

# Recent treatment patterns and survival outcomes in pancreatic cancer according to clinical stage based on single-center large-cohort data

Doo-ho Lee, Jin-Young Jang, Jae Seung Kang, Jae Ri Kim, Youngmin Han, Eunjung Kim, Wooil Kwon, and Sun-Whe Kim

Department of Surgery and Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea

**Backgrounds/Aims:** We performed a retrospective, single-center cohort study to evaluate the impact of various treatment modalities and recent changes in treatment modalities, including the increased application of chemotherapy, on survival in patients with pancreatic cancer. **Methods:** All patients with pancreatic cancer who were diagnosed and treated at Seoul National University Hospital between January 2007 and December 2014 were registered in a prospective clinical database and included in this retrospective study. All patients' radiologic imaging diagnoses were re-reviewed according to the National Cancer Center Network guidelines. The patients were divided into four groups according to their clinical stage, and each clinical stage group was further divided into four groups according to treatment modality. **Results:** Overall, 475 (28.9%) patients had resectable pancreatic cancer, 129 (7.8%) patients borderline resectable pancreatic cancer, 384 (23.3%) patients locally advanced pancreatic cancer, and 658 (40.0%) patients metastatic pancreatic cancer. Among the patients with borderline resectable pancreatic cancer, the median survival was significantly longer in the neoadjuvant therapy (NAT)+surgery groups (24 months) than the surgery without NAT (16 months) group ( $p=0.049$ ). A multivariate survival analysis revealed that compared with the surgery group, the 5-year mortality risk was decreased by 35% in the NAT+surgery group (24 vs. 20 months,  $p=0.045$ ). **Conclusions:** This retrospective cohort study showed that the rates of resectable and surgically treatable pancreatic cancer were 29.1% and 32.2%, which are higher than those reported previously, and aggressive NAT for select advanced-stage patients could lead to better survival outcomes. (*Ann Hepatobiliary Pancreat Surg* 2018;22:386-396)

**Key Words:** Neoadjuvant therapy; Survival rate; Pancreas neoplasms

## INTRODUCTION

Despite improvements in perioperative outcomes, pancreatic cancer has a poor prognosis, with a 5-year survival rate of only 8%-10% among patients.<sup>1,2</sup> Most patients are diagnosed in the advanced stages, and effective systemic therapies are lacking. According to the annual report of cancer statistics in Korea, the 5-year survival rate of overall pancreatic cancer patients was 10% in 2014, with the higher rate due to increased early diagnoses following the introduction of a routine cancer screening program for all citizens conducted by the National Health Insurance, and increased detection of less aggressive pancreatic malign-

ancies.<sup>3</sup> In addition, effective systemic treatments including neoadjuvant therapies (NATs) have been introduced in an attempt to overcome the limitations of prior treatments and to improve patient outcomes, especially in patients with borderline resectable, locally advanced, and even metastatic pancreatic cancer; therefore, the outcomes of pancreatic cancer patients have been improved by additional surgical resection after systemic treatment.<sup>4-6</sup> However, because the definitions of borderline resectable and locally advanced pancreatic cancer differ among institutions, it is impossible to compare survival rates according to clinical stage in pancreatic cancer patients. In addition, the data published by most institutions do not

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**Corresponding author:** Jin-Young Jang

Department of Surgery and Cancer Research Institute, Seoul National University Hospital, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea

Tel: +82-2-2072-2194, Fax: +82-2-741-2194, E-mail: jangjy4@gmail.com

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include patients with metastatic or locally advanced pancreatic cancer.<sup>4,7-9</sup> SEER (Surveillance, Epidemiology, and End Results program, USA) data cover a large number of patients but are limited by the high variation among the involved hospitals and a lack of accurate clinical staging.<sup>10</sup> Furthermore, as there are no recent data on clinical stage based on accurate imaging criteria in overall patients, it is difficult to grasp the actual status of pancreatic cancer treatment in Korea. To date, very few studies have identified trends in the treatment of pancreatic cancers, including locally advanced and metastatic cancers, in a single-center study.

Therefore, the objective of this study was to categorize all patients according to clinical stage using uniform imaging diagnostic criteria and to evaluate the impact of treatment modality on the survival of pancreatic cancer patients included in a large-scale prospective database at Seoul National University Hospital.

## MATERIALS AND METHODS

### Database

We conducted a retrospective cohort study using prospectively recorded information of patients registered in a clinical oncology database at Seoul National University Hospital between January 1, 2007 and December 31, 2014. The study was approved by the Institutional Review Board at Seoul National University (1706-159-863).

### Patients and groups

We included patients who were diagnosed with stage I-IV pancreatic cancer between January 1, 2007 and December 31, 2014 and aged  $\geq 19$  years at diagnosis. The diagnoses were made using computed tomography with a pancreas-specific protocol and/or magnetic resonance imaging, positron emission tomography, endoscopic ultrasonography, with or without cytological or histological confirmation of conventional ductal adenocarcinoma of the pancreas. Patients were excluded if surgery was performed at another hospital or the diagnosis was made outside the index period. The National Comprehensive Cancer Network 2017 guidelines were used for pancreatic cancer staging, based on computed tomography performed at the time of diagnosis (Table 1). The patients were first categorized into four groups according to the clinical stage, as follows: resectable (RPC), borderline resectable (BRPC), locally advanced (LAPC), or metastatic pancreatic cancer (MPC).<sup>4</sup> Patients in each stage group were further categorized according to the treatment modality, as follows: NAT followed by surgery (NAT+surgery group), surgery+adjuvant chemoradiotherapy (surgery group), chemotherapy alone (CTx group), and palliative care (palliative care group). NAT was defined as the first course of chemotherapy, radiation, or concurrent chemoradiotherapy (CCRT) prior to surgery.

**Table 1.** The National Comprehensive Cancer Network definitions for the CT-based staging of pancreatic cancer

#### *Resectable*

Tumor-artery relationship: no radiographic evidence of arterial abutment (celiac, SMA, or hepatic artery)

Tumor-vein relationship: tumor-induced narrowing, if present, is  $\leq 50\%$  of the circumference of the SMV, PV, or SMV-PV confluence

#### *Borderline resectable*

Artery: tumor abutment ( $\leq 180^\circ$  of the circumference) of SMA or celiac artery. Tumor abutment or short segment encasement ( $> 180^\circ$ ) of the common hepatic artery. Tumor abutment  $> 180^\circ$  without involvement of the aorta and amenable to celiac resection (HA-GDA not involved)

Vein: Tumor induced narrowing of  $> 50\%$  of SMV, PV, or SMV-PV, or short segment occlusion of SMV, PV, SMV-PV with suitable PV (above) and SMV (below) to allow for safe vascular reconstruction.

#### *Locally advanced*

Artery: tumor encasement ( $> 180^\circ$  of the circumference) of SMA or celiac artery

Vein (SM-PV confluence): occlusion of SMV, PV, or SMV-PV without suitable vessels above and below the tumor to allow for reconstruction (no distal or proximal target for vascular reconstruction)

Extrapancreatic findings: no evidence of peritoneal, hepatic, extra-abdominal metastases

#### *Metastatic*

Evidence of peritoneal or distant organ metastases

SMA, superior mesenteric artery; SMV, superior mesenteric vein; PV, portal vein; SMV-PV, superior mesenteric-portal vein; HA-GDA, hepatic artery-gastrooduodenal artery

### Data extraction

The primary outcome was survival time, which was defined as the time from the date of diagnosis to the date of death or the last follow-up. The patients' characteristics, date of diagnosis, type of surgery, tumor location, tumor size, serum level of carbohydrate antigen (CA) 19-9 (a tumor marker; normal range <37 U/ml), and pathologic reports were extracted from the medical records.<sup>11</sup> We re-reviewed the images of computed tomography and magnetic resonance examinations performed at the time of diagnosis. The patients were categorized according to clinical stage (according to the National Cancer Center Network 2017 guidelines) and again by treatment modality. The tumor response was defined according to the Response Evaluation Criteria in Solid Tumors using computed tomography performed after NAT, and was categorized as complete response (disappearance of the target lesion), partial response ( $\geq 30\%$  decrease in tumor diameter), stable disease (neither sufficient shrinkage to qualify as partial response nor sufficient increase to qualify as progressive disease), or progressive disease ( $\geq 20\%$  increase in diameter).<sup>12</sup>

The TNM residual tumor classification was recorded in patients who underwent pancreatectomy with curative intent.<sup>13</sup> We used the tumor regression grading system of the College of American Pathologists, which comprises the following four grades according to the extent of residual carcinoma in post-NAT pancreatectomy specimens: grade 0, no viable residual tumor (pathologic complete response); grade 1, marked response (minimal residual cancer with single cells or small groups of cancer cells); grade 2, moderate response (residual cancer outgrown by fibrosis); and grade 3, poor or no response (extensive residual cancer).<sup>14</sup>

### Neoadjuvant chemotherapy and/or radiotherapy

Neoadjuvant chemotherapy regimens included gemcitabine, conventional 5-fluorouracil (5-FU), or FOLFIRINOX. Gemcitabine chemotherapy consisted of 400 mg/m<sup>2</sup> body surface area (BSA) intravenous gemcitabine administered weekly for 6 weeks. Three-dimensional conformal radiotherapy consisted of a total dose of 45 Gy (1.8 Gy daily fraction, 5 fractions per week for 5 weeks) with a boost dose of 9 Gy (1.8 Gy daily fraction, 5 fractions). 5-FU

based CCRT consisted of 20-Gy dose to the tumor given in 10 daily fractions over a 2-week period plus an intravenous bolus of 5-FU (500 mg/m<sup>2</sup> of BSA on each of the first 3 days of radiotherapy and again after a planned break of 2 weeks). FOLPIRINOX consisted of oxaliplatin at a dose of 85 mg/m<sup>2</sup> followed by leucovorin at a dose of 400 mg/m<sup>2</sup> both administered as a 2-hour intravenous infusion with the addition of 180 mg/m<sup>2</sup> irinotecan after 30 minutes given over 90 minutes as an intravenous infusion. This treatment was followed by 5-FU at a dose of 400 mg/m<sup>2</sup> administered as an intravenous bolus followed by a continuous infusion of 2,400 mg/m<sup>2</sup> for a 46-hour period (one cycle) every 2 weeks. The choice of chemotherapy and/or radiotherapy was determined by each patient's general performance and ease of access to the hospital. Dose were reduced depending on the patient's status or when adverse events were noted.

### Adjuvant chemotherapy and/or radiotherapy

Adjuvant chemotherapy and/or radiotherapy was recommended to patients after operation. Adjuvant treatment regimen included gemcitabine, conventional 5-FU, or FOLFIRINOX. Similar to neoadjuvant treatment, the regimen was determined considering each patient's general performance and ease of access to the hospital.

### Statistical analysis

Patient demographics, treatment modalities, and tumor characteristics were compared among the four clinical stages and four treatment groups using analysis of variance or *t* tests for continuous variables and  $\chi^2$  tests for categorical variables. Kaplan-Meier analyses were conducted to compare survival rates among treatment groups according to clinical stage, and log rank tests were used to compare differences in survival. The median survival time was estimated from the Kaplan-Meier curves. Cox proportional hazards models were used to evaluate risk factors affecting survival according to clinical stage. All analyses were performed using PASW software, version 18.0 (SPSS Inc., Chicago, IL, USA). Differences were considered significant at *p*-value < 0.05.

## RESULTS

### Patient characteristics

Overall, 1,646 patients were included in this retrospective study. The patients were divided into four groups according to their clinical stage: RPC (n=475, 28.9%), BRPC (n=129, 7.8%), LAPC (n=384, 23.3%), and MPC (n=658, 40.0%). There were significant differences among the four groups in terms of clinical stage, tumor location, tumor size, and serum CA 19-9 level, but not sex (Table 2). Patients in the RPC group was older than those in the MPC group (64.9 years vs. 63.0 years, respectively,  $p=0.020$ ). The proportions of males and females were similar in all four groups (approximately 60% males). Pancreatic head cancer was dominant in the RPC group compared to the LAPC and MPC groups (Both  $p<0.001$ ). The rate of pancreatic body or tail cancer was greater in the LAPC (47.9%) and MPC (66.6%) than in the RPC (30.5%) and BRPC (20.0%) groups. Tumor size was greater in the BRPC (32.0 mm), LAPC (38.9 mm) and MPC (44.0 mm) groups than in the RPC (26.5 mm) group (All  $p<0.001$ ).

### Treatment groups

The patients in each clinical stage group were further classified according to treatment modality: surgery (n=495, 30.1%), NAT+surgery (n=35, 2.1%), CTx (n=794, 48.2%), and palliative care (n=322, 19.6%). Surgery without NAT was the dominant treatment modality in the RPC group (434/495, 87.6%), NAT+surgery in the BRPC group (28/35, 80.0%), and CTx or palliative care in the LAPC (285/794, 35.9%) and MPC groups (449/794, 56.5%). The surgical procedures performed in the NAT+surgery and surgery groups are summarized in Table 3. Overall, 30 patients (85.7%) in the NAT+surgery group and 428 patients (86.4%) in the surgery group underwent surgical resection with curative intent. There were significant differences between these two groups in terms of the type of surgery ( $p=0.019$ ) and main vessel resection ( $p<0.001$ ), but not the reason for palliative surgery ( $p=0.793$ ). Of 495 patients in surgery group, 353 patients underwent adjuvant treatment after surgical resection and 142 patients did not undergo adjuvant treatment after surgery.

**Table 2.** Baseline characteristics of patients with pancreatic cancer stratified by clinical stage

Variable	RPC (n=475, 28.9%)	BRPC (n=129, 7.8%)	LAPC (n=384, 23.3%)	MPC (n=658, 40.0%)	All patients (n=1646)	p-value		
						RPC vs BRPC	RPC vs LAPC	RPC vs MPC
Age, years	64.9±10.8	63.1±10.3	64.8±9.9	63.0±11.0	64.0±10.7	0.368	0.998	0.020
Sex						0.990	0.560	0.984
Male	288 (60.6)	77 (59.7)	213 (55.5)	412 (62.6)	990 (60.1)			
Female	187 (39.4)	52 (40.3)	171 (44.5)	246 (37.4)	656 (39.9)			
Treatment						0.184	<0.001	<0.001
Surgery	434 (91.4)	45 (34.9)	16 (4.2)	0 (0.0)	495 (30.1)			
NAT+surgery	0 (0.0)	28 (21.7)	4 (1.0)	3 (0.5)	35 (2.1)			
CTx	17 (3.6)	43 (33.3)	285 (74.2)	449 (68.2)	794 (48.2)			
Palliative care	24 (5.1)	13 (10.1)	79 (20.6)	206 (31.3)	322 (19.6)			
Tumor location						0.090	<0.001	<0.001
Head	329 (69.3)	102 (79.1)	195 (50.8)	215 (32.7)	841 (51.1)			
Body or tail	144 (30.3)	27 (20.9)	184 (47.9)	438 (66.6)	793 (48.2)			
Diffuse	2 (0.4)	0 (0.0)	5 (1.3)	5 (0.8)	12 (0.7)			
Tumor size, mm	26.5±10.0	32.0±9.1	38.9±14.0	44.0±17.6	36.8±16.1	<0.001	<0.001	<0.001
Initial CA 19-9						0.984	0.139	0.338
Normal range	124 (26.1)	30 (23.3)	93 (25.5)	117 (19.1)	362 (22.9)			
Elevated	351 (73.9)	99 (76.7)	273 (74.5)	495 (80.9)	1218 (77.1)			

Values are expressed as n (%) or means±standard deviation

RPC, resectable pancreatic cancer; BRPC, borderline resectable pancreatic cancer; LAPC, locally advanced pancreatic cancer; MPC, metastatic pancreatic cancer; NAT, neoadjuvant therapy; CTx, chemotherapy; CA 19-9, carbohydrate antigen 19-9

**Table 3.** Surgical procedures in the NAT plus surgery and Surgery (no NAT) groups

Procedure	NAT+surgery (n=35)	Surgery (n=495)	p-value
Surgery with curative intent	30 (87.5)	428 (86.4)	
Palliative surgery	5 (14.3)	67 (13.5)	
Type of surgery			0.019
PD	11 (31.4)	109 (22.0)	
PPPD	8 (22.9)	186 (37.6)	
DP	8 (22.9)*	119 (24.0)	
TP	4 (11.4)	14 (2.8)	
Open-and-close	4 (11.4)	29 (5.9)	
Palliative bypass	0	38 (7.7)	
Main vessel resection	8 (22.9)	48 (9.7)	<0.001
Portal vein or superior mesenteric vein	6 (17.1)	48 (9.7)	
Hepatic artery	1 (2.9)	0	
Others	1 (2.9) <sup>†</sup>	0	
Reason for palliative surgery			0.793
Main vessel invasion	3 (8.6)	22 (4.4)	
Metastasis to liver	1 (2.9)	15 (3.0)	
Peritoneal seeding	1 (2.9)	28 (5.6)	
Metastasis in the rectal shelf	0	1 (0.2)	
Hemodynamic instability during surgery	0	1 (0.2)	

Values are expressed as n (%)

NAT, neoadjuvant therapy; PD, pancreaticoduodenectomy; PPPD, pylorus-preserving pancreaticoduodenectomy; DP, distal pancreatectomy; TP, total pancreatectomy

\*One patient with pancreatic tail cancer and liver metastasis underwent palliative distal pancreatectomy after NAT due to pancreatico-colonic fistula; <sup>†</sup>One patient with pancreatic head cancer underwent PPPD and partial resection of the inferior vena cava and left renal vein

### Median survival time according to clinical stage

We analyzed the median survival time of the patients according to clinical stage and treatment modality (Table 4). Kaplan-Meier plots for survival according to clinical stage are presented in Fig. 1. In the RPC patients, the median survival time in the surgery group (22 months) was significantly longer than those in the CTx (8 months,  $p < 0.001$ ) and palliative care (11 months,  $p < 0.001$ ) groups. In the BRPC patients, the median survival time in the surgery group (16 months) was significantly different from those in the NAT+surgery (24 months,  $p = 0.049$ ) and palliative care group (7 months,  $p < 0.001$ ) but was not significantly longer than that in the CTx group (12 months,  $p = 0.091$ ). Similarly, in LAPC patients, the median survival time was not significantly different between the surgery and CTx groups (10 and 13 months, respectively,  $p = 0.142$ ). In the MPC patients, the median survival time in the CTx group (7 months) was not significantly different from that in the NAT+surgery group (12 months,  $p = 0.138$ ) but was longer than that in the pal-

liative care group (3 months,  $p < 0.001$ ). In RPC and BRPC groups, the median survival time in the surgery with adjuvant therapy group (25 and 17 months, respectively) was significantly different from those in the surgery without adjuvant therapy (15 and 8 months, respectively, both  $p < 0.001$ ).

### Pathologic profiles and types of NAT

The stage of pancreatic cancer in the 35 patients who received NAT+surgery was borderline resectable in 24, locally advanced in 4 (11.4%), and metastatic in 3 (8.6%). Two patients had single liver metastasis, and one had para-aortic lymph node metastasis; these three patients showed improvements following NAT and then underwent surgical resection. Twenty patients (57.2%) underwent concurrent chemoradiotherapy and 15 patients (42.8%) underwent CTx only. The CTx regimens were gemcitabine in 24 patients (68.6%), FOLFIRINOX (a combination of 5-fluorouracil, oxaliplatin, irinotecan, and leucovorin) in 5 patients (14.3%), gemcitabine plus erlotinib in 4 patients (11.4%), and 5-fluorouracil plus cisplatin

**Table 4.** Median survival of patients with pancreatic cancer

Stage and treatment	n (%)	2-year/5-year (%)	MST (months)	95% CI	p-value
<b>All stages</b>					
Surgery	495 (30.1)	44.6/18.5	20.0	17.3-22.7	Reference
Surgery with adjuvant therapy	353 (21.4)	48.1/20.2	23.0		
Surgery without adjuvant therapy	142 (8.7)	35.9/11.2	13.0		
NAT+surgery	35 (2.1)	42.2/13.8	24.0	20.8-27.2	0.985
CTx	794 (48.2)	9.8/0.7	9.0	8.3-9.6	<0.001
Palliative care	322 (19.6)	0.0/0.0	4.0	3.5-4.5	<0.001
All patients	1646 (100.0)	19.4/6.6	10.0	9.4-10.6	
<b>RPC</b>					
Surgery	434 (91.4)	47.2/19.6	22.0	19.1-24.9	Reference
Surgery with adjuvant therapy	315 (66.3)	50.2/19.9	25.0		
Surgery without adjuvant therapy	119 (25.1)	39.5/12.9	15.0		
NAT+surgery	0 (0.0)	-	-	-	-
CTx	17 (3.6)	0.0/0.0	8.0	5.1-10.8	<0.001
Palliative care	24 (5.1)	0.0/0.0	11.0	6.5-15.4	<0.001
All patients	475 (100.0)	43.9/18.2	20.0	17.4-22.5	
<b>BRPC</b>					
Surgery	45 (34.9)	29.3/16.0	16.0	10.5-21.5	Reference
Surgery with adjuvant therapy	29 (22.4)	33.7/23.1	17.0		
Surgery without adjuvant therapy	16 (12.5)	22.5/0.0	8.0		
NAT+surgery	28 (21.7)	45.7/17.9	24.0	20.9-27.0	0.049
CTx	43 (33.3)	14.0/0.0	12.0	10.2-13.7	0.091
Palliative care	13 (10.1)	0.0/0.0	7.0	3.8-10.1	<0.001
All patients	129 (100.0)	24.1/9.3	13.0	9.4-16.5	
<b>LAPC</b>					
Surgery	16 (4.2)	15.0/0.0	10.0	6.0-13.9	Reference
Surgery with adjuvant therapy	9 (2.3)	11.1/0.0	10.0		
Surgery without adjuvant therapy	7 (1.9)	0.0/0.0	11.0		
NAT+surgery	4 (1.0)	25.0/0.0	19.0	10.2-27.8	0.186
CTx	285 (74.2)	14.8/0.0	13.0	11.8-14.1	0.142
Palliative care	79 (20.6)	1.4/0.0	6.0	4.3-7.6	0.025
All patients	384 (100.0)	12.2/0.0	11.0	9.9-12.0	
<b>MPC</b>					
Surgery	0 (0.0)	-	-	-	-
NAT+surgery	3 (0.5)	0.0/0.0	12.0	7.2-16.8	0.138
CTx	449 (68.2)	4.6/0.8	7.0	6.2-7.7	Reference
Palliative care	206 (31.3)	0.0/0.0	3.0	2.5-3.4	<0.001
All patients	658 (100.0)	3.3/0.5	5.0	4.5-5.5	

MST, median survival time; CI, confidence interval; NAT, neoadjuvant therapy; CTx, chemotherapy; RPC, resectable pancreatic cancer; BRPC, borderline resectable pancreatic cancer; LAPC, locally advanced pancreatic cancer; MPC, metastatic pancreatic cancer

in 2 patients (5.7%). The tumor response after NAT was classified as partial response in 11 patients (31.4%), stable disease in 20 patients (57.2%), and progressive disease in 4 patients (11.4%). The CA 19-9 level after NAT was normalized in 15 patients (42.9%), stable in 16 patients (45.7%), and elevated in 4 patients (11.4%).

In the NAT+surgery and surgery groups in particular, there was no difference in terms of TNM residual tumor

classification, which was classified as R0 in 26 patients (86.7%) in the NAT+surgery group and 362 patients (84.6%) in the surgery group. However, there were significant differences in terms of the pathologic T stage ( $p < 0.001$ ), pathologic N stage ( $p=0.016$ ), and AJCC pathologic stage ( $p=0.004$ ) between these two groups. The mean number of lymph nodes removed was 15.42 in the NAT+surgery group and 17.32 in the surgery group

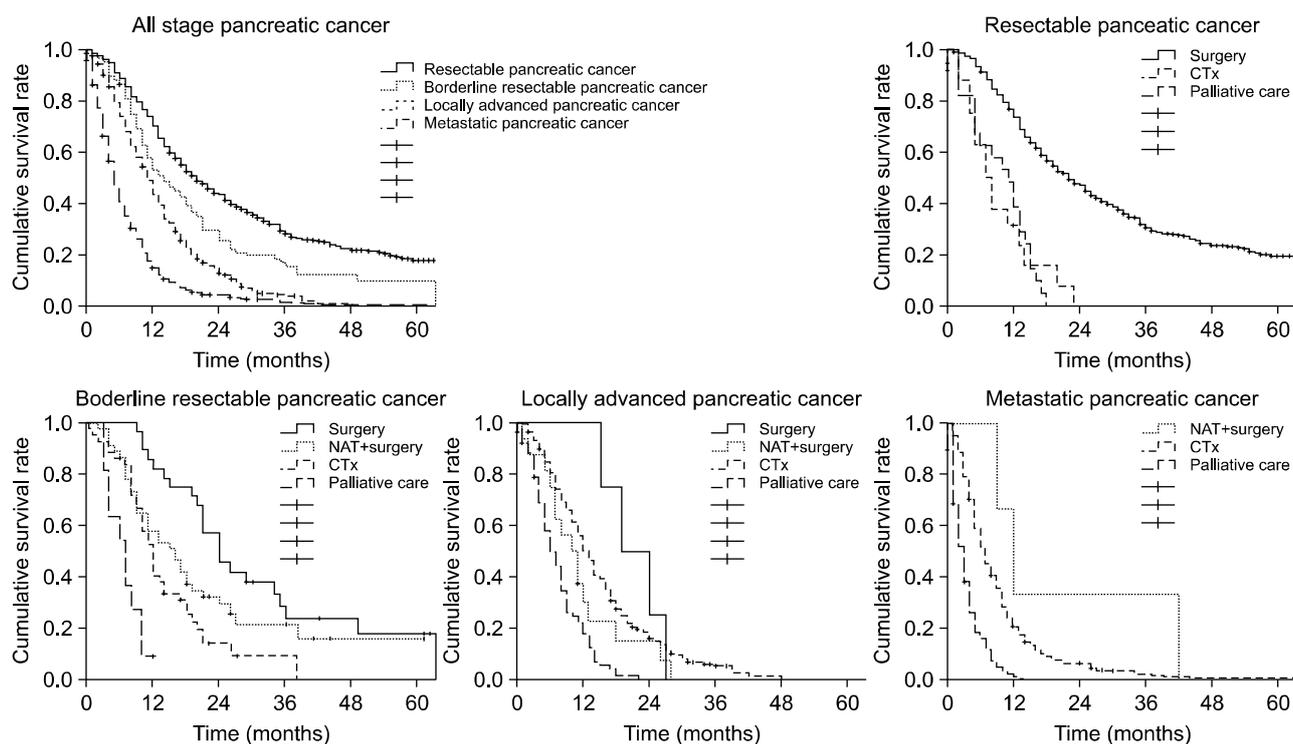


Fig. 1. Overall survival according to clinical stage and treatment.

( $p=0.387$ ). The mean number of metastatic lymph nodes was 0.71 in the NAT+surgery group and 1.87 in the surgery group ( $p<0.001$ ).

#### Prognostic factors for survival according to clinical stage

Table 5 lists the results of the Cox proportional hazards regression analyses. The NAT+surgery group conferred a 35% lower hazard of mortality compared with the surgery group (hazard ratio [HR]=0.65,  $p=0.045$ ). In contrast, the CTx (HR=1.35,  $p=0.032$ ) and palliative care (HR=3.95,  $p<0.001$ ) groups were associated with greater risk compared with the surgery group. The risk of mortality was greater in patients aged 71-80 years (HR=1.39,  $p<0.001$ ) or 81-100 years (HR=1.51,  $p=0.002$ ) at diagnosis than in patients aged 18-60 years at diagnosis. The risk of mortality was lower in females than in males (HR=0.89,  $p=0.035$ ) and was higher in patients with elevated CA 19-9 levels than in patients with normal CA 19-9 levels (HR=1.39,  $p<0.001$ ). Main vessel invasion, regional lymph node metastasis at the time of diagnosis, and tumor location showed no significant effects on survival rate.

Among the RPC patients, compared with the surgery group, regional lymph node metastasis (HR=1.42,  $p=$

0.004) and an elevated initial CA 19-9 level (HR=2.09,  $p<0.001$ ) were associated with higher risk in terms of survival. In BRPC patients, compared with the surgery group, there were no significant differences in risk in the NAT+surgery or CTx group but a higher risk in the palliative care group (HR=3.08,  $p<0.001$ ). In LAPC patients, the NAT+surgery, CTx, and palliative care groups did not show significant differences in risk compared with the surgery group. In MPC patients, the NAT+surgery group did not show a significant difference in risk compared with CTx group, but the palliative care (HR=3.23,  $p<0.001$ ) group was associated with a higher risk compared with the CTx group.

## DISCUSSION

This retrospective cohort study aimed to categorize patients according to clinical stage using uniform imaging diagnostic criteria based on high-resolution imaging and to evaluate the impact of treatment modalities on the survival of pancreatic cancer patients. Of the 1,646 total patients, 475 (28.9%) were diagnosed with RPC, 129 (7.8%) with BRPC, 384 (23.3%) with LAPC, and 658 (40.0%) with MPC. There were 530 (32.2%) surgically treatable

**Table 5.** Multivariate analysis of prognostic factors for survival of patients with pancreatic cancer

Variable	n (%)	MST (months)	Univariate analysis			Multivariate analysis		
			HR	95% CI	p-value	HR	95% CI	p-value
<b>Treatment</b>								
Surgery	495 (30.1)	20.0	Reference			Reference		
NAT+surgery	35 (2.1)	24.0	1.01	0.69-0.48	0.941	0.65	0.43-0.99	0.045
CTx	794 (48.2)	9.0	2.86	2.50-3.26	<0.001	1.35	1.03-1.79	0.032
Palliative care	322 (19.6)	4.0	7.75	6.54-9.17	<0.001	3.95	2.97-5.25	<0.001
<b>Clinical stage</b>								
RPC	475 (29.1)	20.0	Reference			Reference		
BRPC	129 (7.6)	13.0	1.55	1.24-1.94	<0.001	1.44	1.06-1.96	0.018
LAPC	384 (23.3)	11.0	2.26	1.94-2.64	<0.001	1.73	1.27-2.38	0.001
MPC	658 (40.0)	5.0	4.51	3.92-5.18	<0.001	3.34	2.51-4.45	<0.001
<b>Age, years</b>								
18-60	585 (35.5)	12.0	Reference			Reference		
61-70	584 (35.5)	11.0	1.01	0.88-1.13	0.936	1.07	0.94-1.21	0.316
71-80	401 (24.4)	8.0	1.29	1.13-1.48	<0.001	1.39	1.21-1.60	<0.001
81-100	76 (4.6)	6.0	1.81	1.41-2.33	<0.001	1.51	1.16-1.97	0.002
<b>Sex</b>								
Male	990 (60.1)	10.0	Reference			Reference		
Female	656 (39.9)	10.0	1.11	0.99-1.23	0.051	0.89	0.80-0.99	0.035
<b>Tumor location</b>								
Head	841 (51.1)	11.0	Reference					
Body or Tail	793 (48.2)	9.0	1.29	1.16-1.43	<0.001			
Diffuse	12 (0.7)	9.0	1.32	0.72-2.39	0.358			
<b>Main vessel invasion</b>								
None	795 (48.3)	11.0	Reference			Reference		
Artery	319 (19.4)	10.0	1.47	1.27-1.69	<0.001	0.84	0.71-1.01	0.055
Vein	193 (11.7)	10.0	1.20	1.01-1.42	0.030	1.18	0.98-1.44	0.088
Artery and vein	339 (20.6)	8.0	1.55	1.35-1.77	<0.001	1.06	0.89-1.27	0.527
<b>Regional lymph node metastasis</b>								
None	953 (57.9)	12.0	Reference					
Metastasis	693 (42.1)	8.0	1.09	0.97-1.21	0.152			
<b>Initial CA 19-9</b>								
Normal range	362 (22.9)	13.0	Reference			Reference		
Elevated	1218 (77.1)	10.0	1.47	1.28-1.67	<0.001	1.39	1.22-1.59	<0.001

MST, median survival time; HR, relative hazard ratio; CI, confidence interval; NAT, neoadjuvant therapy; CTx, chemotherapy; RPC, resectable pancreatic cancer; BRPC, borderline resectable pancreatic cancer; LAPC, locally advanced pancreatic cancer; MPC, metastatic pancreatic cancer; CA 19-9, carbohydrate antigen 19-9

pancreatic cancer patients, which is more than reported previously, and 35 (2.1%) patients underwent surgery after NAT.<sup>3</sup> Of the 475 RPC patients, 438 (91.4%) underwent surgery, and R0 resection was achieved in 388 (81.0%).

According to the annually reported summary staging of pancreatic cancer by the Korea National Cancer Registry, there were 2,576 (10.9%) localized, 7,492 (31.8%) regional, and 10,735 (45.6%) distant cases of metastasis, and 2,715 (11.7%) unknown cases in 2014, 5-year prevalence (5,948 were newly diagnosed with pancreatic cancer in

2014; however, this report did not include the incidence of pancreatic cancer according to clinical stage).<sup>3</sup> Summary staging is the most basic method of categorizing how far a cancer has spread from its point of origin, but it does not reflect the clinical stage, which has been essential for determining resectability the suitability for NAT.<sup>15</sup>

A large retrospective cohort study using the 2003-2011 dataset from the National Cancer Database based in the U.S. reported that of 18,332 pancreatic cancer patients, 7,095 (38.7%) were clinical stage I, 9,760 (53.2%) clinical stage II, and 1,477 (53.2%) clinical stage III.<sup>10</sup> However,

that study has several limitations in that patients with clinical stage IV or unknown stage pancreatic cancer or those who did not undergo surgical resection were excluded. In addition, BRPC and LAPC were not distinguished in clinical stage III patients, and the multicenter data were heterogeneous because of patient collection from over 1500 facilities. Most of the classification systems focus on anatomical findings and there is still debate whether these are a solid classification, due to a lack of prospective studies in this regard. Guidelines that also incorporate biological features are needed to help predict early recurrence, even in resectable pancreatic cancer, and to support indications for NAT in select patients with resectable pancreatic cancer.<sup>7,9,16,17</sup>

Another recent meta-analysis showed that of 4,394 (from 111 studies) pancreatic cancer patients, 46.9% who were initially staged as unresectable underwent surgical exploration.<sup>18</sup> Of these patients, 69.9% were resected successfully, leading to a resectability rate after NAT of 33.2% (comparable R0 resection rate to that in the initially resectable group), suggesting that patients with pancreatic cancer who can undergo surgical resection are increasing more than one out of five in the past by applying NAT at an advanced stage.<sup>18</sup> Furthermore, an increase in the early diagnosis rate, detection of various low-malignancy-risk pancreatic cancers, and development of surgical techniques have accelerated the surgical resection rate of pancreatic cancer.<sup>3,10</sup>

Katz et al. conducted a prospective, multicenter, single-arm pilot study in 2013 of 22 patients with borderline resectable pancreatic cancer who were treated with a modified FOLFIRINOX regimen and chemoradiotherapy as NAT. The median survival was 21.7 months, and R0 resection was achieved in 20 (93%) patients.<sup>19</sup> In 2014, Tzeng et al. published the results of a retrospective study, in which 84 patients received gemcitabine or 5-fluorouracil-based NAT followed by surgery, and 57 patients underwent NAT without surgery. The R0 resection rate was 92% in the NAT+surgery group. The median survival was 30.9 months in the NAT+surgery group versus 12 months in the NAT only group.<sup>20</sup> In our study, among the patients with BRPC, the median survival was 24 months in the NAT+surgery group, 16 months in the surgery group, 12 months in the CTx group, and 7 months in the palliative care group. Only 32 (6.2%) patients with BRPC or LAPC

underwent surgery after NAT, and 61 (12.0%) underwent surgery without NAT. Few studies have assessed the overall median survival in patients with pancreatic cancer stratified by treatment modality and disease stage in the same period of time.

Among patients who underwent curative resection, the rate of R0 resection was comparable between the NAT+surgery and surgery groups, even though the proportion of patients with advanced cancer was greater in the former group. We recognize that the NAT+surgery group tended to undergo more aggressive surgical procedures than did the surgery group; for example, the main vessel resection rate was greater in the former group (22.9% vs. 9.7%;  $p < 0.001$ ). Since the dense stroma associated with pancreatic cancer may result in little change on computed tomographic imaging, despite an excellent cellular response, there may be some discrepancy between the Response Evaluation Criteria in Solid Tumors criteria and tumor regression grade; hence, adjuvant surgery may be necessary to identify a pathological response.<sup>21</sup>

Tumor response after neoadjuvant treatment were assessed radiologically with pancreatobiliary protocol CT and were categorized according to the new response evaluation criteria in RECIST guidelines in this study. Also, serum concentrations of CA 19-9 were measured at the first visit to the hospital, after neoadjuvant treatment and after surgery. Kim et al. reported a retrospective study in 2017 of 40 BRPC patients who were treated with NAT followed by resection that the RECIST criteria and reduced serum CA 19-9 concentration were associated with biological response.<sup>22</sup> Several recent studies were conducted that Positron Emission Tomography/Computer tomography (PET/CT) could increase the chance of detecting patients with progressive pancreatic cancer after neoadjuvant therapy compared to the conventional anatomical-based assessment of RECIST criteria.<sup>23,24</sup>

We also conducted multivariate analysis using the Cox proportional hazards model to determine prognostic factors for survival in patients with pancreatic cancer. The results showed surgery after NAT compared with surgery or CTx alone, female sex, resectable stage, a CA 19-9 level within the normal range at diagnosis, and tumor location in the pancreatic body or tail to be prognostic factors for improved survival in patients with pancreatic cancer. Tzeng et al. also reported that serum CA 19-9 is a dynam-

ic preoperative marker of tumor biology and the response to NAT, and provides prognostic information in patients with unresected or resected BRPC.<sup>20</sup> In addition, another study revealed that patients with advanced pancreatic cancer whose serum tumor marker levels had normalized after NAT may be appropriate candidates for tumor resection.<sup>25</sup>

Some strengths and limitations of this study also warrant discussion. First, because this was a retrospective analysis of patients treated at a single institution, the results are subject to the biases and limitations inherent to retrospective studies. Nevertheless, this is one of the largest reported cohorts of patients with resectable, borderline resectable, locally advanced, or metastatic pancreatic cancer in which the cancer was staged using objective radiographic criteria and classified using consensus guidelines. Second, we divided the patients into four groups based on their treatment modalities. Unfortunately, the numbers of patients varied among the groups, with some groups being too small for detailed analyses. As a result of ethical issues and difficulty in recruiting patients, no randomized clinical trials of prior surgery compared with NAT have been performed. Nevertheless, several phase I/II trials and on-going phase III clinical trials, such as NEOPAC (NCT01521702) and Prep-02/JSAP-05 (UMIN-No. 000009634) are underway and will hopefully yield further insight into the benefits of NAT.<sup>19,26-28</sup> Third, this study included heterogeneous regimens of NAT, which showed different oncologic outcomes.

In conclusion, based on the results of this retrospective, single-center, large cohort study, categorizing all pancreatic cancer patients according to clinical stage using uniform imaging diagnostic criteria with high-resolution images, the rates of resectable and surgically treatable pancreatic cancer were 29.1% and 32.2%, which are higher than those reported previously. In the RPC group, 434 (91.4%) patients underwent surgery, and R0 resection was achieved in 388 (81.0%). Although our findings support the use of NAT in eligible patients with borderline resectable pancreatic cancer, the survival rate of advanced-stage patients is still low; thus, more effective systemic therapies are required. In addition, further studies are needed to evaluate the effects of specific NAT regimens and to update consensus guidelines with biological features.

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