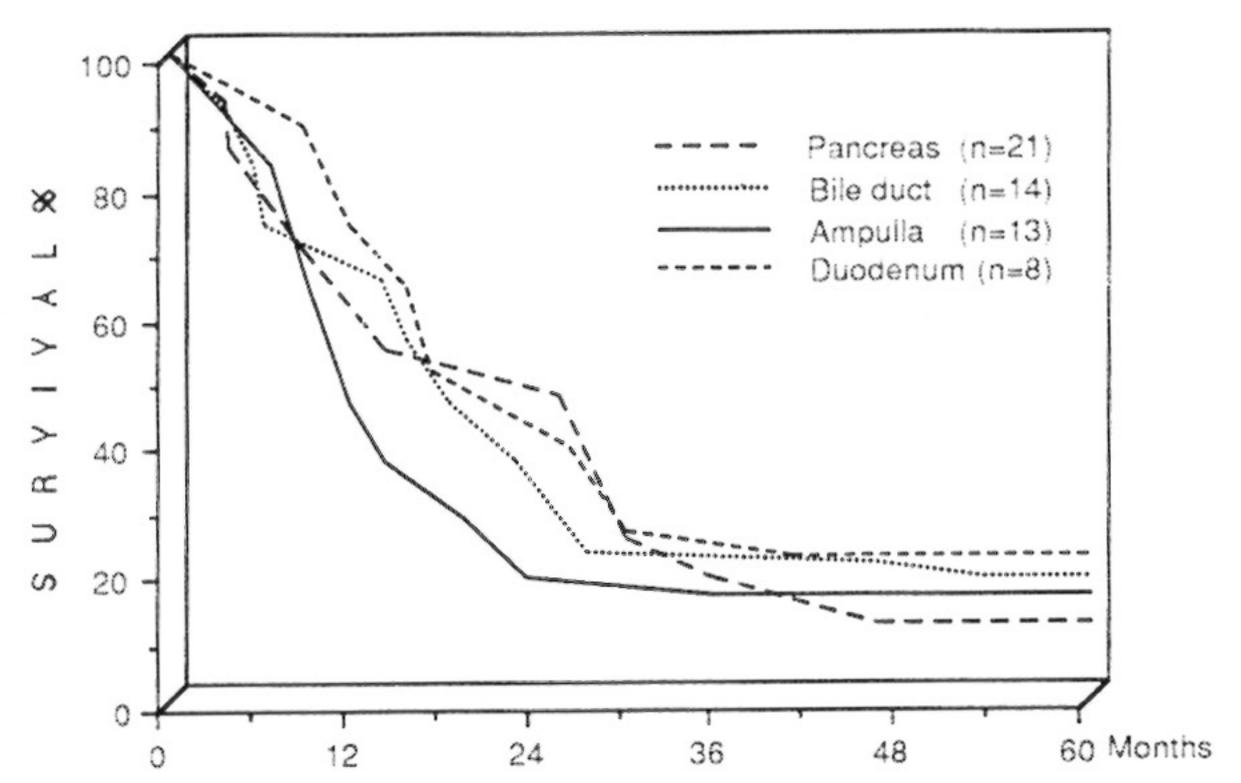
K.U.H.: Korea University Hospital, CBD: common bile duct

tripled over the last two decades. And now, among cancer deaths, it has been the 4th leading cause in males, and the 6th in females (Nagano, 1990). Suzuki (1989) suggested that factors such as smoking, alcohol or coffee consumption, certain chemical exposures, radiation exposures, diabetes, and chronic pancreatitis have been postulated to cause an increased risk of pancreatic cancer.

Age-specific incidence rate in the present series indicates that the most common age group was the 6th decade with an average age of 54.6 years. It might be 10 years younger than that in the studies from Japan and the United States (Gordis et al., 1984; Nagano, 1990). The male to female ratio of 1.7 to 1 was similar to the studies from Japan and the United



**Fig. 1.** Actuarial survival rates at 1, 3, and 5 years in resected group were 68%, 25%, and 15%, respectively. But in non-resected group, actuarial survival rates at 1, and 2 years were 7%, and 0%, respectively (Kaplan-Meier Method, p=0.0001 by Wilcoxon test).



**Fig. 2.** For duodenal cancer, the 5-year survival rate was 22%, whereas for cancer of common bile duct, ampulla of Vater, and head of pancreas, it was 18%, 15%, and 12%, respectively. But a difference of survival according to tumor location was not statistically significant (p=0.513)

<sup>#:</sup> excluding cases of total pancreatectomy

<sup>\*</sup>Total No. of complicated patients: 24/58(41%) #: Two out of 3 patients with leakage and 2 out of 3 patients with bleeding died.

States. Distribution of tumor location showed approximately sixty percent of lesion was in the head of the pancreas, and the distal portion of the common bile duct, the ampulla of Vater, and the duodenum were followed in descending order (Table 1). Western studies (Crist et al., 1987; Grace et al., 1986; Lygidakis et al., 1989; Trede et al., 1990) showed higher incidence of ampullary cancer than cancer of distal common bile duct. The reasons of this difference are may be due to the inaccuracy of histological classification of tumor location (Crist et al., 1987; Trede et al., 1990), and due to including nonresected cases in our series, although the distinction of tumor location is best made on the basis of gross resected surgical anatomy (Hayes et al., 1987). The most common clinical presentations may be related to which portions of the gland are involved by the tumor (Nagano, 1990; Warshaw et al., 1988; Crist et al., 1987).

Serologic markers, as one of diagnostic tools for cancer of the pancreas, have been studied. Reviewing Korean literatures (Choi et al., 1990; Kwon et al., 1989; Park et al., 1987), we found highest positivity of CEA to be 73%, of CA 19-9 87%, and of CA 125 56%. Combinations of these markers increased the positivity; CA 19-9/CEA 93%, CA 125/CEA 87%, and CA 19-9/CA 125 100%. Sakamoto et al. (1987) also found that the combination of CA 19-9/CA 125 was most sensitive in diagnosing cancer of the pancreas. But Nagano (1990) insisted that diagnostic serologic markers were unreliable in the early stage of the disease. The sensitivity of radiologic diagnostic modalities according to our literature review was as follow: ultrasonography 54% (range: 18~69%), computed tomography (CT) 85% (range: 75 ~ 92%), endoscopic retrograde cholangiopancreatography (ERCP) 71% (range: 52 ~ 92%), percutaneous transhepatic cholangiography 72% (range: 60 ~ 94%). CT scan has been the most reliable test. Nagano (1990) reported that combined CT scan and ERCP were employed to increase diagnostic accuracy, especially in detection for early T<sub>1</sub> lesion. Recently, endoscopic ultrasonography in addition to ERCP has been attempted in several institutions for a diagnosis (Go et al., 1981; Nagano, 1990).

The resection rate for cancer of the head of the pancreas was reported as 5-25% (Connolly et al., 1987; Singh et al., 1990; Trede et al., 1990; Warshaw et al., 1988), and that of other periampullary tumors as 60-88% (Hayes et al., 1987; Trede et al., 1990; Warshaw et al., 1990). Table 5 lists the resection rates of various locations of tumor which reported in the Korean literature. Although there were great variabilities from one series to the other, average resection

rates were 21% for cancer of the head of the pancreas, 37% for cancer of distal bile duct, 85% for amupllary cancer, and 50% for cancer of the duodenum. The overall resection rate was 36%. The resectability of all periampullary cancers depends on aggressiveness of the surgeon and thoroughness of staging (Warshaw et al., 1988). According to our own series (Kim and Kim, 1992) total pancreatectomy was performed on 6 cases of pancreatic cancer and 1 case of distal bile duct cancer, in which frozen-section showed tumor at the intended points of division of the pancreas, or in which the gland was judged to be too soft and friable for safe anastomosis. Fortner (1981) reported 2-year survival rate for patients who had a regional pancreatectomy was 27%. But this procedure failed to gain popularity because of the extensiveness of the procedure, the considerable morbidity and mortality rates, and the lack of any significant increase in the survival rate. There was only 2 experiences of our own within the reviewed literature. A pyloric preserving resection was initially proposed with the theoretical advantage of a decreased incidence of complications such as delayed gastric emptying or marginal ulceration, which was mostly contributed to the antrectomy of standard pancreatoduodenectomy. Park et al. (1991) reported 10 experiences of pyloric preserving procedure with low incidence of complications. However, recent data have failed to show a significant difference in the incidence of these complications (Braasch et al., 1986; Crist et al., 1987; Grace et al., 1986), and Sharp et al. (1989) pointed out the limitation of lymph node dissection for treatment of pancreatic carcinoma.

The collective review of our 8 hospitals revealed the morbidity rate after pancreatoduodenectomy ranged from 27% to 63% with a mean of 44% and the mortality rate ranged form 7% to 25% with a mean of 12%. Crist et al. (1987) reported the morbidity and mortality rates as 47% and 12.5%, respectively. However, several authors (Braasch et al., 1986; Grace et al., 1986; Trede and Chir, 1985), in the last ten years of their studies, reported much improved results; i.e. morbidity of 30% and mortality around 5%.

In general, the 5-year survival rate for cancer of the head of the pancreas is 5 to 25 percent, which is less favorable than 35 to 70 percent of other periampullary cancer (Braasch et al., 1986; Crist et al., 1987; Grace et al., 1986; Trede and Chir, 1985). It is well known that lymph node metastasis is one of the main factors influencing the prognosis of patients with periampullary cancer. Crist et al. (1987) reported the 5-year survival rate for cancer of the head of the pancreas with negative lymph node metastasis was up to 48%.

Grace et al. (1986) explained that their good survival resulted from relatively high number of negative lymph node metastatic patients. In case of our own (Kim and Kim, 1992), the 5-year survival rate for cancer of the head of the pancreas was 11%, and that of other periampullary cancers which were located at the duodenum, the distal portion of the common bile duct, and the ampulla of Vater were 21%, 18%, and 15%, respectively. Fourteen of 24 patients (58%) with pancreatic head cancer, 16 of 18 (89%) patients with distal bile duct cancer, 8 of 15 patients (53%) with ampullary cancer, and 5 of 8 patients (63%) with duodenal cancer had lymph node involvement. This factor may explain the poor 5-years survival rate observed in our own series. In nonresected group, none survided over 18 months after treatment. We insist the only possibility of cure for these patients is a surgical resection.

Considering the dismal survival rate of the pancreatic cancers after resection, there is a need for better understanding of the factors influencing in prognosis. Nagano (1990) emphasized nodal status (n factor), capsular invasion (s factor), and retropancreatic tissue invasion (rp factor) for an accurate prognosis. He concluded that the extended radical pancreatectomy encompassing retropancreatic tissue and peripancreatic lymphatics were most important to increase the survival rate. Lee et al. (1989) found that, for pancreatic cancer in stages I and II, major determinants of prognosis were tumor size, capsular invasion, and vascular invasion. Excellent results with curative extended radical operation have been reported by Nagano (1990); 41.2% of 5-year survival. Proponents of the radical procedure believe a wide en bloc resection with a microscopically free margin is important to improve the survival (Ishikawa et al., 1988; Trede et al., 1990).

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