ANTICANCER RESEARCH *41*: 5171-5177 (2021)
doi:10.21873/anticanres.15335

Clinical Predictors of Unresectable Disease at Laparotomy in Patients With Pancreatic Ductal Adenocarcinoma Planning to Undergo Surgical Resection

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Abstract. *Background/Aim: Computed tomography and positron emission tomography cannot detect all minute distant metastases and fully evaluate extensive vascular invasion in patients with pancreatic ductal adenocarcinoma (PDAC). The aim of this study was to investigate predictors of laparotomy only and palliative surgery in PDAC patients planning surgical resection. Patients and Methods: We reviewed 239 PDAC patients planning surgical resection. Patients were divided into two groups based on resection status. Multivariate analyses were performed to identify predictors of unresectable disease at laparotomy. Results: Twenty-five patients had unresectable disease at laparotomy. Multivariate analysis revealed that anatomical borderline resectable status (yes/no) (HR=5.458, p=0.012), pretreatment CA19-9 (>260/≤260 ng/ml) (HR=4.907, p=0.041), and tumor size (>25/≤25 mm) (HR=21.42, p=0.004) were associated with unresectable disease at laparotomy. Conclusion: Borderline resectable status, pretreatment CA19-9, and tumor size were closely associated with unresectable disease at laparotomy in PDAC patients planning surgical resection.*

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer-related mortality in the United States (1). The median overall survival (OS) rate of patients with PDAC is 20% at 1 year and 8% at 5 years (2), while surgical outcomes for resectable PDAC include a 5-year OS rate of 18% (3). These results indicate that the prognosis and treatment outcomes of patients with PDAC remain poor.

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Key Words: Pancreatic ductal adenocarcinoma, unresectable disease at laparotomy borderline resectable, CA19-9, maximum tumor size.

To improve the postoperative outcomes of patients with PDAC, the utility of neoadjuvant chemotherapy (NAC) was recently reported (4). Because NAC can improve postsurgical outcomes in PDAC and increase the R0 resection rate compared with surgery alone (5, 6), several clinical trials of neoadjuvant therapies for resectable PDAC are ongoing (7). However, some PDAC patients cannot undergo surgical resection even if NAC is administered because of unexpected factors that make them unresectable disease at laparotomy, such as peritoneal dissemination, para-aortic lymph node metastasis, liver metastasis, and extensive vascular invasion. Accurate preoperative assessment of unresectable disease is required to reduce unnecessary laparotomy and to determine whether neoadjuvant therapy is indicated. Multi-detector computed tomography (CT) and positron emission tomography (PET) are useful for preoperative assessment of PDAC. Multi-detector CT has been shown to be superior to other imaging modalities for detection of vascular invasion by PDAC (sensitivity: 73.0%, specificity: 95.0%) (8). The sensitivity (96.0%) and specificity (78.0%) of PET for the detection of distant metastasis were higher than those of CT (sensitivity: 91.0%, specificity: 56.0%) (9). However, these imaging tests cannot completely assess all factors that influence the possibility of resection. In addition to multi-detector CT and PET, identification of further predictors of unresectable disease at laparotomy are required. Herein, we investigated predictors of unresectable disease at laparotomy among PDAC patients who planned to undergo surgical resection.

Patients and Methods

We retrospectively reviewed the records of 239 patients planning to undergo surgical resection for PDAC between April 2005 and January 2019 at the Second Department of Surgery, Dokkyo Medical University Hospital. We excluded patients with preoperatively diagnosed peritoneal dissemination and distant metastasis. This study was approved by the Institutional Review

Board (provided ID number: R-18-3J) on the basis of the Ethical Guidelines for Clinical Research of the Ministry of Health, Labour and Welfare in Japan.

Patients were divided into two groups based on eligibility to undergo surgical resection. Patients able to undergo surgical resection were assigned to the operable (OP) group. Patients who had unresectable disease at laparotomy were assigned to the unresectable at laparotomy (UR-L) group.

Preoperative imaging assessment. Helical dynamic CT and PET were routinely performed before surgery for PDAC in order to judge whether surgical resection can be performed. All 239 patients had received helical dynamic CT and PET before surgery, and a judgment on operative cases for PDAC was made preoperatively.

Anatomical borderline resectable cases were diagnosed on the basis of the international consensus on the definition and criteria of borderline resectable PDAC (10). Using pretreatment CT imaging, anatomical borderline resectable cases were classified as follows. BR-PV was defined as 1) tumor contact with 180˚ of the superior mesenteric vein (SMV)/portal vein (PV) and/or narrowing/occlusion of the SMV/PV due to tumor and not exceeding the inferior border of the duodenum; and 2) no tumor contact/invasion with the superior mesenteric artery (SMA), celiac artery (CA), or common hepatic artery (CHA). BR-A was defined by 1) tumor contact of <180˚ without showing deformity/stenosis of the SMA/CA; and/or 2) tumor contact with the CHA without tumor contact with the proper hepatic artery and/or CA. In this study, patients with BR-PV and BR-A were classified as anatomical borderline resectable cases.

Pretreatment serum tumor markers and neoadjuvant chemotherapy. If patients underwent NAC, pretreatment serum tumor markers were measured before NAC. If patients did not undergo NAC, pretreatment serum tumor markers were measured before surgery.

NAC has been performed for 84 patients with resectable and borderline PDAC since December 2013 in our department, using the following gemcitabine plus S-1 regimen: gemcitabine 1,000 mg/m^2 on days 1 and 8 plus S-1 orally twice daily according to body surface area (BSA; <1.25 m^2, 40 mg; ≥1.25 to <1.5 m^2, 50 mg; ≥1.5 m^2, 60 mg) on days 1 through 14 of a 21-day cycle (11). After two cycles, patients underwent surgery within 6 weeks. If gemcitabine plus S-1 could not be administered due to adverse events, two cycles of gemcitabine plus nab-paclitaxel were administered or NAC was not performed.

Operative procedure. After Kocher maneuver, we routinely palpate para-aorta lymph node. If para-aorta lymph node is swelling, we sample it. Sampled lymph node is subjected to pathological assessment. If sampled lymph node is metastasis of PDAC, we judge the patient unresectable case and perform laparotomy closure.

Combined resection and reconstruction of the SMV is generally performed in our department. However, patients with tumor infiltration distal to the SMV branching to the ileocolic vein and jejunal vein are defined as unresectable cases, because SMV reconstruction is judged to be impossible.

Combined atrial resection and reconstruction are conducted in strictly selected patients in our department due to the high risk of perioperative mortality and poor survival after surgery (12). Combined hepatic artery resection and distal pancreatectomy with celiac axis resection (DP-CAR) is sometimes feasible. Patients with tumors infiltrating the SMA were defined as unresectable cases.

Statistical analysis. Chi-squared and Mann–Whitney *U*-testing were performed to evaluate the significance of differences between groups. Data are presented as averages and standard deviations. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated by univariate or multivariate analyses using logistic regression models. To identify factors associated with laparotomy only and palliative surgery, multivariate analysis of clinical characteristics was performed for factors demonstrating a p-value <0.05 in univariate analysis. All statistical analyses were performed using SPSS software (version 25.0; IBM Co., New York, NY, USA), and differences with a p-value <0.05 were considered statistically significant.

The cut-off values for various clinical characteristics were determined using receiver operating characteristic (ROC) curve analyses. The recommended cut-off values for characteristics were defined using the most prominent point on the ROC curve (Youden index=maximum [sensitivity – (1 – specificity)]), and we also calculated the area under the ROC (AUROC) curve (13). Except for pretreatment serum levels of carcinoembryonic antigen (CEA) (ng/ml), duke pancreatic monoclonal antigen type 2 (DUPAN-2) (U/ml), s-pancreas-1 antigen (SPAN-1) (U/ml), and elastase-1 (ng/dl), other cut-off values including age (years), body mass index (BMI) (kg/m^2), pretreatment carbohydrate antigen 19-9 (CA19-9) (U/ml), pretreatment maximum tumor size (cm), preoperative platelet count (×104/mm^3), and preoperative serum level of albumin (g/dl) were calculated using the Youden index.

Results

Clinical characteristics of PDAC patients planning to undergo surgical resection. Patients in the OP group underwent the following surgical procedures: pancreaticoduodenectomy (n=139), distal pancreatectomy (n=58), and total pancreatectomy (n=17). With respect to operative curability in the OP group, 184 patients underwent R0 resection, 28 patients underwent R1 resection, and 2 patients underwent R2 resection.

Patients in the UR-L group underwent the following surgical procedures: laparotomy only (n=18) and gastrojejunostomy (n=7). Reasons for unresectability among patients in the UR-L group were SMA invasion (n=8), extensive SMV (n=6), liver metastasis (n=4), peritoneal dissemination (n=3), para-aortic lymph node metastasis (n=3), and CA invasion (n=1).

Seventy-eight patients underwent peritoneal lavage cytology before resection. Although 13 patients among them had malignant cells, surgical resection was performed in 12 patients because of resectability. One patient was moved to the UR-L group because of peritoneal dissemination.

With regard to biliary drainage, 120 patients underwent preoperative biliary drainage. Among them, 93 patients underwent endoscopic drainage, 26 patients underwent percutaneous transhepatic drainage and one patient underwent percutaneous transhepatic gallbladder drainage. Pretreatment tumor markers of 42 patients were examined before biliary drainage.

Table I shows the surgical characteristics of patients in the OP and the UR-L groups. Twenty-five patients (10.5%, 25/239) underwent laparotomy only and palliative surgery

Table I. *The clinical characteristics of patients with pancreatic ductal adenocarcinoma divided into the OP group and UR-L group by surgical resection.*

Variable	OP group (n=214)	UR-L group (n=25)	*p*-Value
Age (year)	68±9	67±12	0.738
Preoperative BMI (kg/m^2)	21.4±3.5	21.5±2.9	0.696
Gender (male/female)	124/90	15/10	0.844
Preoperative serum albumin (g/dl)	3.5±0.5	3.5±0.5	0.998
Preoperative platelet count (×10^4/mm^3)	21.7±8.8	24.5±10.3	0.631
Pretreatment CEA (ng/ml)	10.7±51.3	12.9±29.9	0.129
Pretreatment CA19-9 (ng/ml)	1556±5575	4444±5139	0.002
Pretreatment DUPAN-2 (U/ml)	1980±3269	1980±3269	0.006
Pretreatment SPAN-1 (U/ml)	193±429	614±974	<0.001
Pretreatment elastase-1 (ng/dl)	795±1089	1136±2058	0.785
Pretreatment maximum tumor size (mm)	25±24	35±7	0.035
Anatomical borderline resectable cases (yes/no/NA)	94/118/2	17/4/4	0.001
Preoperative chemotherapy (yes/no)	76/138	8/17	0.728
Operation procedure	PD: 139, DP: 58, TP: 17	LO: 18, GJ: 7	-
Curability (R0/R1/R2)	184/28/2	-	-
Inoperable reason	-	Vascular invasion: 15 Distant metastasis: 10	-
		Average±SD	
		Chi-squared test and Mann-Whitney *U*-test, $p<0.05$.	

BMI: Body mass index; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; DUPAN-2: Duke-Pancreas 2; SPAN-1: s-pancreas-1 antigen; PD: pancreaticoduoduodenectomy; DP: distal pancreatectomy; LO: laparotomy only; GJ: gastrojejunostomy; TP: total pancreatectomy; OP: operable; UR-L: unresectable disease at laparotomy.

and were assigned to the UR-L group. Chi-squared and Mann-Whitey *U* testing revealed significant intergroup differences in pretreatment CA19-9 levels, pretreatment DUPAN-2 levels, pretreatment SPAN-1 levels, maximum tumor size, and anatomical borderline resectable status.

Uni- and multivariate analysis for laparotomy only and palliative surgery in PDAC patients. Table II shows the results of uni- and multivariate analysis. Univariate analyses among PDAC patients revealed associations between the unresectable disease at laparotomy and pretreatment CA19-9 levels (>260/≤260 ng/ml), pretreatment DUPAN-2 levels (>170/≤170 U/ml), pretreatment SPAN-1 levels (>110/≤110 U/ml), maximum tumor size (25>/≤25 mm), and anatomical borderline resectable status (yes/no). Multivariate analysis using the results of univariate analyses revealed that pretreatment CA19-9 levels (>260/≤260 ng/ml) (HR=4.907; 95%CI=1.069-22.53; $p=0.041$), maximum tumor size (>25/≤25 mm) (HR=21.42; 95%CI=2.684-171.0; $p=0.004$), and anatomical borderline resectable status (yes/no) (HR=5.458; 95%CI=1.443-20.64; $p=0.012$) were significantly associated with unresectable disease at laparotomy among PDAC patients planning to undergo surgical resection.

ROC curve of three clinical predictors for unresectable disease at laparotomy in PDAC patients planning to undergo surgical resection. The optimal cut-off values for pretreatment CA19-9 levels and maximum tumor size for unresectable disease at laparotomy were 260 U/ml and 25 mm, respectively. Pretreatment CA19-9 levels, pretreatment maximum tumor size, and anatomical borderline resectable status provided sensitivities of 80.0%, 95.2%, and 81.0%, specificities of 54.0%, 56.7%, and 55.7%, and AUROC curves of 0.683, 0.691, and 0.809, respectively (Figure 1A-C). The arrows show the most prominent point on the ROC curve for each characteristic (Figure 1A-C).

Discussion

Multivariate analysis revealed that pretreatment CA19-9 levels (>260 ng/ml), maximum tumor size (>25 mm), and anatomical borderline resectable status were significantly associated with unresectable disease at laparotomy in patients who planned to undergo surgical resection for PDAC (Table II).

Previous studies have revealed that CA19-9 levels and maximum tumor size reflect tumor progression and predict outcomes of patients with PDAC (14, 15). These two characteristics are closely associated with distant metastases (16). Recently, Isaji et al. defined patients with borderline resectable PDAC according to three distinct dimensions: anatomical, biological, and conditional (10). This novel definition is very reasonable for preoperative assessment of

Table II. *Univariate and multivariate analyses in relation to unresectable disease at laparotomy in 239 patients with pancreatic ductal adenocarcinoma planning to surgical resection.*

	Univariate analyses			Multivariate analyses		
Variable	*p*-Value	HR	95%CI	*p*-Value	HR	95%CI
Age (>65/≤65, year)	0.592	0.793	0.339-1.852			
Preoperative BMI (≤21.0/>21.0, kg/m^2)	0.229	1.678	0.722-3.903			
Gender (male/female)	0.844	0.919	0.639-2.138			
Preoperative serum albumin (≤3.5/>3.5, g/dl)	0.832	1.095	0.475-2.524			
Preoperative platelet count (>19.5/≤19.5, ×10^4/mm^3)	0.381	1.484	0.614-3.590			
Pretreatment CEA (>5/≤5, ng/ml)	0.050	2.310	1.001-5.329			
Pretreatment CA19-9 (>260/≤260, ng/ml)	0.003	4.694	1.699-12.97	0.041	4.907	1.069-22.53
Pretreatment DUPAN-2 (>170/≤170, U/ml)	0.016	3.513	1.263-9.769	0.098	2.908	0.820-10.31
Pretreatment SPAN-1 (>110/≤110, U/ml)	0.004	3.651	1.517-8.788	0.759	0.819	0.229-2.932
Pretreatment elastase-1 (>300/≤300, ng/dl)	0.995	1.003	0.422-2.384			
Pretreatment maximum tumor size (25>/≤25, mm)	0.002	26.20	3.450-199.0	0.004	21.42	2.684-171.0
Anatomical borderline resectable cases (yes/no)	0.003	5.335	1.737-16.39	0.012	5.458	1.443-20.64
Preoperative chemotherapy (yes/no)	0.728	0.854	0.352-2.072			

CI: Confidence interval; HR: hazard ratio; BMI: body mass index; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; DUPAN-2: Duke-Pancreas 2; SPAN-1: s-pancreas-1 antigen.

patients with PDAC compared with previous definitions because preoperative CA19-9 levels and patient status other than CT findings are added to preoperative assessment (10). Preoperative CA19-9 levels have previously been shown to be closely associated with tumor resection rate and positive surgical margin in PDAC patients undergoing surgery (17, 18). This suggests that pretreatment CA19-9 levels and tumor size are useful for predicting unresectable disease at laparotomy among PDAC patients planning to undergo surgical resection.

Several studies have revealed that the surgical resection rate in patients with anatomical borderline resectable disease after neoadjuvant therapy is low (39-48%) (19-21). Tumor progression, development of distant metastasis, and worse performance status were identified as reasons for inoperability in these patients (19-21). These results suggest that anatomical borderline resectable status is closely associated with unresectable disease at laparotomy among patients with PDAC. Actually, most of anatomical borderline resectable PDAC could not avoid vascular resection. Although vascular resection enables patients with anatomical borderline resectable PDAC to undergo curative surgery, pancreatic surgery with vascular resection for PDAC had a large amount of intraoperative blood loss, high rate of morbidity and mortality (22, 23). It is discussable whether up-front surgery or neoadjuvant chemotherapy should be performed for patients with anatomical borderline resectable PDAC. Further studies would be required to resolve this question.

These three predictors of unresectable disease at laparotomy can be used to develop pretreatment strategies. For example, these predictors can be used to determine indications for diagnostic laparoscopy. A previous study demonstrated that diagnostic laparoscopy and laparoscopic ultrasound were useful for detection of minute liver metastases and peritoneal dissemination that could not be detected on PET (24). In addition, selective use of staging laparoscopy based on CA19-9 levels and tumor size decreased the frequency of unnecessary laparotomy by detecting minute metastases in patients with potentially or borderline resectable PDAC (25). Finally, staging laparoscopy significantly shorten an interval time between surgery and chemotherapy compared as that of patients with unresectable PDAC undergoing exploratory laparotomy (26). These suggests that diagnostic laparoscopy is useful for detection of minute metastases that cannot be detected by multi-detector CT or PET. Therefore, diagnostic laparoscopy is recommended for PDAC patients with these predictors to prevent unnecessary laparotomy.

In the present study, two cycles of NAC with gemcitabine plus S-1 were administered. Whether this NAC regimen is appropriate for PDAC patients with unresectable predictors at laparotomy such as high pretreatment serum CA19-9 levels (>260 ng/ml), high pretreatment maximum tumor size (>25 mm), and borderline resectable status must be discussed. In fact, prolonged neoadjuvant therapy can offer further benefit to surgical resection for locally advanced PDAC (27). Even if two cycles of NAC with gemcitabine plus S-1 are completed, prolonged administration of gemcitabine plus S-1 for such patients may improve resection rates and surgical outcomes Further studies of prolonged NAC with gemcitabine plus S-1 in such patients are needed.

Conversely, NAC with gemcitabine plus S-1 might be insufficient for improving the outcomes of PDAC patients with these three predictors. Gemcitabine plus nab-paclitaxel

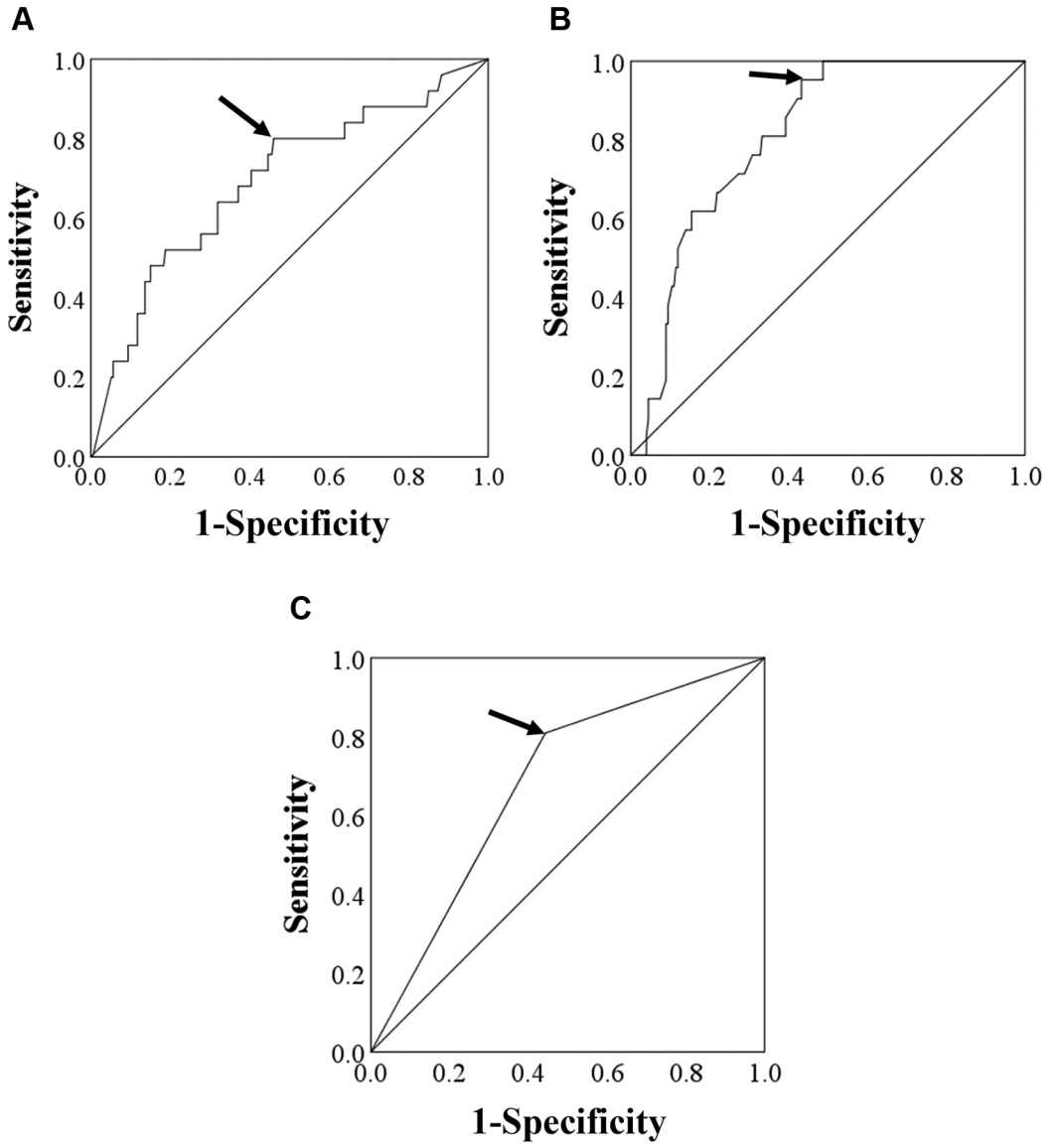

Figure 1. *The receiver operating characteristic curve for predicting unresectable disease at laparotomy of pretreatment CA19-9 level (ng/ml) (A), pretreatment maximum tumor size (mm), (B) and borderline resectable status (C) in patients who planned to undergo surgical resection for pancreatic ductal adenocarcinoma.*

and FOLFIRINOX have also been reported to be useful NAC regimens for patients with PDAC (28, 29). From the aspect of local control, patients with locally advanced PDAC who received neoadjuvant chemoradiation had a significantly better Evans stage and were less likely to develop lymph node metastasis compared with patients who received NAC (30). NAC with other regimens or neoadjuvant chemoradiation might be indicated for PDAC patients with these three predictors to improve their outcomes.

The limitations of our study should be acknowledged. The definition of unresectable disease at laparotomy owing to locally advanced PDAC was different in each department. This retrospective study included both patients who did and did not receive NAC. Any changes in tumor size and tumor marker levels due to NAC were not investigated. Although NAC was not significantly associated with unresectable disease at laparotomy, patients who received NAC prior to surgical resection might have been included in the OP group. Further analyses, such as propensity score matching analyses and prospective studies, which have fewer biases, are required.

In summary, pretreatment CA19-9 levels (>260 U/ml), pretreatment maximum tumor size (>25 mm), and anatomical

borderline resectable status were significantly associated with laparotomy only and palliative surgery in PDAC patients who planned to undergo surgical resection. In patients with anatomical borderline resectable status, NAC regimens other than gemcitabine plus S-1 should be considered to improve surgical outcomes.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this article.

Authors' Contributions

TS – preparation of manuscript; TA, KK – revision of the manuscript; MI – statistical analysis; SS, TS, MT, YS, SM, YI – performed surgery and chemotherapy.

Acknowledgements

The Authors wish to thank Dr. TA, MI, and KK for their advice on experimental design. In addition, the Authors would like to thank the timely help given by Dr SS, TS, MT, YS, SM, and YI in analyzing the large amount of patient's data.

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Received August 3, 2021
Revised August 29, 2021
Accepted August 31, 2021