

# Evaluation of Preoperative Diagnostic Methods for Resectable Pancreatic Cancer

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## Research Article

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# Abstract

**Background:** In pancreatic cancer clinical practice guideline 2016, it is recommended to perform pathological diagnosis as much as possible, but priorities and algorithms for diagnostic methods have not yet been established. In recent years, EUS-FNA has become mainstream as a method of collecting tissues from pancreatic disease, but the effect of EUS-FNA on surgical results and prognosis has not been clarified.

**Aims:** To evaluate the diagnostic ability of EUS-FNA and preoperative diagnosis affects surgical outcome and prognosis of pancreatic cancer.

**Methods:** Between January 2005 and June 2017, 293 patients who had surgical resection for pancreatic cancer were retrospectively evaluated. The interested outcomes were diagnostic ability of EUS-FNA and the influence for surgical result and prognosis.

**Results:** The diagnostic sensitivity of EUS-FNA was 94.4%, which was significantly higher than ERCP (45.5%) ( $p < 0.001$ ). The adverse event rate in ERCP was 10.2%, which was significantly higher than EUS-FNA (1.3%) ( $p = 0.001$ ).

Patients were divided into FNA group (N=160) and non-FNA group (N=133) for each preoperative diagnostic method. In the study of surgical curability R0 between two groups, there was no significant difference in FNA group: 65.0% (104/160) and non-FNA group: 64.7% (86/133), ( $p = 1.000$ ). In the prognostic study, the total of 256 patients with curability R0 or R1, the recurrence rate was 54.3% (70/129) in the FNA group and 57.4% (73/127) in non-FNA group. Moreover peritoneal dissemination occurred 34.3% (24/70) in the FNA group and 21.9% (16/73) in the non-FNA group, neither of which showed significant difference. The median survival time of FNA group and non-FNA group were 955 days and 799 days, respectively, and there was no significant difference between the two groups (Log rank  $p = 0.735$ ). In the Cox proportional hazards model examining factors influencing prognosis, staging, curability and adjuvant chemotherapy were dominant factors, but preoperative diagnostic method (EUS-FNA) itself was not.

**Conclusions:** As a preoperative examination of pancreatic cancer, EUS-FNA was shown to be a safe procedure with high diagnostic ability. It was considered to be the first choice without the influence of surgical curability, postoperative recurrence, peritoneal dissemination and prognosis.

## Background

Pancreatic cancer is the fourth leading cause of cancer-related deaths in the United States, and there are 227,000 deaths per year worldwide (1, 2). Surgical resection is strongly recommended for resectable pancreatic cancer, since resection is the only method to obtain complete cure. However, surgical resection of pancreas is associated with certain rates of adverse events due to invasive nature of surgery itself. Therefore, accurate preoperative differential diagnosis and staging are very important to avoid

unnecessary surgery. It is also recommended to make a diagnosis of pancreatic cancer based on pathological analysis as much as possible, although priorities and algorithms for diagnostic methods have not been established yet.

Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) was first reported by Vilmann et al(3) in 1992 and has been increasingly used worldwide to obtain pathological samples from pancreatic tumors. The diagnostic capabilities for malignancy of EUS-FNA were considered as very high for pancreatic cancer and has been reported as the sensitivity of 0.85-0.89 and specificity of 0.96-0.98 in the meta-analyses (4-6). The adverse event rate of EUS-FNA was reported as 1.7% (7) and is considered as safe procedure. However, indications of EUS-FNA for pancreatic tumor prior to surgery have remained controversial because of concern for needle-track seeding and tumor dissemination. Some reports have suggested that the use of EUS-FNA neither increased the risk of peritoneal recurrence nor influenced recurrence free survival or overall survival (8-10). However, there have been several case of needle-track seeding at the gastric wall which was most likely caused by EUS-FNA(11-15). The purpose of this study was to examine the diagnostic ability of EUS-FNA and the influence for surgical result and prognosis in patients with pancreatic cancer.

## Patients And Methods

### Patients

This was a multi-centers, retrospective, cohort study undertaken at one academic and two tertial care centers. The analysis included data regarding all patients who underwent surgical resection for pancreatic cancer between January 2005 and June 2017. However, patients who met the following conditions were excluded from the analysis: previous history of the upper intestinal surgery or previous history of any kinds of malignancy in 5 years from the surgery. Written informed consent for endoscopic procedures was obtained from all patients. The consent for participation of patients in this study and its publication was obtained through an opt-out methodology. The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board at each institution and was registered at UMIN Clinical Trials Registry (UMIN000025993).

### Definitions

The patients were divided into two groups; 160 patients who underwent preoperative EUS-FNA (FNA group) and 133 patients who did not (non-FNA group). Survival time was calculated from the day of surgery to the day of death. The operative curability was defined as follows. R0: no evidence of residual tumor, R1: there is residual tumor in pathological analysis, R2: there is residual tumor in macroscopically. And we made staging based on General Rules for the Study of Pancreatic Cancer (The 6<sup>th</sup> Edition, Revised Version) of Japan Pancreas Society. Adverse Events of the endoscopic procedures were defined

according to the lexicon for endoscopic adverse events by the American Society of Gastrointestinal Endoscopy (ASGE) (16).

## Endoscopic procedures

All endoscopic procedures were performed by well experienced endoscopists both EUS- and ERCP-related procedures. EUS-FNA was performed under conscious sedation with the administration of intravenous midazolam and pentazocine. A convex-type echoendoscopes (GF-UC240P-AL5, or GF-UCT260: Olympus, Tokyo, Japan) were used for examinations. In EUS-FNA, the pancreatic lesion was visualized by EUS, after which, the needle was advanced into the lesion through the gastric or duodenal wall. After removal of the stylet, a syringe was attached to the needle to apply negative pressure followed by to-and-fro movement several times. The needle was then pulled back and removed from EUS. The specimen obtained by FNA was spelled out on a glass slide by reinsertion of the stylet into the needle. The whitish visible specimen was placed into a formalin bottle for histological analysis. Smear was made with the remaining specimen on the glass slide and fixed with pure alcohol for cytological analysis.

## Data analysis

The primary outcome in this study was to evaluate the influence of EUS-FNA for surgical outcome and prognosis in pancreatic cancer. The secondary outcomes were diagnostic capability of EUS-FNA for pancreatic tumor, adverse event rates from endoscopic procedures. Comparisons were done using Fisher's exact test or Pearson's chi-squared test, as appropriate for categorical variables and the Mann-Whitney U-test for continuous variables. The Kaplan-Meier method was used to estimate survival time and the log-rank test was used for comparing the two groups. A Cox proportional-hazards model was used to estimate hazard ratios (HR) for prognosis, and possible risk factors associated with survival time were also assessed. The following variables were considered to be candidate risk factors: pre-operative diagnostic methods (FNA or non-FNA), age, sex, tumor location, tumor diameter, clinical stage, operation curability, and adjuvant chemotherapy. In the analyses, continuous variables were transformed to dichotomous variable with a cut-off value of its median number. Factors with a  $P < 0.20$  in the univariate analyses and the diagnostic method (EUS-FNA) were further assessed using a multivariate analysis. A two-sided  $P$ -value of  $<0.05$  was considered to be statistically significant. Statistical analyses were carried out using JMP version 10 (SAS Institute, Inc., Cary, NC, USA) or R ver. 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria; <http://www.R-project.org/>).

## Results

### Basic characteristics

The retrospective analysis identified 293 patients (165 males, 128 females) with a median age of 70 years (range, 42-90). The tumor location was head: 203, body: 72, and tail: 18. Median tumor diameter

was 23 mm (0-89). Main pancreatic duct dilation was observed in 82.3% (241/293), and obstructive jaundice was complicated at 40.6% (119/293) (Table 1). The preoperative diagnostic methods of pancreatic cancer were comprised EUS-FNA in 130 patients, ERCP in 58 patients and both EUS-FNA and ERCP in 30 patients. In the remaining 75 patients, pancreatic cancer was diagnosed only by imaging study findings. Furthermore, we classified the patients into FNA group and non-FNA group. The patient's breakdown was shown in Figure 1.

Baseline characteristics of patients with solid pancreatic tumor	
	N=293
Male	165 (56.3)
Age, y.o	70 (42-90)
Tumor diameter, (mm)	23 (0-89)
Tumor location	
-head	203 (69.3)
-body	72 (24.6)
-tail	18 (6.1)
Main pancreatic duct dilation	241 (82.3)
Obstructive jaundice	119 (40.6)
Data are shown in number (%) or median (range).	

## Outcomes of Endoscopic procedures

In the EUS-FNA group (N=160), the median diameter of long axis of tumor was 23 mm (7-53), and median diameter of short axis was 19 mm (5-40). FNA was performed from the stomach in 57 patients, the duodenal bulb in 60 patients, the second portion of the duodenum in 39 patients, both stomach and duodenal bulb in 3 patients, and duodenal bulb and second portion in 1 patient. The size of the FNA needles were 19-gauge in 83 patients, 22-gauge in 46 patients, 25-gauge in 25 patients, 20-gauge in 4 patients, 21-gauge in 2 patients. The median number of passes during FNA was 3(1-8) (Table 2). EUS-FNA had a cytological diagnostic sensitivity of 91.9%(147/160), a histological diagnostic sensitivity of 83.1%(133/160), the overall diagnostic sensitivity of EUS-FNA for pancreatic cancer was 94.4% (151/160). Pathological samples were obtained during ERCP in 88 patients, pancreatic juice cytology in 24 patients, pancreatic ductal brush cytology in 23 patients, fluoroscopic pancreatic duct biopsy in 9 patients, biliary juice cytology in 15 patients, bile duct brush cytology in 11 patients, and bile duct forceps

biopsy in 48 patients. The malignant diagnostic sensitivity of each method was as follows: pancreatic juice cytology: 25.0%(6/24) (95% confidential interval (CI):0.11-0.44), pancreatic duct brush cytology: 34.8%(8/23) (95%CI:0.19-0.55), fluoroscopic pancreatic duct biopsy: 44.4%(4/9)(95%CI:0.19-0.73), bile juice cytology: 46.7%(7/15)(95%CI:0.25-0.70), bile duct brush cytology: 18.2%(2/11)(95%CI:0.051-0.48), fluoroscopic bile duct biopsy: 41.7%(20/48) (95%CI:0.29-0.56). (Table 3) The diagnostic sensitivity of ERCP was 45.5%(40/88), EUS-FNA showed significantly higher diagnostic ability than ERCP ( $p < 0.001$ ). In the EUS-FNA + ERCP combination group ( $n=30$ ), only 1 patient showed an additional effect by ERCP in eight patients which failed to obtain diagnosis with FNA. Adverse events were recognized 1.3%(2/160) in EUS-FNA and 10.2%(9/88) in ERCP, and were significantly lower in EUS-FNA ( $p=0.001$ ). There were bleeding in 1 patient and abdominal pain in 1 patient in EUS-FNA and post-ERCP mild pancreatitis in 5 patients, post-Endoscopic Sphincterotomy (EST) bleeding in 3 patients, and bile duct perforation in 1 patient in ERCP. All adverse events were successfully managed conservatively in EUS-FNA, meanwhile 2 patients of post-EST bleeding required hemostasis treatment in ERCP. (Table 4)

Table 2	
Results of the EUS-FNA in patients with pancreatic cancer	
	N=160
Puncture routes, (%)	
-Stomach	57 (35.6)
-Duodenal bulb	60 (37.5)
-2nd portion	39 (24.4)
-Stomach / Duodenal bulb	3 (1.9)
-Duodenal bulb / 2nd portion	1 (0.6)
The size of the puncture needle, (%)	
-19G	83 (51.9)
-22G	46 (28.8)
-25G	25 (15.6)
-20G	4 (2.5)
-21G	2 (1.2)
Number of punctures, median, (range)	3 (1-8)
FNA, fine needle aspiration.	
Data are shown in number (%) or median (range).	

Table 3

Results of the diagnostic ability of EUS-FNA and ERCP in patients with pancreatic cancer

EUS-FNA	
Cytological diagnosis	91.9% (147/160)
-positive	125
-suspicious positive	22
-negative	13
Histological diagnosis	83.1% (133/160)
-adenocarcinoma	120
-suspicious adenocarcinoma	13
-no diagnosis	27
Overall	94.4% (151/160)
ERCP	
Sample collection methods	
-Pancreatic juice cytology	25.0% (6/24)
-Pancreatic ductal brush cytology	34.8% (8/23)
-Fluoroscopic pancreatic duct biopsy	44.4% (4/9)
-Biliary juice cytology	46.7% (7/15)
-Bile duct brush cytology	18.2% (2/11)
-Fluoroscopic bile duct biopsy	41.7% (20/48)
Overall	45.5% (40/88)
FNA, fine needle aspiration; ERCP, endoscopic retrograde cholangiopancreatography.	

Table 4			
Adverse events			
	EUS-FNA (N=160)	ERCP (N=88)	p value
Adverse events, n (%)	2 (1.3)	9 (10.2)	0.001
-mild pancreatitis	0	5	
-bleeding	1	3	
-bile duct perforation	0	1	
-abdominal pain	1	0	
EUS-FNA, endoscopic ultrasonography - fine needle aspiration; ERCP, endoscopic retrograde cholangiopancreatography.			
Data are shown in number (%).			

## Surgical outcomes and prognosis

The types of surgery were as follows; pancreatoduodenectomy (PD) in 182 patients, distal pancreatectomy (DP) in 75 patients, total pancreatectomy (TP) in 5 patients, middle pancreatectomy (MP) in 1 patient, and unresectable in 28 patients. The curability was R0: 190 patients, R1: 66 patients, R2: 37 patients. The final stage was I: 21 patients, II: 25 patients, III: 95 patients, IVa: 112 patients, IVb: 40 patients, and postoperative chemotherapy was conducted at 80.2% (235/293). In the study of surgical curability R0 between two groups, there was no significant difference in FNA group: 65.0% (104/160) and non-FNA group: 64.7% (86/133), ( $p=1.000$ ). In the prognostic study, the total of 256 patients with curability R0 or R1, the recurrence rate was FNA group: 54.3% (70/129), non-FNA group: 57.4% (73/127), and peritoneal dissemination occurred 34.3% (24/70) in the FNA group and 21.9% (16/73) in the non-FNA group, neither of which showed significant difference (Table 5). The median survival time of FNA group and non-FNA group were 955 days and 799 days, respectively, and there was no significant difference between the two groups (Log rank  $p=0.735$ ) (Figure 2). The univariate and multivariate analyses showed staging, curability and adjuvant chemotherapy were identified as an independent risk factor for survival, however, EUS-FNA itself was not (Table 6).

Table 5			
The surgical curability and postoperative recurrence of two groups			
Curability	FNA group (N=160)	Non-FNA group (N=133)	p value
R0	104 (65.0)	86 (64.7)	1.000
R1 / R2	56 (35.0)	47 (35.3)	
	FNA group R0 / R1 (N=129)	Non-FNA group R0 / R1 (N=127)	
Recurrence	70/129 (54.3)	73/127 (57.4)	0.616
Peritoneal dissemination	24/70 (34.3)	16/73 (21.9)	0.135
FNA, fine needle aspiration.			
Data are shown in number (%).			

Table 6

Cox proportional hazards model examining factors influencing prognosis

Factors		Univariate analysis		Multivariate analysis	
		HR (95% CI)	p value	HR (95% CI)	p value
Age	≥70 y.o	1.345 (0.974-1.858)	0.071	1.123 (0.789-1.596)	0.517
Sex	male	1.385 (0.998-1.939)	0.050	1.222 (0.862-1.747)	0.260
Diagnostic method	EUS-FNA	0.946 (0.685-1.306)	0.735	0.882 (0.632-1.233)	0.464
Tumor location	head	1.320 (0.924-1.924)	0.128	1.357 (0.943-1.994)	0.100
Tumor diameter	≥23mm	1.531 (1.107-2.129)	0.009	1.359 (0.965-1.926)	0.078
Stage	I	2.612 (1.865-3.690)	<0.001	2.026 (1.407-2.942)	<0.001
Curability	R0	0.383 (0.275-0.536)	<0.001	0.463 (0.324-0.664)	<0.001
Adjuvant Chemotherapy	Yes	0.561 (0.378-0.860)	0.009	0.446 (0.288-0.709)	<0.001

EUS-FNA, endoscopic ultrasonography-fine needle aspiration; HR, hazard ratio; 95% CI, 95% confidence interval.

## Discussion

In the present study, we analyzed preoperative diagnosis of 293 patients with pancreatic cancer. The overall diagnostic sensitivity of EUS-FNA for pancreatic cancer was 94.4% which was significantly higher than that of ERCP (45.5%) ( $p<0.001$ ). Adverse event rates associated with endoscopic procedures were

1.3% (2/160) with EUS-FNA, whereas 10.2% (9/88) with ERCP related procedures, and the adverse event rate was significantly lower with EUS-FNA ( $p=0.001$ ). In the comparison between patients underwent EUS-FNA (FNA group) and those who did not undergo FNA (non-FNA group), there were no significant difference in the surgical outcomes, surgical curability, and recurrence rate. Kaplan–Meier analysis also confirmed the absence of a significant difference in overall survival between the two groups ( $p=0.735$ ). In the Cox proportional-hazards model for the overall survival, EUS-FNA was not an independent risk factor.

There are two methods to obtain pathological specimens from pancreatic tumors: the transpapillary approach (ERCP) and the transintestinal approach (EUS-FNA). The sensitivity of malignant diagnosis of the transpapillary approach is not sufficient, and endoscopic-related adverse events such as post-ERCP pancreatitis are also a concern (17). On the other hand, EUS-FNA has higher preoperative diagnostic capability than other modalities, with a diagnostic accuracy of 75%-95%(18-23). It is noteworthy that the reported specificity of EUS-FNA for pancreatic solid neoplasms is almost 100% (5) and that the associated complication rate is < 1% (24). Previous study by Wakatsuki et al. compared diagnostic ability of EUS-FNA (53 patients) and ERCP (30 patients) in pancreatic mass. They reported that in the FNA group, the overall results for the available samples were sensitivity 92.9% and accuracy 94.3%. In contrast, in the ERCP group the overall results were sensitivity 33.3% and accuracy 46.7%. The result suggested that, EUS-FNA is more accurate for the cytopathological diagnosis of suspected pancreatic masses as compared with cytology during ERCP(17). In this study, the diagnostic ability of EUS-FNA revealed a sensitivity of 94.4% (151/160), it was significantly higher than that of ERCP 45.5% (40/88). The major adverse events reported with EUS-FNA are infections, bleeding, pancreatitis, and duodenal perforation, with an overall rate between 1 and 2 %(25). In our study, the adverse event rate of EUS-FNA was only 1.3% (2/160), all were relieved with conservative treatment. It was significantly lower than that of ERCP. Considering diagnostic ability and short-term adverse events, EUS-FNA is considered to be an adequate and much-needed procedure in preoperative diagnosis of patients with suspected pancreatic cancer.

There are a few articles reported about long-term outcomes of preoperative EUS-FNA in patients underwent surgical resection of pancreatic cancer. A retrospective study by Ngamruengphong et al. evaluated 256 patients underwent pancreatectomy, including 208 patients had EUS-FNA for pancreatic tumor (FNA group) and 48 patients who did not have FNA (non-FNA group) with the median length of follow-up period of 23 months (range 0 - 111 months) and showed a gastric or peritoneal recurrence in a total of 19 patients: 13 patients (7.7%) in the FNA group versus 6 patients (15.4%) in the non-EUS-FNA group ( $p=0.21$ ). In this study, three patients had recurrence in the gastric wall: one (2.6%) patient in the non-EUS-FNA group versus two patients (1.2%) in EUS-FNA group ( $p=0.46$ ) (8). Another retrospective study by Kudo *et al.* evaluated 82 patients with resectable pancreatic cancer. Of these, 54 underwent EUS-FNA before surgery (FNA group) and 28 underwent surgery without preoperative EUS-FNA (non-FNA group). The study reported that the median relapse-free survival (RFS) of FNA group and non-FNA group was 742 and 265 days, respectively ( $p=0.009$ ), and the median overall survival (OS) was 1042 and 557 days, respectively ( $p=0.007$ ). FNA group had better RFS and OS than non-FNA group, because more patients in the FNA group underwent adjuvant chemotherapy. Multivariate analysis revealed that tumor

size and adjuvant chemotherapy were both prognostic factors in this study. It was possible that patients in the FNA group benefited from the chemotherapy administered immediately after surgery (9). Tsutsumi *et al.* also carried out a retrospective study evaluating the impact of preoperative EUS-FNA. They divided 209 patients with pancreatic cancer into two groups: 126 patients who underwent preoperative EUS-FNA (FNA group) and 83 patients who did not undergo preoperative EUS-FNA (non-FNA group). They evaluated long-term outcomes of preoperative EUS-FNA, especially disease-free survival, needle tract seeding and recurrence. Kaplan-Meier analysis indicated no significant difference in disease-free survival between the FNA and non-FNA groups. The site of recurrence was not significantly different between the two groups, and needle tract seeding was not observed (10). In our study, the surgical curability (R0) was not significantly different between the FNA and non-FNA group. And there was no significant difference among two groups in the recurrence rate, peritoneal dissemination incidence, and survival time after surgery. Moreover, in multivariate analysis of factors related to prognosis, staging, curability and adjuvant chemotherapy were identified as dominant factors, but EUS-FNA itself was not. These studies including our one indicate that preoperative EUS-FNA does not adversely affect surgery or prognosis nor does it increase the risk of gastric wall or peritoneal recurrence in patient with resectable pancreatic cancer.

Recently, neoadjuvant chemotherapy for borderline resectable pancreatic cancer has been reported to have excellent effects on survival (26-30). Motoi *et al.* also evaluated neoadjuvant chemotherapy for resectable pancreatic cancer. They performed a randomized, controlled trial to compare neoadjuvant chemotherapy using gemcitabine and S-1 (NAC-GS) with upfront surgery (Up-S) for patients planned resection of pancreatic cancer. It found that the NAC-GS group showed a significant increase in overall survival (Prep-02/JSAP05) (31). Considering these results, importance of preoperative pathological diagnosis might increase even in cases with indications of surgical resection. EUS-FNA is recommended as the first choice for tissue sample collection method considering the high diagnostic capability and lower adverse event rate in comparison with transpapillary approach.

Although preoperative EUS-FNA for pancreatic cancer did not influence RFS, OS, or peritoneal dissemination as we discussed above, this is a matter of concern especially in patients with pancreatic body or tail cancer, since FNA was performed into the pancreatic tumors through the intestinal wall and peritoneal cavity and needle tract is not included surgically resected area. There have been several case reports regarding suspected tumor seeding related to preoperative EUS-FNA. In those reports, all recurrences occurred in the gastric wall (11-14). Minaga *et al.* summarized the clinical features and outcomes of 15 cases with needle tract seeding. In 13 (86.7%) of 15 cases, EUS-FNA was performed via the gastric body to preferentially diagnose pancreatic body or tail lesions. The remaining 2 cases performed EUS-FNA for perigastric and mediastinal lymph nodes(32). Yane *et al.* investigated the long-term outcomes, including the needle tract seeding ratio, of patients undergoing distal pancreatectomy for pancreatic body and tail cancer diagnosed preoperatively by EUS-FNA. Of the 301 total patients analyzed, 176 underwent preoperative EUS-FNA (FNA group) and 125 did not (non-FNA group). The median RFS or OS was not significantly different between the FNA group and the non-FNA group (23.7 vs 16.9 months:  $p=0.205$ ; 48.0 vs 43.9 months:  $p=0.392$ ). However, six patients (3.4%) in the FNA group were diagnosed as having needle tract seeding, the 5-year cumulative needle tract seeding rate estimated using Fine and

Gray's method was 3.8% (95% CI 1.6-7.8%)(33). These data suggest that needle tract seeding after EUS-FNA is observed to have a non-negligible rate. In particular, when performing EUS-FNA for a resectable tumor located in the pancreatic body or tail, there is a possibility of needle tract seeding, so it is necessary to pay attention to the size of the needle and the number of punctures.

The present study has several limitations. A retrospective study design might bias study outcomes. Since the study included only high-volume centers for both EUS and ERCP related procedures, the external validity might be low especially in the endoscopic procedure.

In conclusion, EUS-FNA was safe with high diagnostic ability as a preoperative examination of pancreatic cancer. It was considered to be the first choice without the influence of surgical curability, postoperative recurrence, peritoneal dissemination and prognosis. However, since needle tract seeding is observed to have certain probability, EUS-FNA for resectable tumors especially located in the pancreatic body or tail, requires careful consideration of the relationship between risk and benefit. A randomized controlled trial in a multicenter setting is needed to confirm the study results.

## Abbreviations

EUS-FNA, **endoscopic ultrasound-guided fine needle aspiration**; ERCP, **endoscopic retrograde cholangiopancreatography**; UMIN, university hospital medical information network; 95% CI, 95% confidence interval; EST, endoscopic sphincterotomy; PD, pancreatoduodenectomy; DP, distal pancreatectomy; TP, total pancreatectomy; MP, middle pancreatectomy; RFS, relapse-free survival; OS, overall survival

## Declarations

## Ethics approval and consent to participate:

The study protocol followed the guidelines of STROBE. The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by Ethical Committee of Gifu University Graduate School of Medicine. The informed consent for participation of patients in this study was obtained through an opt-out methodology. And this study included deceased participants, the informed consent for participation of them in this study was obtained through an opt-out methodology from their parents, legally authorized representative, or from their Next of kin.

## Consent for publication:

Not applicable

## Availability of data and materials:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Competing interests:

Akinori Maruta, Takuji Iwashita, Kensaku Yoshida, Shinya Uemura, Ichiro Yasuda, Masahito Shimizu do not have any competing interests needed to be declared.

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## Author Contributions:

Akinori Maruta and Takuji Iwashita wrote the manuscript. Akinori Maruta, Takuji Iwashita, Kensaku Yoshida, Shinya Uemura, Ichiro Yasuda, Masahito Shimizu managed the patients. Takuji Iwashita took the correspondence.

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## Figures

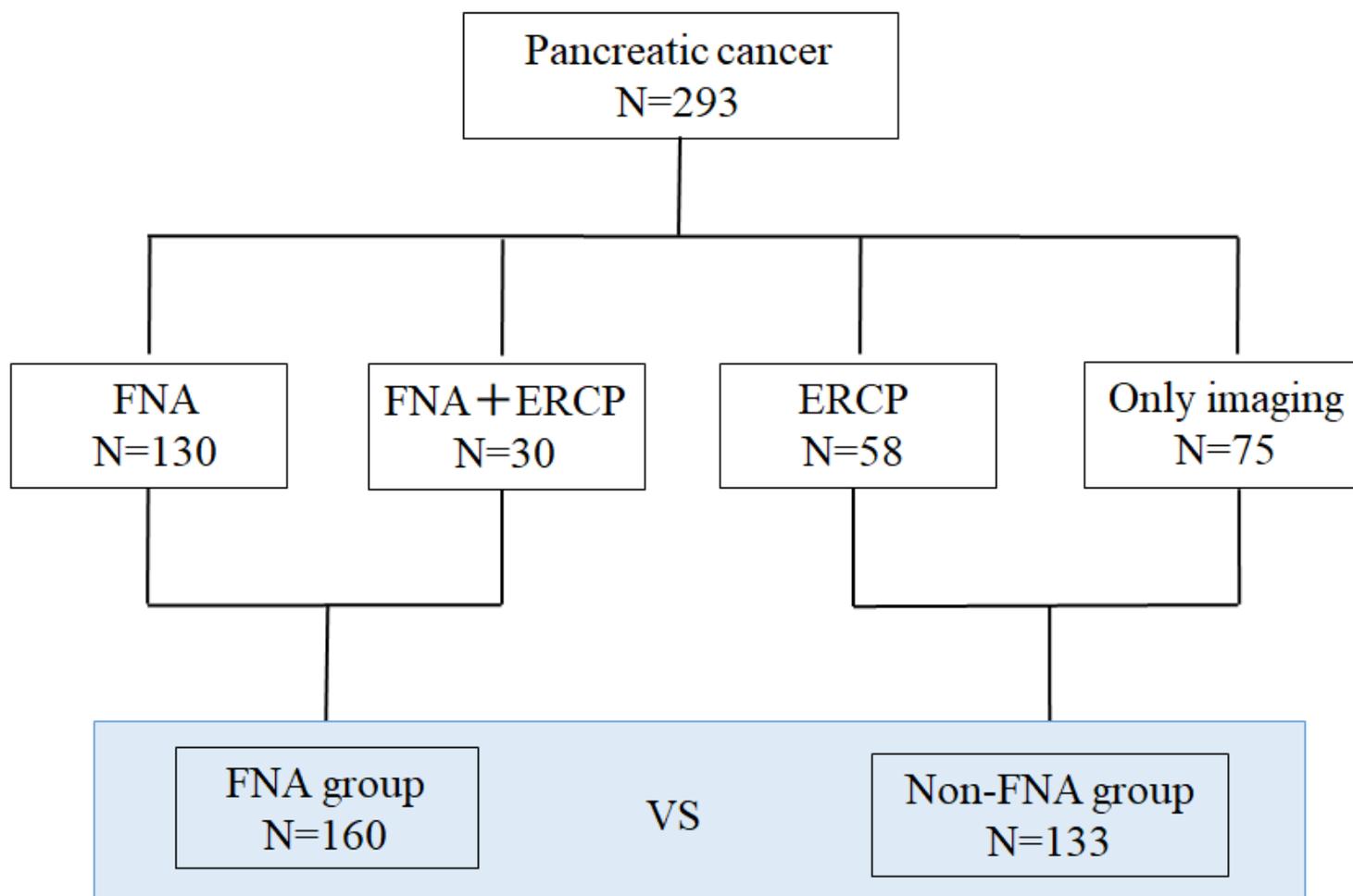


Figure 1

Patient flow of this study. FNA, fine needle aspiration; ERCP, endoscopic retrograde cholangiopancreatography.

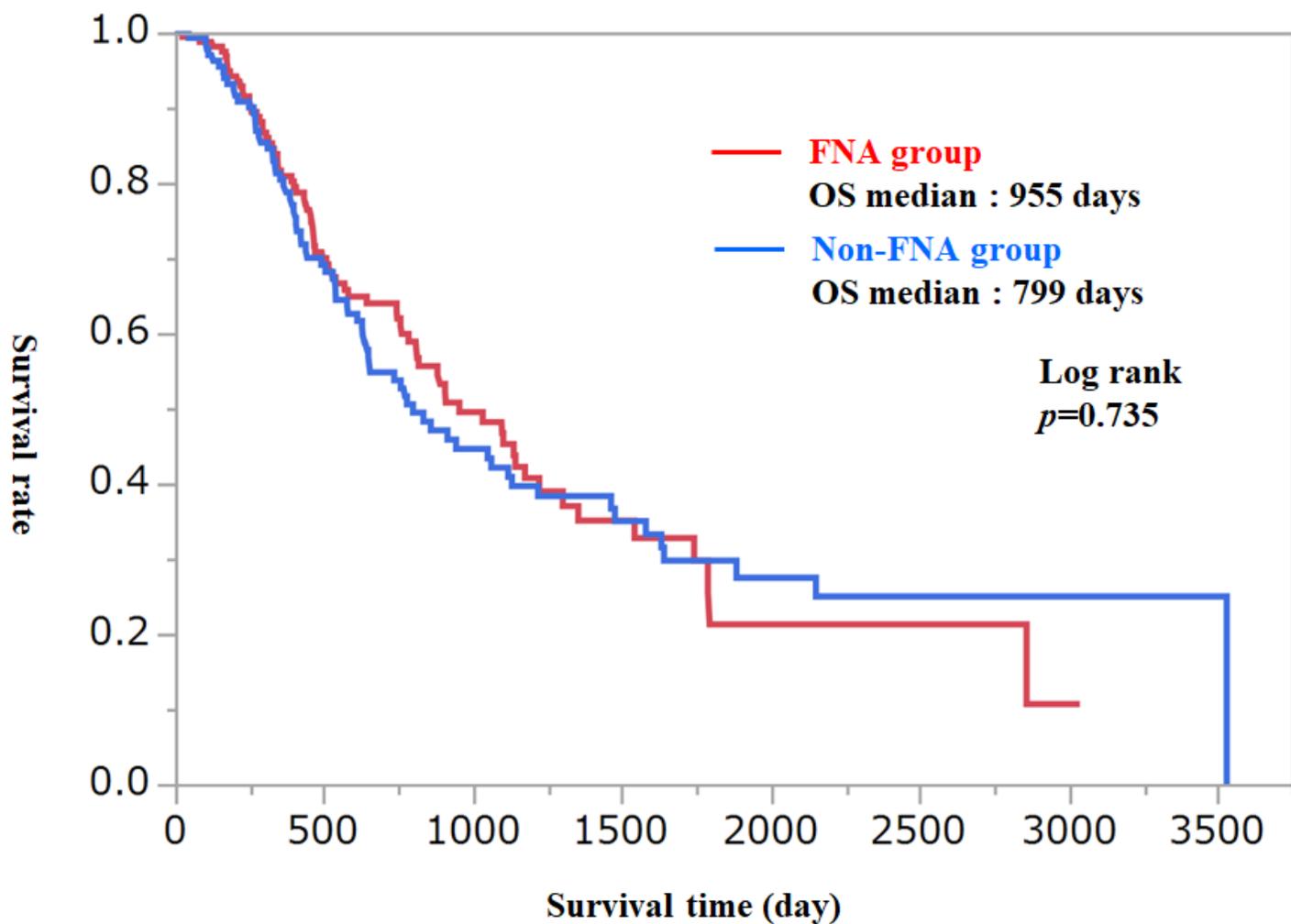


Figure 2

The survival rate of the two groups. FNA, fine needle aspiration.