A Prospective Randomized Controlled Study Comparing Outcomes of Standard Resection and Extended Resection, Including Dissection of the Nerve Plexus and Various Lymph Nodes, in Patients With Pancreatic Head Cancer

Jin-Young Jang, MD, PhD, Mee Joo Kang, MD, PhD,* Jin Seok Heo, MD, PhD,† Seong Ho Choi, MD, PhD,† Dong Wook Choi, MD, PhD,† Sang Jae Park, MD, PhD,‡ Sung-Sik Han, MD, PhD,‡ Dong Sup Yoon, MD, PhD,§ Hee Chul Yu, MD, PhD,¶ Koo Jeong Kang, MD, PhD,|| Sang Geol Kim, MD, PhD,** and Sun-Whe Kim, MD, PhD, FACS**

Objective: To prospectively evaluate the survival benefit of dissection of the nerve plexus and lymphadenectomy in patients with pancreatic head cancer.

Background: Despite randomized controlled trials on the extent of surgery in pancreatic cancer, attempts have been made to perform more extended resections.

Methods: A total of 244 patients were enrolled; of these, 200 were randomized to undergo standard resection or extended resection, with the latter including the dissection of additional lymph nodes and the right half of the nerve plexus around the superior mesenteric artery and celiac axis. We evaluated 167 patients from 7 centers who fulfilled all of the required criteria.

Result: Operation time was longer and estimated blood loss was higher in the extended resection group than in the standard resection group, but the R0 resection rate was comparable. The mean number of lymph nodes retrieved per patient was higher in the extended resection group than in the standard resection group (33.7 vs 17.3; $P < 0.001$). The morbidity rate was slightly higher in the extended resection group than in the standard resection group. Two patients in the extended resection group died in hospital. Median survival after R0 resection was similar in the extended resection and standard resection groups (18.0 vs 19.0 months; $P = 0.239$) regardless of lymph node metastasis. Adjuvant chemoradiation had a positive impact on overall survival.

Conclusions: This study suggests that extended lymphadenectomy with dissection of the nerve plexus does not provide a significant survival benefit compared with standard resection in pancreatic head cancer. Standard resection can be performed safely and efficiently, without negatively affecting oncologic efficacy or long-term survival, when compared with extended pancreaticoduodenal resection. (NCT00679913)?

Keywords: cancer, lymph node, nerve, pancreas, survival analysis

(*Ann Surg* 2013;00:1–9)

From the *Department of Surgery, Seoul National University College of Medicine, Seoul; †Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul; ‡Center for Liver Cancer, National Cancer Center, Gyeonggido; §Pancreatobiliary Cancer Clinic, Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul; ¶Department of Surgery, Chonbuk National University Medical School, Jeonbuk; ||Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, Keimyung University Dongsan Medical Center, Daegu; and **Department of Surgery, Kyungpook National University College of Medicine, Daegu.

Disclosure: Supported by the National R&D Program for Cancer Control, Ministry of Health & Welfare, Republic of Korea (grant nos. 0820030 and 1120310). The authors declare no conflicts of interest.

The study sponsor had no involvement in trial design, collection, analysis, interpretation of data, or writing this report. The corresponding author had full access to all data and had final responsibility for the decision to submit the report for publication.

Reprints: Sun-Whe Kim, MD, PhD, FACS, Department of Surgery and Cancer Research Institute, Seoul National University College of Medicine, 28 Yongon-dong, Chongno-gu, Seoul 110-744, South Korea. E-mail: sunkim@plaza.snu.ac.kr.

ISSN: 0003-4932/13/00000-0001
DOI: 10.1097/SLA.0000000000000384

Pancreatic cancer remains one of the most aggressive and lethal malignancies worldwide, and it is the fourth leading cause of cancer-related deaths in Western countries.[1] Furthermore, it is an important cancer type in Asian countries, where its incidence and lethality have been steadily increasing.[2,3] Despite recent improvements in treatment modalities, pancreatic cancer remains a devastating disease for which there is no definitive treatment except surgical resection. However, at initial diagnosis of the disease, only 15% to 25% of patients with pancreatic cancer are eligible for curative resection.[4,5] Efforts have been made to enhance resectability and survival using aggressive extended resection, including extended lymphadenectomy and dissection of the nerve plexus around major vessels.[6–8]

Randomized controlled studies have found that despite its theoretical advantages, extended pancreatectomy does not have survival advantages compared with standard pancreatectomy.[9–16] However, previous randomized controlled trials (RCTs) have had limitations such as small numbers of patients, the lack of an objectively shown operating field, the absence of a statistical determination of the required number of patients, the inclusion of patients with nonpancreatic ductal adenocarcinoma, and different extents of clearance of retroperitoneal tissue/nerve plexus and lymph nodes.

Because many pancreatic surgeons regard extended pancreatectomy to be better than standard pancreatectomy, additional well-designed RCTs are needed, with larger sample sizes and standardized surgical methods of operation, focusing on the dissection of the nerve plexus and lymph nodes. We therefore compared standard with extended pancreatectomy, including lymphadenectomy with dissection of the nerve plexus, in the resection of ductal adenocarcinomas at the head of the pancreas.

MATERIALS AND METHODS

Study Design

This randomized, controlled, single-blind (subject), parallel-group trial compared standard versus extended pancreatoduodenectomy for pancreatic ductal adenocarcinoma. The study complied with the Declaration of Helsinki and was approved and overseen by the institutional review board of each participating hospital. This study has been registered at ClinicalTrials.gov (no. NCT00679913).

Inclusion and Exclusion Criteria

Patients were included if they (1) were 20 to 85 years of age; (2) had no history of cancer including pancreatic cancer; (3) had a Karnofsky performance score above 70; (4) had potentially curable ductal adenocarcinoma of the pancreatic head (stage I or II), as shown by preoperative imaging (computed tomography, magnetic resonance imaging, and positron emission tomography); and (4) provided written informed consent. After enrollment, some patients were excluded because of (1) unresectable condition or metastasis found during surgery, (2) surgical rule violation, (3) inadequate case report form, or (4) pathologic diagnosis other than conventional ductal adenocarcinoma.

Participating Hospitals

Initially, 18 hospitals agreed to participate in this study. Patients were ultimately enrolled from 7 tertiary referral hospitals, which submitted case report forms without rule violation. All operations were performed by 17 surgeons specializing in pancreatic surgery.

Randomization and Data Management

After confirming patient eligibility, patients were randomized 1:1 to standard or extended pancreatoduodenectomy, using a Web-based system just before surgery. The allocation sequence was computer generated and randomly stratified by surgeon.

After randomization, all clinical and pathologic data, including operation field photographs, were uploaded and stored in a central database (https://mrcc.snuh.org/). All serious adverse events were submitted to the Clinical Trials Unit, Seoul National University Hospital, Seoul, Korea, and evaluated periodically by an independent data and safety monitoring board blinded to the treatment groups.

Surgical Procedures and Standardization

Pylorus-preserving pancreatoduodenectomy was defined as the standard procedure, although classical pancreatoduodenectomy was allowed, depending on the clinical situation. In standard resection, lymph nodes around the pancreas head (LN 13, 17) and gallbladder (LN 12c) were removed without nerve dissection around the hepatic artery or superior mesenteric artery (SMA). During extended resection, lymph nodes around the common hepatic artery (LN 8), celiac axis (LN 9), peripancreatic area (LN 13, 17), hepatoduodenal ligament (LN 12), SMA (LN 14), and para-aortic area (LN 16) between the celiac axis and the inferior mesenteric artery were dissected. All soft tissues around the hepatoduodenal ligament were completely dissected and skeletonized. The nerve plexus or ganglion on the right side of the celiac axis and SMA was dissected semicircumferentially. Differences in the extent of resection are summarized in Table 1.

The surgical extent of standard and extended resection was determined by the participating surgeons, all of whom performed more than 30 pancreatoduodenectomies per year. This group met 4 times before the start of patient enrollment and adjusted detailed operation techniques. Photographs of surgical fields were taken after resection and uploaded into the central database (https://mrcc.snuh.org/) to verify the optimal extent of surgery in each group (Fig. 1). These photographs were reviewed by the study committee of Seoul National University Hospital.

Adjuvant Treatment After Resection

Chemoradiation and maintenance chemotherapy were recommended for all patients except for those with a T1N0 lesion and no residual tumor, those with poor performance status or organ dysfunction, and those who refused adjuvant treatment. External beam radiation therapy was administered at a total dose of 45 Gy in 25 fractions 5 days per week for 5 weeks, with a tumor bed boost of 5.4 Gy in 3 fractions every other day. 5-Fluorouracil (5-FU) was administered concomitantly during radiotherapy as a radiosensitizer. Maintenance chemotherapy consisted of 6 cycles of 5-FU (375–500 mg/m^2 per day) every 4 weeks or 4 cycles of gemcitabine (1000 mg/m^2) every 3 weeks.

TABLE 1. Summary of Difference of the Extent of Surgical Dissection According to the Study Group

Tissues	Location	Standard Pancreatectomy	Extended Pancreatectomy
Lymph node	Superior pyloric (5)	X	O
	Inferior pyloric (6)	X	O
	Common hepatic artery (8)	X	O
	Celiac axis (9)	X	O
	Hepatoduodenal ligament (12)	Partial (12b, 12c)	O
	12a: proper hepatic artery	X	O
	12p: portal vein	X	O
	12b: bile duct	O	O
	12c: cystic duct	O	O
	12h: hilar area	X	O
	Posterior pancreaticoduodenal (13)	O	O
	SMA (14)	X	O
	14a: origin of SMA	X	O
	14b: right side of SMA	X	O
	14c: anterior SMA at middle colic	X	O
	14d: left side of SMA	X	O
	Aortocaval nodes (16)	X	O
	16a2: celiac to left renal vein	X	O
	16b1: left renal vein to IMA	X	O
	Anterior pancreaticoduodenal (17)	O	O
Soft tissue	Vascular skeletonization	X	O
Nerve plexus	Celiac and SMA plexus	X	O (right side)

O indicates dissected; X, not dissected.

Study Endpoints and Patient Numbers

The primary endpoint of this study was 2-year overall survival (OS) rate. Our trial was powered for superiority of survival data at 2 years according to the operation, assuming that the 2-year survival rate (37%) of patients who underwent extended pancreatectomy was 17% higher than that of the standard group (20%). Enrolling 224 patients would therefore provide 80% power to detect the superiority of a procedure with a 1-sided $\alpha = 0.05$, $\beta = 0.2$, and an expected dropout rate of 30%, as determined by the Freedman formula. During recruitment, we added an additional 20 patients because of the high dropout rate (>30%); this change was accepted by the data controlling center and participating surgeons. The secondary endpoints were 2-year disease-free survival (DFS) rate and 5-year OS rate.

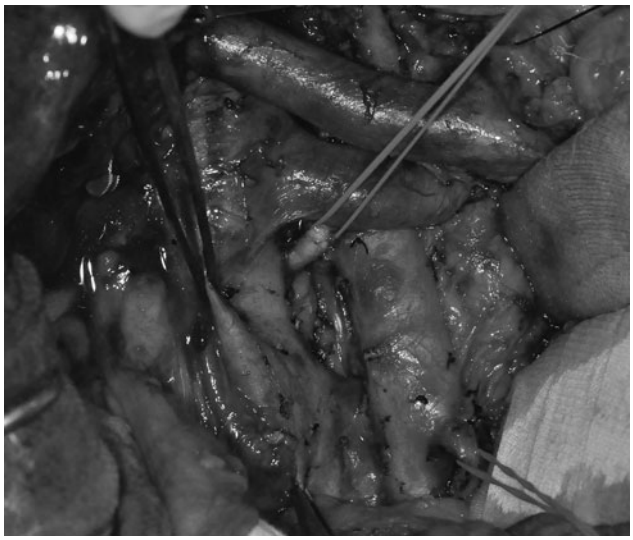

FIGURE 1. Representative case of extended resection.

Statistical Analysis

Patients who underwent the operation to which they were originally allocated and satisfied the criteria for optimal surgery based on photographs uploaded to our data center were evaluated. Results are presented as mean ± standard error of the mean. Nominal data were compared using χ^2 tests and continuous variables using Student *t* tests. Survival outcomes were calculated using the Kaplan-Meier method and compared using the log-rank test. Only variables statistically significant by univariate analysis were included in the multivariate analysis, which was performed using a Cox proportional hazards regression model. All statistical analyses were performed using SPSS, version 18.0 (SPSS Inc, Chicago, IL), with 2-sided *P* values less than 0.05 considered statistically significant.

RESULTS

Patient Enrollment and Demographic Findings

Between June 2006 and November 2009, a total of 244 patients were enrolled in this study, after excluding the 9 patients who refused to participate after initial agreement. After enrollment, 44 patients were excluded because of having unresectable or metastatic tumors, as determined intraoperatively (Fig. 2).

Of the remaining 200 patients, 101 were randomized to standard pancreatectomy and 99 to extended pancreatectomy. Of these, 31 patients were excluded because of (1) having a nonductal adenocarcinoma (n = 8), such as intraductal papillary mucinous carcinoma or adenosquamous carcinoma; (2) having undergone inadequate surgery, as revealed by reviewing the photograph of the surgical field (n = 13); or (3) having inadequate case report forms (n = 10). We therefore evaluated a total of 169 patients, 83 in the standard group and 86 in the extended group. The 2 groups were well matched for mean age, sex distribution, operation type (pylorus-preserving pancreatoduodenectomy or classical pancreatoduodenectomy), resection rate of the portal vein, and follow-up duration (Table 2). Operation time was 64 minutes longer in the extended group than in the standard group, with estimated blood loss greater in the extended group (563.0 ± 56.3 mL) than in the standard group

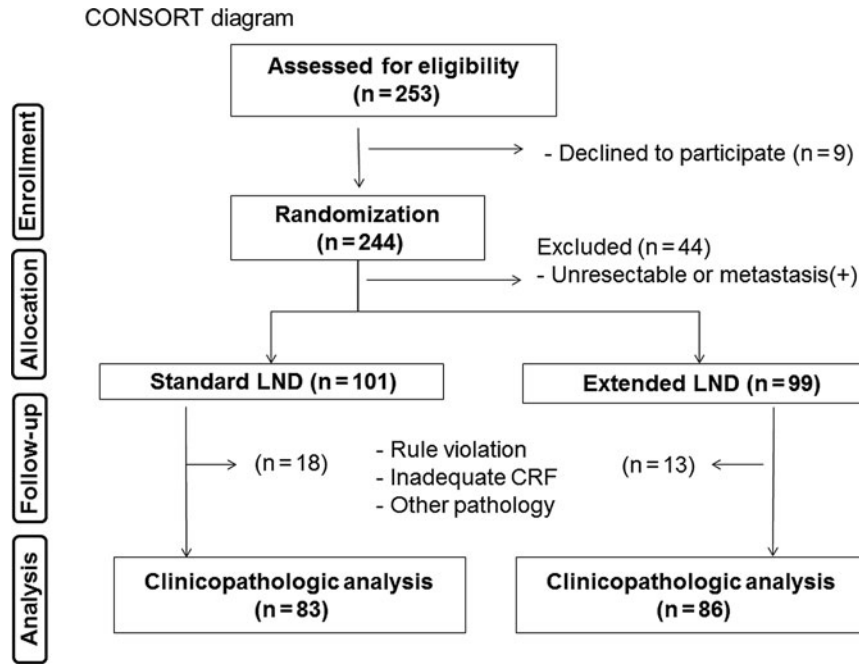

FIGURE 2. Trial profile and patient allocation. CRF indicates case report form; LND, lymph node dissection.

TABLE 2. Demographic and Pathologic Findings Between two Groups

	Standard (n = 83)	Extended (n = 86)	*P*
Clinical variables			
Age, mean ± SD, yr	62.0 ± 8.7	63.4 ± 9.5	0.317
Sex, M:F	1.44:1	1.05:1	0.304
Initial CEA, mean ± SD, ng/ml	4.1 ± 5.3	3.9 ± 5.8	0.754
Initial CA19-9, mean ± SD, U/ml	677.9 ± 1720.7	996.9 ± 3037.7	0.404
OP time, mean ± SEM, min	355.5 ± 12.4	419.6 ± 13.0	0.001
Transfusion (RBC pack) mean ± SD, unit	0.10 ± 0.05	0.25 ± 0.09	0.140
EBL, mean ± SD, mL	372.3 ± 22.4	563.0 ± 56.3	0.002
F/U, median, mo	18.8	16.4	
OP type (PPPD/PD)	62/21	60/26	0.474
Portal vein resection	17 (20.5%)	23 (26.7%)	0.338
Pathologic variables			
R1 resection	12 (14.5%)	8 (9.3%)	0.300
Tumor size, mean ± SD, cm	2.98 ± 0.84	3.12 ± 0.91	0.517
T stage			0.157
T1	8 (9.6%)	3 (3.5%)	
T2	2 (2.4%)	3 (3.5%)	
T3	73 (88.0%)	80 (93.0%)	
LN(+)	57 (68.7%)	57 (66.3%)	0.740
Total retrieved LNs	17.3 ± 10.6	33.7 ± 15.1	<0.001
No. positive LNs	2.2 ± 2.6	2.6 ± 3.5	0.421
LN ratio	0.15 ± 0.19	0.09 ± 0.11	0.012
AJCC stage (6th edition)			0.443
IA	6 (7.2%)	1 (1.2%)	
IB	1 (1.2%)	2 (2.3%)	
IIA	19 (22.9%)	26 (30.2%)	
IIB	57 (68.7%)	57 (66.3%)	

AJCC indicates American Joint Committee on Cancer; CA19-9, cancer antigen 19-9; CEA, carcinoembryonic antigen; EBL, estimated blood loss; F/U, follow-up; LN, lymph node; OP, operation; PD, pancreatoduodenectomy; PPPD, pylorus-preserving pancreatoduodenectomy; RBC, red blood cells.

(372.3 ± 22.4 mL). A total of 122 patients underwent adjuvant treatment after surgical resection.

Pathologic Differences Between the 2 Groups

Table 2 shows the pathologic characteristics of the 2 groups. Although the percentage of patients with positive margins was slightly higher in the standard group (14.5%) than in the extended group (9.3%), the difference was not statistically significant. We also observed no between-group differences in tumor size, T stage, lymph node metastasis rate, and AJCC (American Joint Committee on Cancer) stage. Although the total number of retrieved lymph nodes was significantly lower in the standard group (17.3 ± 10.6) than in the extended group (33.7 ± 15.1) ($P < 0.001$), there was no between-group difference in the number of metastatic lymph nodes. The lymph node ratio was significantly higher in the standard group (0.15 ± 0.19) than in the extended group (0.09 ± 0.11) ($P = 0.012$).

Morbidity and Mortality

Morbidity was slightly higher in the extended group than in the standard resection group, although the difference was not statistically significant (43% vs 32.5%; $P = 0.160$) (Table 3). In addition, there were no significant differences between detailed complication rates and surgical extent. Only 13 of the 86 patients (15.1%) in the extended resection group experienced postoperative diarrhea, indicating that right-sided 180-degree dissection of the nerve plexus had little effect on intestinal motility. None of the patients in the standard group died postoperatively compared with 2 patients in the extended group, 1 died of pneumonia and 1 died of sepsis associated with an SMA pseudoaneurysm.

Survival Data and Recurrence

After excluding the 2 patients who died postoperatively, the median OS of the enrolled patients was 18.7 months and the 2-, 3-, and 5-year OS rates were 39.9%, 25.8%, and 18.8%, respectively. There were no between-group differences in the OS (Fig. 3A) and DFS rates. The 2-year OS rate and the median survival of the standard group were 44.5% and 18.8 months, respectively, slightly higher than those of the extended group, which were 35.7% and 16.5 months, respectively; however, neither of these variables differed significantly between the groups ($P = 0.401$).

The primary endpoint of the study, the 2-year OS rate, was 44.5% (standard error = 5.5%) in the standard group and 35.7% (standard error = 5.2%) in the extended group {difference in 2-year OS rate [95% lower confidence interval (CI): −8.8 to −21.25; 1-sided $P = 0.1225$]}. The lower CI was within the noninferiority margin and thus the result for the 2-year OS rate met the criteria for noninferiority of extended versus standard resection (noninferiority margin: %)

Intention-to-treat analysis, which included all patients randomly assigned to the standard (n = 101) and extended (n = 99) groups, yielded similar results. The 2-year OS rate of the standard and extended groups was 46.1% and 36.4% ($P = 0.285$), respectively, and their median OS values were 19.0 and 18.0 months, respectively.

There were no survival differences between patients who were positive and those who were negative for lymph node metastases (Fig. 3B). The median OS of patients with lymph node metastases who underwent extended surgery was 18 months, similar to 17.4 months of the standard group ($P = 0.566$) (Fig. 3B).

Median OS was longer for the 122 patients who received adjuvant chemoradiation than for the 45 patients who did not (20.8 vs

TABLE 3. Morbidity and Mortality Between two Groups

	Standard (n = 83)	Extended (n = 86)	*P*
Postoperative hospital stay, mean ± SD, d	19.7 ± 9.4	22.8 ± 17.1	0.147
In-hospital death	0	2 (2.3%)*	NS
Complications	27 (32.5%)	37 (43.0%)	0.160
Intra-abdominal bleeding	3	5	
Severe sepsis	0	1	
Pancreatic fistula	8	11	
Intra-abdominal abscess	6	6	
Wound infection	6	11	
Delayed gastric emptying	8	5	
Diarrhea (POD 3 mo)	10	13	
Others	4	5	

*One pneumonia, 1 sepsis with SMA pseudoaneurysm.
NS indicates not significant; POD, postoperative day.

14.0 months). The benefits of adjuvant treatment were especially prominent in the standard group ($P = 0.016$; Fig. 3C).

There were no differences in the pattern and time of recurrence in the standard and extended groups (Table 4). Interestingly, during follow-up, peritoneal seeding was more frequently detected in the extended group than in the standard group (25.9% vs 8.3%; $P = 0.011$).

Prognostic Factors

Univariate analyses showed that poor tumor differentiation, the presence of endovascular tumor emboli in resected specimens, and the absence of postoperative adjuvant therapy were associated with adverse outcomes (Table 5). In a multivariate Cox proportional hazards model, all 3 remained statistically significant: histologic differentiation [hazard ratio (HR), 3.847; 95% CI, 1.296–11.416; $P = 0.015$], endovascular tumor emboli (HR, 1.634; 95% CI, 1.129–2.363; $P = 0.009$), and adjuvant treatment (HR, 1.738; 95% CI, 1.156–2.612; $P = 0.008$).

DISCUSSION

In an effort to overcome the dismal results typically achieved among patients with pancreatic cancer, many surgeons perform more aggressive surgery, including extensive dissection of lymph nodes, the nerve plexus, and combined vascular resection. This approach has been supported by retrospective analyses showing that larger tumor negative margins are associated with longer survival in these patients.[6–8,17–19] RCTs, however, are needed to determine the effect of extended surgery on survival in patients with pancreatic cancer. Surgery on the pancreas entails more delicate procedures than surgery on other gastrointestinal organs, providing several options for pancreatectomy. As a result, different types of operations have been described using the same terminology, making it difficult to compare the results of studies assessing the effect of surgical extent on survival. Despite these obstacles, 4 RCTs have assessed the effect of extended pancreatectomy on survival in patients with pancreatic cancer, but all failed to establish its superiority.[9–16] Consistent with this, the findings of the present study indicated that extended pancreatectomy had no survival benefit.

One trial found no differences in morbidity, mortality, and survival between groups of patients undergoing standard (n = 40) and extended (n = 40) surgical procedures, although results suggested prolonged survival in node-positive patients who underwent extended pancreatectomy.[9] In another trial, 294 patients with periampullary lesions were randomized to undergo standard or extended surgery but only 57% had tumors of pancreatic origin.[10] Mortality and survival rates were comparable, whereas morbidity rates were significantly higher in the extended resection group (29% vs 43%; $P < 0{\cdot}010$). In addition to evaluating patients of mixed pathology, the extended group in that trial underwent different types of surgery, such as distal gastrectomy, which may have affected morbidity rates. These 2 studies in Western countries were criticized for a lack of sufficient retroperitoneal clearance and an absence of dissection of the nerve plexus, both of which have been stressed during surgery for pancreatic cancer.[7,8,19,20]

A report from the Mayo Clinic may be the only Western study accepted by aggressive Japanese surgeons.[11] In that RCT, 40 patients underwent standard surgery and 39 underwent extended surgery. The mean number of resected lymph nodes was greater in the extended group (36 vs 15), but morbidity and mortality rates were comparable, as were 1-, 3-, and 5-year OS rates. Some patients in that trial underwent 360-degree circumferential dissection of the nerve plexus around the celiac axis and SMA, an approach that had the inevitable outcome of intractable diarrhea. Concerns about nutritional and immunologic problems in those patients may have affected their quality of life and survival.

A recent Japanese RCT yielded similar morbidity and survival results as the RCT from the Mayo Clinic.[12] Interestingly, the Japanese trial did not include adjuvant treatments for fear of masking the effects of surgical treatment despite some ethical problems.

The results of these 4 RCTs could not be directly compared because of the lack of uniformity of their protocols for lymphadenectomy and the extent of dissection of the nerve plexus around the celiac axis and SMA. Moreover, 3 of these studies enrolled only 40 or 50 patients per arm and did not calculate the minimum number of patients required under their statistical assumptions. An RCT designed to determine the potential survival benefit of lymphadenectomy would require too many patients to be practical.[13,21]

Besides lymphadenectomy, dissection of the nerve plexus has been considered important in increasing R0 resection and reducing local recurrence.[19,20,22] Both extrapancreatic nerve plexus and perineural invasion have been found prognostic in patients with pancreatic head cancer.[20]

The extent of optimal dissection of the nerve plexus remains unclear. Although total circumferential dissection of the nerve plexus around the celiac axis and SMA was frequently performed, especially in Japan,[23] it may result in intractable diarrhea, malnutrition, and lower quality of life, which may have adverse effects on patient survival after extended pancreatectomy.

Of the 4 RCTs, 2 considered circumferential dissection of the nerve plexus a requisite procedure.[11,12] Both trials reported that this type of extended resection reduced patient quality of life,

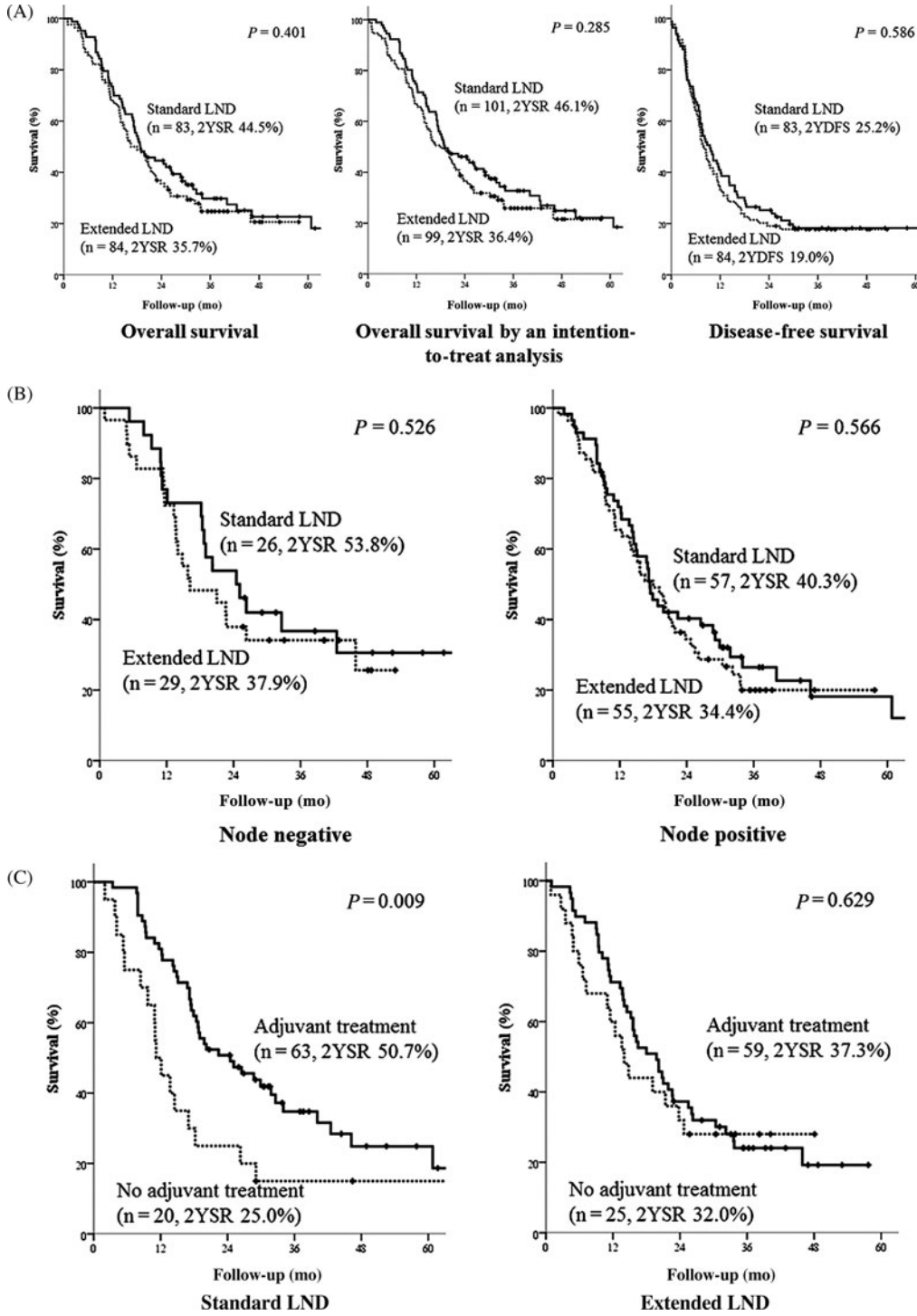

FIGURE 3. A, OS and DFS curves according to the type of surgery. B, Survival curves according to the type of surgery without or with lymph node metastasis. C, Survival curves according to the adjuvant treatment in the standard and extended groups. LND indicates lymph node dissection; 2YDFS, 2-year survival rate; 2YSR, 2-year survival rate.

TABLE 4. Recurrence Pattern According to the Extent of Surgery

	Standard (n = 83)	Extended (n = 86)	*P*
Recurrence	60 (74.1%)	58 (69.0%)	0.493
Locoregional	23/60 (38.3%)	15/58 (25.9%)	0.147
Systemic	53/60 (88.3%)	56/58 (96.6%)	0.182
Liver	37/60 (61.7%)	35/58 (60.3%)	0.882
Peritoneal seeding	5/60 (8.3%)	15/58 (25.9%)	0.011
Lung	8/60 (13.3%)	7/58 (12.1%)	0.838
Para-aortic LN	3/60 (5.0%)	8/58 (13.8%)	0.100
Mesenteric LN	8/60 (13.3%)	5/58 (8.6%)	0.414
Others	1/60 (1.7%)	4/58 (6.9%)	0.341
Time to progression, median (range), mo	7.1 (0.2–37.0)	7.0 (1.1–26.8)	

LN indicates lymph node.

TABLE 5. Prognostic Factors in Univariate Analysis

	n	2YSR, %	*P*
Age, <65/≥65	92/75	46.6/32.0	0.094
Sex, M/F	91/76	43.7/35.5	0.508
Initial CEA, <5.0/≥5.0	135/32	41.4/33.7	0.246
Initial CA19-9, <37.0/≥37.0	47/120	44.7/38.2	0.094
OP type, PD/PPPD	47/120	40.3/38.9	0.943
OP extent, standard/extended	83/84	44.5/35.7	0.401
Portal vein resection, No/Yes	128/39	44.3/25.6	0.053
R state, R0/R1	147/20	42.0/25.0	0.068
T stage, T1/T2/T3	10/5/152	50.0/40.0/38.6	0.655
N stage, N0/N+	55/112	45.3/37.3	0.174
Stage, IA/IB/IIA/IIB	7/3/45/112	42.9/33.3/44.2/37.3	0.576
Histology, WD/MD/PD	7/124/25	42.9/43.3/20.0	0.001
Perineural invasion, −/+	29/138	44.6/38.1	0.398
Endolymphatic invasion, −/+	74/93	41.4/36.4	0.462
Endovascular tumor emboli, −/+	105/62	44.5/28.7	0.005
Adjuvant treatment, −/+	45/122	28.7/43.2	0.032

CA19-9 indicates cancer antigen 19-9; CEA, carcinoembryonic antigen; OP, operation; 2YSR, 2-year survival rate; WD/MD/PD, well, moderately, and poorly differentiated.

primarily due to high rates of postoperative diarrhea with resulting malnutrition. To minimize the adverse effects of total circumferential nerve dissection, right-sided 180-degree dissection of the nerve plexus has been widely used in Japan.[20,23,24] New trials are needed to determine whether adjustment of the extent of nerve dissection can avoid nutritional and functional deterioration.

Another important concern is the standardization or uniformity of surgical procedures performed by surgeons participating in clinical trials, especially multicenter trials. The inspection and objective recording of surgical fields are needed to reduce any intentional or unintentional misgrouping of enrolled patients.

To overcome the limitations of previous RCTs, we designed and performed an RCT that assessed the extent of pancreatectomy for pancreatic ductal adenocarcinoma before the Japanese data were published. Beginning in 2005, quarterly board meetings of the Korean Pancreas Study Club were held to determine the extent of surgery and methods to qualify it. We began enrolling patients in 2006. To maintain the quality of the study and to optimize enrollment, we held board meeting every 4 months.

Although the incidence of R0 resection and the number of retrieved lymph node were higher in the extended group than in the standard group, there were no differences in OS or DFS. Extended surgery was not associated with survival benefits relative to standard surgery in any of our patient subgroups, even in those with lymph node metastases.

Although the number of retrieved lymph nodes was almost 2-fold higher in the extended group than in the standard group, the number of positive lymph nodes was similar and the lymph node ratio of the extended group (0.09 ± 0.11) was lower than that of the standard group (0.15 ± 0.19). In addition to having no survival benefits, the removal of regional lymph nodes was unnecessary.

We also assessed the optimal dissection of the nerve plexus around the celiac axis and SMA. Perineural invasion frequently occurs around major vessels and is prognostic for survival in patients with pancreatic cancer.[7,8,23,25] Although the significance of nerve dissection around the major vessels adjacent to the pancreas head has been emphasized,[23,24] the optimal extent and therapeutic benefits of nerve dissection around the celiac axis and SMA have not yet been clarified.

Previous RCTs did not have uniform criteria for nerve dissection, although 2 trials, one from the Mayo Clinic[11] and the other from Japan,[12] included circumferential dissection of the nerve plexus around the celiac axis and SMA. Those procedures, however, were associated with intractable diarrhea, resulting in chronic malnutrition and functional loss, which may have a negative effect on patient survival. In contrast, we dissected the right half of the nerve plexus,

minimizing these procedure-associated adverse events.[23,24] We found that the rate of postoperative diarrhea at 3 months was similar in the standard (12%) and extended (15%) groups, with none of these patients having severe intractable diarrhea. Although the morbidity and mortality rates were similar in the 2 groups, an SMA aneurysm, an procedure-specific complication, was observed in 2 patients in the extended group. One patient with bleeding from an SMA aneurysm died of related sepsis. Nerve dissection around the major vessels could increase operative risk, indicating the need for caution during these procedures.

Although there was no statistical difference between the 2 groups, hospital stay was 3 days longer in the extended group than in the standard group. Two patients in the extended group died in hospital, and the complication rate was slightly higher in the extended group, which may have been associated with the longer hospital stay. Hospital stay in our study was slightly longer than that in previous studies. Prolonged hospitalization is mainly caused by the low costs of hospitalization in Korea, with national health insurance paying for 95% of hospital fees for cancer patients. Because of these low medical costs, patients are reluctant to be discharged until they fully recover after surgery. According to a study by the Korean government, the average hospital stay after surgery for pancreatic cancer is 30.5 days.

We observed that patients who underwent nerve dissection did not show a survival benefit compared with patients of the standard group. Similarly, the results of the RCTs from the Mayo Clinic and Japan found that dissection of the nerve plexus had no therapeutic benefit regardless of the extent of dissection.

In this study, we did not randomize the patients considering adjuvant chemoradiation. Of our 169 patients, 122 (72.2%) received adjuvant chemoradiation, followed by maintenance chemotherapy. The role of radiation therapy remains somewhat inconclusive, but chemoradiation is a standard, often-used option for patients in both Korea and the United States.[26]

Because of the limitations of national insurance guidelines for patients with resectable pancreatic cancer, more than 90% of chemotherapy-treated patients received 5-FU–based chemotherapy. In Korea, national health insurance pays only for some chemotherapeutic drugs. New chemotherapeutic drugs are allowed, but their costs must be covered by the patient. In Korea, 5-FU has been designated a primary chemotherapeutic agent for resectable pancreatic cancer and gemcitabine a primary agent for unresectable or metastatic pancreatic cancer, with 95% of the cost covered by national health insurance. Other drugs, including targeted agents, are not covered.

There were no differences in age, sex, stage, and extent of surgery between patients who did and did not receive adjuvant treatment (data not shown). Interestingly, the median survival of patients who received adjuvant chemoradiation was 20.8 months, higher than the 14.0 months for patients who did not receive adjuvant treatment. Despite nonrandomization of chemotherapy, its therapeutic effect remained significant for survival even after multivariate analysis. The benefits of adjuvant treatment were more prominent in the standard resection group ($P = 0.016$), with a 2-year survival rate of 50.7%, significantly higher than that of patients who did not receive adjuvant treatment (25.0%). However, adjuvant treatment had no effect on survival in the extended resection group. Extensive dissection around the pancreas may impair vascularity, reducing the postoperative effects of chemoradiation and increasing the likelihood of tumor spillage due to prolonged and extensive manipulation around the tumor. Indeed, we found that peritoneal seeding was significantly more frequent in the extended group (25.9%) than in the standard group (8.3%) ($P = 0.011$).

CONCLUSIONS

Extended pancreatectomy including extensive dissection of lymph nodes and the nerve plexus does not improve the long-term outcome of patients with pancreatic ductal adenocarcinoma. The early recovery and lower morbidity rate observed with standard pancreatic resection, followed by adjuvant treatment, suggest that this option enhances safety and efficacy in these patients.

ACKNOWLEDGMENTS

The authors thank the study participants not listed in authors' list (Joon Seong Park from Yonsei University, Baik Hwan Cho from Chonbuk National University, and Yoon-Seok Yoon and Ho-Seong Han from Seoul National University) for generously sharing their experiences and the data for taking part in this study.

Author contributions are as follows: study concept and design: J.Y. Jang, S.W. Kim; acquisition of data: J.Y. Jang, S.W. Kim, J.S. Heo, S.H. Choi, D.W. Choi, S.J. Park, D.S. Yoon, H.C. Yu, K.J. Kang, S.G. Kim; analysis and interpretation of data: M.J. Kang, J.Y. Jang; drafting of manuscript: J.Y. Jang, M.J. Kang; critical revision and study supervision: S.W. Kim.

REFERENCES

1. Landis SH, Murray T, Bolden S, et al. Cancer statistics, 1999. *CA Cancer J Clin.* 1999;49:8–31.
2. Shin HR, Ahn YO, Bae JM, et al. Cancer incidence in Korea. *Cancer Res Treat.* 2002;34:405–408.
3. The Editorial Board of Cancer Statistics in Japan. *Cancer Statistics in Japan 2005*. Tokyo: Foundation for Promotion of Cancer Research; 2005.
4. Nitecki SS, Sarr MG, Colby TV, et al. Long-term survival after resection for ductal adenocarcinoma of the pancreas. Is it really improving? *Ann Surg.* 1995;221:59–66.
5. Kang MJ, Jang JY, Lee SE, et al. Comparison of the long-term outcomes of uncinate process cancer and non-uncinate process pancreas head cancer: poor prognosis accompanied by early locoregional recurrence. *Langenbecks Arch Surg.* 2010;395:697–706.
6. Fortner JG, Kim DK, Cubilla A, et al. Regional pancreatectomy: en bloc pancreatic, portal vein and lymph node resection. *Ann Surg.* 1977;186: 42–50.
7. Ishikawa O, Ohhigashi H, Sasaki Y, et al. Practical usefulness of lymphatic and connective tissue clearance for the carcinoma of the pancreas head. *Ann Surg.* 1988;208:215–220.
8. Manabe T, Ohshio G, Baba N, et al. Radical pancreatectomy for ductal cell carcinoma of the head of the pancreas. Cancer. 1989;64:1132–1137.
9. Pedrazzoli S, DiCarlo V, Dionigi R, et al. Standard versus extended lymphadenectomy associated with pancreatoduodenectomy in the surgical treatment of adenocarcinoma of the head of the pancreas: a multicenter, prospective, randomized study. Lymphadenectomy Study Group. *Ann Surg.* 1998;228:508–517.
10. Yeo CJ, Cameron JL, Sohn TA, et al. Pancreaticoduodenectomy with or without extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma: comparison of morbidity and mortality and short-term outcome. *Ann Surg.* 1999;229:613–622; discussion 622–624.
11. Farnell MB, Pearson RK, Sarr MG, et al; Pancreas Cancer Working Group. A prospective randomized trial comparing standard pancreatoduodenectomy with pancreatoduodenectomy with extended lymphadenectomy in resectable pancreatic head adenocarcinoma. *Surgery.* 2005;138:618–628; discussion 628–630.
12. Nimura Y, Nagino M, Takao S, et al. Standard versus extended lymphadenectomy in radical pancreatoduodenectomy for ductal adenocarcinoma of the head of the pancreas: long-term results of a Japanese multicenter randomized controlled trial. *J Hepatobiliary Pancreat Sci.* 2012;19: 230–241.
13. Michalski CW, Kleeff J, Wente MN, et al. Systematic review and meta-analysis of standard and extended lymphadenectomy in pancreaticoduodenectomy for pancreatic cancer. *Br J Surg.* 2007;94:265–273.
14. Yeo CJ, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma, part 2: randomized controlled

trial evaluating survival, morbidity and mortality. *Ann Surg.* 2002;236: 355–368.

15. Nguyen TC, Sohn TA, Cameron JL, et al. Standard versus radical pancreaticoduodenectomy for periampullary adenocarcinoma: a prospective randomized trial evaluating quality of life in pancreaticoduodenectomy survivors. *J Gastrointest Surg.* 2003;7:1–11.
16. Riall TS, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma, part 3: update on 5-year survival. *J Gastrointest Surg.* 2005;9:1191–1206.
17. Popiela T, Kedra B, Sierzega M. Does extended lymphadenectomy improve survival of pancreatic cancer patients? *Acta Chir Belg.* 2002;102: 78–82.
18. Iacono C, Accordini S, Bortolasi L, et al. Results of pancreaticoduodenectomy for pancreatic cancer: extended versus standard procedure. *World J Surg.* 2002;26:1309–1314.
19. Nakao A, Takeda S, Sakai M, et al. Extended radical resection versus standard resection for pancreatic cancer: the rationale for extended radical resection. *Pancreas.* 2004;28:289–292.
20. Kimura W. Strategies for the treatment of invasive ductal carcinoma of the pancreas and how to achieve zero mortality for pancreaticoduodenectomy. *J Hepatobiliary Pancreat Surg.* 2008;15:270–277.
21. Pawlik TM, Abdalla EK, Barnett CC, et al. Feasibility of a randomized trial of extended lymphadenectomy for pancreatic cancer. *Arch Surg.* 2005;140:584–589; discussion 589–591.
22. Nagakawa T, Kayahara M, Ueno K, et al. Clinicopathological study on neural invasion to the extrapancreatic nerve plexus in pancreatic cancer. *Hepatogastroenterology.* 1992;39:51–55.
23. Takada T. Surgery for carcinoma of the pancreas in Japan. Past, present, and future aspects. *Digestion.* 1999;60(suppl 1):114–119.
24. Miyazaki I, Kayahara M, Nagakawa T. [Changes in lymph node dissection for pancreatic cancer]. *Nihon Geka Gakkai Zasshi.* 1997;98:610–614.
25. Takahashi H, Ohigashi H, Ishikawa O, et al. Perineural invasion and lymph node involvement as indicators of surgical outcome and pattern of recurrence in the setting of preoperative gemcitabine-based chemoradiation therapy for resectable pancreatic cancer. *Ann Surg.* 2012;255:95–102.
26. Chaulagain CP, Ng J, Wazer D, et al. Adjuvant therapy of pancreatic cancer. *JOP.* 2012;13:349–353.

