**Name of Journal:** *World Journal of Gastrointestinal Surgery*

**Manuscript NO:** 67554

**Manuscript Type:** ORIGINAL ARTICLE

***Retrospective Study***

**Preoperative serum carbohydrate antigen 19-9 levels predict early recurrence after the resection of early-stage pancreatic ductal adenocarcinoma**

Hong S *et al*. Early recurrence of early-stage PDAC

Sarang Hong, Ki Byung Song, Dae Wook Hwang, Jae Hoon Lee, Woohyung Lee, Eunsung Jun, Jaewoo Kwon, Yejong Park, Seo Young Park, Naru Kim, Dakyum Shin, Hyeyeon Kim, Minkyu Sung, Yunbeom Ryu, Song Cheol Kim

**Sarang Hong, Ki Byung Song, Dae Wook Hwang, Jae Hoon Lee, Woohyung Lee, Eunsung Jun, Yejong Park, Dakyum Shin, Hyeyeon Kim, Minkyu Sung, Yunbeom Ryu, Song Cheol Kim,** Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, Asan Medical Center, Seoul 05505, South Korea

**Jaewoo Kwon,** Department of Surgery, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul 03181, South Korea

**Seo Young Park,** Department of Statistics and Data Science, Korea National Open University, Seoul 03087, South Korea

**Naru Kim,** Department of Surgery, Uijeongbu St. Mary's Hospital, College of Medicine, Gyeonggido 11765, South Korea

**Author contributions:** Hong S and Song KB designed the research; Hong S wrote the paper; Hwang DW, Lee JH, Lee W, Kwon J, and Park Y provided clinical advice; Jun E and Park SY performed analyses and interpretation of the data; Kim N, Shin D, Kim H, Sung M, Ryu Y performed the data curation; Song KB and Kim SC supervised the report.

**Corresponding author: Ki Byung Song, MD, PhD, Associate Professor,** Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, Asan Medical Center, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, South Korea. mtsong21c@amc.seoul.kr

**Received:** May 3, 2021

**Revised:** May 31, 2021

**Accepted:** August 23, 2021

**Published online:** November 27, 2021

**Abstract**

BACKGROUND

Pancreatic ductal adenocarcinoma (PDAC) is a serious disease with a poor prognosis. Only a minority of patients undergo surgery due to the advanced stage of the disease, and patients with early-stage disease, who are expected to have a better prognosis, often experience recurrence. Thus, it is important to identify the risk factors for early recurrence and to develop an adequate treatment plan.

AIM

To evaluate the predictive factors associated with the early recurrence of early-stage PDAC.

METHODS

This study enrolled 407 patients with stage I PDAC undergoing upfront surgical resection between January 2000 and April 2016. Early recurrence was defined as a diagnosis of recurrence within 6 mo of surgery. The optimal cutoff values were determined by receiver operating characteristic (ROC) analyses. Univariate and multivariate analyses were performed to identify the risk factors for early recurrence.

RESULTS

Of the 407 patients, 98 patients (24.1%) experienced early disease recurrence: 26 (26.5%) local and 72 (73.5%) distant sites. In total, 253 (62.2%) patients received adjuvant chemotherapy. On ROC curve analysis, the optimal cutoff values for early recurrence were 70 U/mL and 2.85 cm for carbohydrate antigen 19-9 (CA 19-9) levels and tumor size, respectively. Of the 181 patients with CA 19-9 level > 70 U/mL, 59 (32.6%) had early recurrence, compared to 39 (17.4%) of 226 patients with CA 19-9 level ≤ 70 U/mL (*P <* 0.001). Multivariate analysis revealed that CA 19-9 level > 70 U/mL (*P* = 0.006), tumor size > 2.85 cm (*P* = 0.004), poor differentiation (*P* = 0.008), and non-adjuvant chemotherapy (*P* = 0.025) were significant risk factors for early recurrence in early-stage PDAC.

CONCLUSION

Elevated CA 19-9 level (cutoff value > 70 U/mL) can be a reliable predictive factor for early recurrence in early-stage PDAC. As adjuvant chemotherapy can prevent early recurrence, it should be recommended for patients susceptible to early recurrence.

**Key Words:** Pancreatic ductal adenocarcinoma; Early recurrence; Upfront surgery; Carbohydrate antigen 19-9; Adjuvant chemotherapy

**©The** **Author(s) 2021.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Citation:** Hong S, Song KB, Hwang DW, Lee JH, Lee W, Jun E, Kwon J, Park Y, Park SY, Kim N, Shin D, Kim H, Sung M, Ryu Y, Kim SC. Preoperative serum carbohydrate antigen 19-9 levels predict early recurrence after the resection of early-stage pancreatic ductal adenocarcinoma. *World J Gastrointest Surg* 2021; 13(11): 1423-1435

**URL:** https://www.wjgnet.com/1948-9366/full/v13/i11/1423.htm

**DOI:** https://dx.doi.org/10.4240/wjgs.v13.i11.1423

**Core Tip:** Pancreatic ductal adenocarcinoma (PDAC) is a serious disease with a poor prognosis. Only a minority of patients undergo surgery due to the advanced stage of the disease, and recurrence, an important prognostic factor, often occurs even after surgical resection. We identified the factors associated with the early recurrence of early-stage PDAC evaluating 407 patients with stage I PDAC undergoing upfront surgical resection. Early recurrence was defined as disease recurrence within 6 mo of surgery. Preoperative carbohydrate antigen 19-9 level > 70 U/mL determined by receiver operating characteristic analyses was a significant risk factor for early recurrence in early-stage PDAC.

**INTRODUCTION**

Pancreatic ductal adenocarcinoma (PDAC) is a serious disease with a poor prognosis, with a 5-year survival rate of only 6%-10%[1,2]. While surgical resection offers the only possibility of cure[3], only a minority of patients are diagnosed with resectable disease because of local advancement or metastases at initial presentation[4]. Furthermore, even if patients undergo surgical treatment, about 70% experience disease recurrence[5-7]. Thus, efforts have been made to improve prognosis by early detection of the disease. However, even if patients are diagnosed and undergo surgery in the early stages, recurrence often occurs, and early recurrence is an important factor associated with a poor prognosis[8-10]. Therefore, it is necessary to identify the factors associated with the early recurrence of early-stage PDAC.

Various factors associated with PDAC prognosis have been reported including tumor size, preoperative carbohydrate antigen 19-9 (CA 19-9) concentration, histological grade, resection margin status, lymph node metastasis, and vascular invasion[11,12]. Among them, CA 19-9 levels, histological grade, and microvascular invasion are also associated with early recurrence[9,13-15]. Especially, serum CA 19-9 level, the only parameter that can be evaluated before surgery, has been regarded as a means of diagnosing malignant pancreatic neoplasms with high sensitivity and specificity[16,17]. Previous studies have also shown that CA 19-9 levels are a predictive factor for poor prognosis[18-22]. Elevated serum CA 19-9 levels are suggestive of pancreatic cancer recurrence, and serum CA 19-9 measurement is usually performed during surveillance, along with imaging tests, to detect cancer progression. Although imaging tests are performed to confirm cancer recurrence, CA 19-9 measurement is easier and more reproducible in terms of surveillance.

To improve the prognosis of pancreatic cancer, the risk factors for early recurrence should be evaluated, and active treatment, such as surgical treatment followed by chemotherapy, should be performed. Furthermore, as patients with early-stage disease, who are expected to have a better prognosis, often experience early recurrence, it is important to identify the risk factors for early recurrence and develop an adequate treatment plan. Pre- and post-operative CA 19-9 levels have been used to predict disease progression; however, few studies have demonstrated the effectiveness of CA 19-9 as a marker for early recurrence. This study evaluated the risk factors for early recurrence in patients with American Joint Committee on Cancer (AJCC) 8th edition stage I PDAC after upfront surgery. We set the optimal cutoff CA 19-9 level and evaluated the power of CA 19-9 as a detector of early recurrence of early-stage PDAC. We also evaluated the importance of adjuvant chemotherapy as a therapeutic modality for early-stage patients to reduce the chance of early recurrence.

**MATERIALS AND METHODS**

Between January 2000 and April 2016, 2029 consecutive patients underwent surgical resection for PDAC at Asan Medical Center (Seoul, South Korea). PDAC was histologically confirmed in all patients, and patients with other pancreatic tumors such as intraductal papillary mucinous adenocarcinoma, adenosquamous carcinoma, mucinous carcinoma, acinar cell carcinoma, and malignant endocrine carcinoma were excluded. Of these, 648 patients had tumor-node-metastasis (TNM) stage IA and IB disease based on permanent pathologic reports. Forty-eight patients who received neoadjuvant chemotherapy, forty-four who were lost to follow-up, and five with incomplete data on preoperative serum CA 19-9 levels were excluded. Patients whose CA 19-9 levels were measured when they had jaundice (preoperative total bilirubin levels ≥ 2 mg/dL) were excluded to avoid the effect of obstructive jaundice on CA 19-9 values. Patients with preoperative CA 19-9 level < 2 U/mL were considered as Lewis antibody-negative patients; thus, they were considered to be unable to express CA 19-9 and were excluded from this study. Finally, 407 patients who underwent upfront surgical resection for stage I PDAC were enrolled in this study (Figure 1). Data regarding age, sex, body mass index, type of operation, pathology, recurrence, and preoperative serum CA 19-9 levels were obtained retrospectively from medical records. All patients underwent either abdominal computed tomography (CT), magnetic resonance imaging, or both preoperatively for the evaluation of tumor lesion and resectability. The pathologic stage was determined according to the TNM Classification of Malignant Tumors, 8th edition, from the AJCC.

All serum CA 19-9 values were measured using an electrochemiluminescence immunoassay kit in the institution’s laboratory. The recommended upper normal limit for CA 19-9 is 37 U/mL. CA 19-9 levels were examined within 1 mo before the surgery. When patients developed jaundice due to tumor invasion of the biliary tract, interventions were performed, including endoscopic nasobiliary drainage, endoscopic retrograde biliary drainage, or percutaneous transhepatic biliary drainage.

Distal pancreatectomy was the standard procedure for tumors of the pancreatic neck, body, or tail. Pancreaticoduodenectomy (pylorus-preserving or pylorus-resecting) was performed for tumors located in the pancreas head or uncinate. Total pancreatectomy was performed in patients in whom intra-operative frozen biopsy showed positive resection margin, remnant pancreas was atrophied, pancreatitis was very severe involving the whole pancreas, and pancreatic duct was dilated throughout the pancreas. The surgeries were performed using either an open approach or laparoscopically. The pathologic characteristics included tumor size, resection margin status, lymph node metastasis, differentiation, lymphovascular invasion, and perineural invasion status. The resection margins were evaluated by a pathologist as either R0 (no cancer cells observed microscopically at the resection margin) or R1 (cancer cells observed microscopically at the resection margin or a free margin of < 1 mm).

The patients were followed up with abdominal CT and blood tests, including tests for tumor markers, CA 19-9, and carcinoembryonic antigen levels, every 3 mo for the first 2 years after surgery and every 3-6 mo thereafter. When the CA 19-9 level was elevated or abdominal CT suggested tumor recurrence, additional positron emission tomography (PET) was performed. Tumor recurrence was defined based on radiological or biopsy-proven evidence. Radiological recurrence was determined by radiologists and defined as progressive soft-tissue growth or hypermetabolic lesions at specific sites, as determined by CT or PET. Biopsy was not routinely required for the diagnosis of tumor recurrence.

Overall survival (OS) was defined as the time from surgery to the date of death from any cause or the last follow-up visit. Disease-free survival (DFS) was defined as the time from surgery to the first documented detection of recurrence on CT or PET during regular follow-up or death, whichever occurred first. Early recurrence was defined as disease relapse within 6 mo of surgery.

***Statistical analyses***

Continuous variables are expressed as medians and interquartile ranges. OS and DFS were estimated using the Kaplan–Meier method, and the values were compared using log-rank tests. Receiver operating characteristic (ROC) curves were constructed to estimate the optimal cutoff values for preoperative CA 19-9 levels and tumor size as predictors of postoperative early recurrence, with the Youden index used as a summary measure of the ROC curve. The *χ*2 or Fisher’s exact test was performed for categorical variables. Univariate and multivariate analyses were performed using a logistic regression model to determine the predictive variables associated with early recurrence. *P* < 0.05 was considered statistically significant. The statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, United States).

**RESULTS**

***Patient’s characteristics***

This study included 407 patients. Of them, 225 (55.3%) were male and 182 (44.7%) were female, with a median age of 62 years (30-88). The median follow-up time was 31 mo (1-227). A total of 254 patients (62.4%) underwent pancreatectomy for tumors located at the head or uncinate, and 151 (37.1%) underwent pancreatectomy for tumors located at the pancreatic neck, body, or tail. Permanent biopsy result revealed that the tumor involved both head and body in two cases (0.5%). The median tumor size was 2.5 cm (0.3-4), and the median number of harvested lymph nodes was 14. A total of 253 patients (62.2%) received adjuvant chemotherapy. The median OS durations in the early and non-early recurrence groups were 11 and 42 mo, respectively (*P <* 0.001). The demographic and pathologic findings are summarized in Table 1.

The median follow-up duration was 31 mo. A total of 304 patients (75.4%) showed disease recurrence, with a median time to recurrence of 10 mo. In this study, 99 (32.6%) and 205 (67.4%) patients had local and distant recurrences, respectively. Among the patients with distant recurrence, the most common recurrence site was the liver, followed by peritoneal seeding and the lungs. A total of 98 patients (24.1%) had early recurrence, and 309 (75.9%) had either non-early or no recurrence. Among patients with early recurrence, 26 (26.5%) had local recurrence and 72 (73.5%) had distant recurrence. The most common recurrence site was the liver (37.8%).

***Preoperative serum CA 19-9 and early recurrence***

ROC curve analysis revealed 70 U/mL as the optimal cutoff preoperative CA 19-9 level for predicting early recurrence (area under the curve [AUC] 0.605; sensitivity 60.2%, specificity 60.5%; Figure 2A). In this study, 181 patients had preoperative serum CA 19-9 level ≥ 70 U/mL; among them, 59 patients (32.6%) had early recurrence. In contrast, 39 of the 226 patients (17.4%) with CA 19-9 level < 70 U/mL had early recurrence (*P <* 0.001). We had postoperative serum CA 19-9 values checked within 1 mo after the operation. Among the 181 patients with preoperative serum CA 19-9 values ≥ 70 U/mL, 171 patients (94%) had decreased serum CA 19-9 values after the operation, and of these, 49 patients (28.7%) experienced early disease recurrence. Nine patients had rather increased serum CA 19-9 value, and all of these patients experienced early recurrence. In one patient, we did not check the postoperative CA 19-9 value. ROC curve analysis also revealed 2.85 cm as the optimal cutoff tumor size for predicting early recurrence (AUC 0.619; sensitivity 56.1%, specificity 65.0%; Figure 2B).

***Multivariate analysis on risk factors for early recurrence***

Table 2 shows the risk factors associated with early recurrence after curative surgical resection for TNM stage I PDAC. In the univariate analysis, preoperative serum CA 19-9 level (*P <* 0.001), tumor size (*P <* 0.001), and differentiation (*P* = 0.005) were significant. In the multivariate analysis, a CA 19-9 level ≥ 70 U/mL (odds ratio [OR] 1.987; *P* = 0.006), tumor size ≥ 2.85 cm (OR 2.039; *P* = 0.004), poor differentiation (OR 3.493 for poorly differentiated *vs* well differentiated; *P* = 0.008), and non-adjuvant chemotherapy (OR 1.745; *P* = 0.025) were significantly associated with early recurrence after surgical resection.

***Early recurrence vs non-early recurrence***

Table 3 shows the comparisons between the early and non-early recurrence groups. Of the 407 patients, 98 (24.1%) had early disease recurrence and 309 (75.9%) had non-early or no recurrence. The preoperative CA 19-9 level significantly differed between the groups (*P* = 0.004), with higher CA 19-9 levels prevalent among patients in the early recurrence group. Tumors in the early recurrence group were larger (*P* = 0.001) and showed a more poorly differentiated histology (*P* = 0.002) than those in the non-early recurrence group. Although the difference was not significant (*P* = 0.058), more patients in the non-early recurrence group received adjuvant chemotherapy. The recurrence pattern did not differ between the two groups.

**DISCUSSION**

PDAC is one of the most lethal malignancies and is a leading cause of cancer-related deaths worldwide. Despite substantial improvements in the survival rates of patients with other major malignancies, the survival rates of patients with PDAC have remained relatively unchanged. PDAC is usually detected in the advanced stage, and restricted treatment options contribute to its poor overall prognosis. Approximately 70%-80% of patients with PDAC experience locoregional and/or distant recurrence after surgery[5-7]. Recent efforts have sought to improve the early diagnosis of PDAC[23-27]. Early detection and treatment of PDAC can help improve the dismal prognosis of this aggressive cancer. We evaluated the OS of 407 early-stage (stage I) PDAC patients who underwent upfront pancreatic surgery between January 2000 and April 2016. The median OS of those with early-stage disease was 34.5 mo, significantly longer than that of those with advanced-stage disease (18.5 mo; *P* < 0.001). However, patients with early-stage PDAC often experience early recurrence after curative resection, leading to a poor prognosis. The results of the present study suggested the presence of a heterogeneous microenvironment in terms of pre-existing occult metastasis in early-stage PDAC as 24.1% (*n* = 98) of patients with early recurrence showed a relatively poor prognosis compared to that in the non-early recurrence group (75.9%, *n* = 309) (median OS: 11 *vs* 42 mo; *P* < 0.001). Therefore, it is important to identify the clinicopathological factors and therapeutic modalities that are significantly associated with early recurrence in early-stage PDAC to improve the prognosis of this dismal disease.

Several studies have reported risk factors associated with OS and recurrence after surgical resection for PDAC, including tumor size, histological grade, resection margin status, lymph node metastasis, perineural invasion, venous invasion, and preoperative CA 19-9 levels[6,28-31]. The results of our study suggested that high preoperative serum CA 19-9 levels, large tumor size, poor differentiation, and non-adjuvant chemotherapy were independent predictors of early recurrence in early-stage PDAC.

Tumor size is an independent predictor of poor prognosis in patients with PDAC[32-34]. Based on previous studies, we further evaluated the effect of tumor size on recurrence and survival in patients with early-stage PDAC treated with curative resection. The median DFS and OS were 10 mo and 23 mo, respectively, in the larger tumor group (≥ 2.85 cm) and 21 mo and 38 mo in the smaller tumor group (< 2.85 cm), demonstrating that tumor size was an independent clinical predictor for early recurrence in early-stage PDAC. Since tumor size, as expected, affected disease prognosis and early recurrence even in early-stage disease, scheduled surveillance for detecting early recurrence is necessary in early-stage patients with large tumors.

Tumor histological grade is an important independent prognostic factor for PDAC. In general, poorly differentiation reflects aggressive malignant behavior accompanying a larger tumor size, a high rate of nodal metastases, microvascular invasion, and perineural invasion, causing poor OS[35-38]. The results of this study demonstrated that poor tumor differentiation was a significant factor for early recurrence in early PDAC compared to well differentiation (*P* = 0.008). Tumor grade is associated with not only survival but also recurrence. Although tumor grade is not used to evaluate tumor stage in PDAC according to the AJCC 8th edition guidelines, it should be considered critical for predicting disease prognosis and recurrence, especially in patients with early-stage PDAC.

CA 19-9, also referred to as Sialyl Lewis-A, is regularly expressed on cancer cells and can be detected by the monoclonal antibody 19-9[8]. Although it was originally isolated from a human colorectal cancer cell line[39], CA 19-9 is a good marker for the diagnosis of PDAC and the detection of recurrence during routine surveillance. It can be easily evaluated by a simple blood test, and numerous reports have suggested CA 19-9 as a meaningful tumor marker not only for diagnosis but also for prognosis prediction[18]. However, the specific role of CA 19-9 and the optimal serum CA 19-9 cutoff values for predicting early PDAC recurrence have remained controversial. We focused on early-stage PDAC patients who underwent primary pancreatectomy to evaluate the clinical impact of preoperative serum CA 19-9 levels on early recurrence. To the best of our knowledge, this is the first study to identify the independent relationship between serum CA 19-9 levels and early recurrence of early-stage PDAC in a large number of patients. In this study, we demonstrated that an elevated CA 19-9 level (cutoff value: > 70 U/mL) can be a reliable predictive marker for early recurrence in early-stage PDAC. This finding supports the notion that preoperative serum CA 19-9 levels could reflect biological aggressiveness and the presence of tumor micrometastases in early-stage PDAC.

Adjuvant chemotherapy was introduced following the assessment of its benefits, in which 5-fluorouracil (5-FU) and gemcitabine (GEM)-based regimens showed a survival effect[40,41]. The CONKO-005 trial also demonstrated that adjuvant chemotherapy with GEM and capecitabine doubled the 5-year OS rate to approximately 30%-50% compared to mono-regimen chemotherapy[42]. Adjuvant chemotherapy improved not only OS but also DFS[43,44]. In our institution, adjuvant chemotherapy is recommended to basically all patients regardless of the disease stage. However, the final decision is made based on the oncologists’ decision and patients’ postoperative general condition. In our study, patients who were in poor general condition, with postoperative complication, old, or reluctant to chemotherapy did not undergo adjuvant chemotherapy. Otherwise, 5-FU or GEM-based regimens were generally administered. We found that the number of patients who received adjuvant chemotherapy was higher in the late- and non-recurrence groups than in the early recurrence group (*n* = 200 *vs* 53), with adjuvant chemotherapy being an independent predictor of early recurrence (OR 0.573 [0.352–0.933]; *P* = 0.025) in early-stage PDAC. As few studies have assessed the effect of chemotherapy in early-stage disease, this result is meaningful in that we focused on early-stage patients. Adjuvant chemotherapy could be an effective treatment modality for reducing recurrence rates even in early-stage patients.

**CONCLUSION**

In conclusion, early recurrence often occurs even in stage I PDAC patients after upfront surgery, suggesting the need for the evaluation of predictive factors for early recurrence. In particular, CA 19-9 levels can be easily checked preoperatively and elevated CA 19-9 level (cutoff value > 70 U/mL) can be a reliable predictive factor. Furthermore, adjuvant chemotherapy should be considered for patients who are susceptible to early recurrence to achieve a better prognosis, even in patients with early-stage PDAC.

**ARTICLE HIGHLIGHTS**

***Research background***

One of the reasons that pancreatic ductal adenocarcinoma (PDAC) has a poor prognosis is that the disease is diagnosed at advanced stage. Various factors associated with PDAC prognosis have been evaluated and effort have been made to improve prognosis by early detection of the disease.

***Research motivation***

Serum carbohydrate antigen 19-9 (CA 19-9) has been used as a means of diagnosing malignant pancreatic neoplasm and detection of disease recurrence. However, the effectiveness of CA 19-9 as a marker for early recurrence of disease has not been well studied yet.

***Research objectives***

This study aimed to set the optimal cutoff preoperative CA 19-9 level and evaluate the effectiveness of CA 19-9 as a detector of early recurrence of early-stage PDAC.

***Research methods***

A total of 407 patients with stage I PDAC undergoing upfront surgical resection between January 2000 and April 2016 were evaluated. The optimal cutoff values were determined by receiver operating characteristic and the risk factors for early recurrence were identified using a logistic regression model.

***Research results***

Ninety-eight patients (24.1%) experienced early disease recurrence. The optimal cutoff value of preoperative CA 19-9 for early recurrence was determined as 70 U/mL. Patients with high CA 19-9 level showed the tendency to have early recurrence more frequently. Tumor size > 2.85 cm, poor differentiation, and non-adjuvant chemotherapy were also demonstrated to be significant risk factors for early recurrence in early-stage PDAC.

***Research conclusions***

Elevated CA 19-9 level can be regarded as a reliable parameter predicting early disease recurrence. Adjuvant chemotherapy should be recommended for patients susceptible to early recurrence.

***Research perspectives***

Preoperative CA 19-9 can be a guidance for patients to undergo effective treatment modality to reduce early recurrence, thus leading to a better prognosis.

**REFERENCES**

1 **Siegel RL**, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* 2018; **68**: 7-30 [PMID: 29313949 DOI: 10.3322/caac.21442]

2 **Tempero MA**, Malafa MP, Al-Hawary M, Asbun H, Bain A, Behrman SW, Benson AB 3rd, Binder E, Cardin DB, Cha C, Chiorean EG, Chung V, Czito B, Dillhoff M, Dotan E, Ferrone CR, Hardacre J, Hawkins WG, Herman J, Ko AH, Komanduri S, Koong A, LoConte N, Lowy AM, Moravek C, Nakakura EK, O'Reilly EM, Obando J, Reddy S, Scaife C, Thayer S, Weekes CD, Wolff RA, Wolpin BM, Burns J, Darlow S. Pancreatic Adenocarcinoma, Version 2.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2017; **15**: 1028-1061 [PMID: 28784865 DOI: 10.6004/jnccn.2017.0131]

3 **Yamada S**, Fujii T, Yabusaki N, Murotani K, Iwata N, Kanda M, Tanaka C, Nakayama G, Sugimoto H, Koike M, Fujiwara M, Kodera Y. Clinical Implication of Inflammation-Based Prognostic Score in Pancreatic Cancer: Glasgow Prognostic Score Is the Most Reliable Parameter. *Medicine (Baltimore)* 2016; **95**: e3582 [PMID: 27149487 DOI: 10.1097/MD.0000000000003582]

4 **Jamieson NB**, Denley SM, Logue J, MacKenzie DJ, Foulis AK, Dickson EJ, Imrie CW, Carter R, McKay CJ, McMillan DC. A prospective comparison of the prognostic value of tumor- and patient-related factors in patients undergoing potentially curative surgery for pancreatic ductal adenocarcinoma. *Ann Surg Oncol* 2011; **18**: 2318-2328 [PMID: 21267785 DOI: 10.1245/s10434-011-1560-3]

5 **Sperti C**, Pasquali C, Piccoli A, Pedrazzoli S. Recurrence after resection for ductal adenocarcinoma of the pancreas. *World J Surg* 1997; **21**: 195-200 [PMID: 8995078 DOI: 10.1007/s002689900215]

6 **Tummers WS**, Groen JV, Sibinga Mulder BG, Farina-Sarasqueta A, Morreau J, Putter H, van de Velde CJ, Vahrmeijer AL, Bonsing BA, Mieog JS, Swijnenburg RJ. Impact of resection margin status on recurrence and survival in pancreatic cancer surgery. *Br J Surg* 2019; **106**: 1055-1065 [PMID: 30883699 DOI: 10.1002/bjs.11115]

7 **Vincent A**, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. *Lancet* 2011; **378**: 607-620 [PMID: 21620466 DOI: 10.1016/S0140-6736(10)62307-0]

8 **Ballehaninna UK**, Chamberlain RS. The clinical utility of serum CA 19-9 in the diagnosis, prognosis and management of pancreatic adenocarcinoma: An evidence based appraisal. *J Gastrointest Oncol* 2012; **3**: 105-119 [PMID: 22811878 DOI: 10.3978/j.issn.2078-6891.2011.021]

9 **Sugiura T**, Uesaka K, Kanemoto H, Mizuno T, Sasaki K, Furukawa H, Matsunaga K, Maeda A. Serum CA19-9 is a significant predictor among preoperative parameters for early recurrence after resection of pancreatic adenocarcinoma. *J Gastrointest Surg* 2012; **16**: 977-985 [PMID: 22411488 DOI: 10.1007/s11605-012-1859-9]

10 **Yamamoto Y**, Ikoma H, Morimura R, Konishi H, Murayama Y, Komatsu S, Shiozaki A, Kuriu Y, Kubota T, Nakanishi M, Ichikawa D, Fujiwara H, Okamoto K, Sakakura C, Ochiai T, Otsuji E. Optimal duration of the early and late recurrence of pancreatic cancer after pancreatectomy based on the difference in the prognosis. *Pancreatology* 2014; **14**: 524-529 [PMID: 25287158 DOI: 10.1016/j.pan.2014.09.006]

11 **Izumo W**, Higuchi R, Furukawa T, Yazawa T, Uemura S, Shiihara M, Yamamoto M. Evaluation of preoperative prognostic factors in patients with resectable pancreatic ductal adenocarcinoma. *Scand J Gastroenterol* 2019; **54**: 780-786 [PMID: 31180790 DOI: 10.1080/00365521.2019.1624816]

12 **Fang LP**, Xu XY, Ji Y, Huang PW. The Prognostic Value of Preoperative Neutrophil-to-Lymphocyte Ratio in Resected Patients with Pancreatic Adenocarcinoma. *World J Surg* 2018; **42**: 3736-3745 [PMID: 30014292 DOI: 10.1007/s00268-018-4686-7]

13 **Nishio K**, Kimura K, Amano R, Yamazoe S, Ohrira G, Nakata B, Hirakawa K, Ohira M. Preoperative predictors for early recurrence of resectable pancreatic cancer. *World J Surg Oncol* 2017; **15**: 16 [PMID: 28069033 DOI: 10.1186/s12957-016-1078-z]

14 **Tsuchiya N**, Matsuyama R, Murakami T, Yabushita Y, Sawada YU, Kumamoto T, Endo I. Risk Factors Associated With Early Recurrence of Borderline Resectable Pancreatic Ductal Adenocarcinoma After Neoadjuvant Chemoradiation Therapy and Curative Resection. *Anticancer Res* 2019; **39**: 4431-4440 [PMID: 31366541 DOI: 10.21873/anticanres.13615]

15 **Kurahara H**, Maemura K, Mataki Y, Sakoda M, Iino S, Kawasaki Y, Arigami T, Mori S, Kijima Y, Ueno S, Shinchi H, Natsugoe S. A Therapeutic Strategy for Resectable Pancreatic Cancer Based on Risk Factors of Early Recurrence. *Pancreas* 2018; **47**: 753-758 [PMID: 29771771 DOI: 10.1097/MPA.0000000000001066]

16 **Mann DV**, Edwards R, Ho S, Lau WY, Glazer G. Elevated tumour marker CA19-9: clinical interpretation and influence of obstructive jaundice. *Eur J Surg Oncol* 2000; **26**: 474-479 [PMID: 11016469 DOI: 10.1053/ejso.1999.0925]

17 **Goonetilleke KS**, Siriwardena AK. Systematic review of carbohydrate antigen (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer. *Eur J Surg Oncol* 2007; **33**: 266-270 [PMID: 17097848 DOI: 10.1016/j.ejso.2006.10.004]

18 **Azizian A**, Rühlmann F, Krause T, Bernhardt M, Jo P, König A, Kleiß M, Leha A, Ghadimi M, Gaedcke J. CA19-9 for detecting recurrence of pancreatic cancer. *Sci Rep* 2020; **10**: 1332 [PMID: 31992753 DOI: 10.1038/s41598-020-57930-x]

19 **Bergquist JR**, Puig CA, Shubert CR, Groeschl RT, Habermann EB, Kendrick ML, Nagorney DM, Smoot RL, Farnell MB, Truty MJ. Carbohydrate Antigen 19-9 Elevation in Anatomically Resectable, Early Stage Pancreatic Cancer Is Independently Associated with Decreased Overall Survival and an Indication for Neoadjuvant Therapy: A National Cancer Database Study. *J Am Coll Surg* 2016; **223**: 52-65 [PMID: 27049786 DOI: 10.1016/j.jamcollsurg.2016.02.009]

20 **Dong Q**, Yang XH, Zhang Y, Jing W, Zheng LQ, Liu YP, Qu XJ. Elevated serum CA19-9 Level is a promising predictor for poor prognosis in patients with resectable pancreatic ductal adenocarcinoma: a pilot study. *World J Surg Oncol* 2014; **12**: 171 [PMID: 24890327 DOI: 10.1186/1477-7819-12-171]

21 **Takagi C**, Kikuchi Y, Shirakawa H, Hoshimoto S, Tomikawa M, Ozawa I, Hishinuma S, Ogata Y. Predictive Factors for Elevated Postoperative Carbohydrate Antigen 19-9 Levels in Patients With Resected Pancreatic Cancer. *Anticancer Res* 2019; **39**: 3177-3183 [PMID: 31177164 DOI: 10.21873/anticanres.13455]

22 **Asaoka T**, Miyamoto A, Maeda S, Tsujie M, Hama N, Yamamoto K, Miyake M, Haraguchi N, Nishikawa K, Hirao M, Ikeda M, Sekimoto M, Nakamori S. Prognostic impact of preoperative NLR and CA19-9 in pancreatic cancer. *Pancreatology* 2016; **16**: 434-440 [PMID: 26852169 DOI: 10.1016/j.pan.2015.10.006]

23 **Pereira SP**, Oldfield L, Ney A, Hart PA, Keane MG, Pandol SJ, Li D, Greenhalf W, Jeon CY, Koay EJ, Almario CV, Halloran C, Lennon AM, Costello E. Early detection of pancreatic cancer. *Lancet Gastroenterol Hepatol* 2020; **5**: 698-710 [PMID: 32135127 DOI: 10.1016/S2468-1253(19)30416-9]

24 **Zhou B**, Xu JW, Cheng YG, Gao JY, Hu SY, Wang L, Zhan HX. Early detection of pancreatic cancer: Where are we now and where are we going? *Int J Cancer* 2017; **141**: 231-241 [PMID: 28240774 DOI: 10.1002/ijc.30670]

25 **Melo SA**, Luecke LB, Kahlert C, Fernandez AF, Gammon ST, Kaye J, LeBleu VS, Mittendorf EA, Weitz J, Rahbari N, Reissfelder C, Pilarsky C, Fraga MF, Piwnica-Worms D, Kalluri R. Glypican-1 identifies cancer exosomes and detects early pancreatic cancer. *Nature* 2015; **523**: 177-182 [PMID: 26106858 DOI: 10.1038/nature14581]

26 **O'Brien DP**, Sandanayake NS, Jenkinson C, Gentry-Maharaj A, Apostolidou S, Fourkala EO, Camuzeaux S, Blyuss O, Gunu R, Dawnay A, Zaikin A, Smith RC, Jacobs IJ, Menon U, Costello E, Pereira SP, Timms JF. Serum CA19-9 is significantly upregulated up to 2 years before diagnosis with pancreatic cancer: implications for early disease detection. *Clin Cancer Res* 2015; **21**: 622-631 [PMID: 24938522 DOI: 10.1158/1078-0432.CCR-14-0365]

27 **Zhou M**, Diao Z, Yue X, Chen Y, Zhao H, Cheng L, Sun J. Construction and analysis of dysregulated lncRNA-associated ceRNA network identified novel lncRNA biomarkers for early diagnosis of human pancreatic cancer. *Oncotarget* 2016; **7**: 56383-56394 [PMID: 27487139 DOI: 10.18632/oncotarget.10891]

28 **Lüttges J**, Schemm S, Vogel I, Hedderich J, Kremer B, Klöppel G. The grade of pancreatic ductal carcinoma is an independent prognostic factor and is superior to the immunohistochemical assessment of proliferation. *J Pathol* 2000; **191**: 154-161 [PMID: 10861575 DOI: 10.1002/(sici)1096-9896(200006)191:2<154::Aid-path603>3.0.Co;2-c]

29 **Takahashi H**, Ohigashi H, Ishikawa O, Gotoh K, Yamada T, Nagata S, Tomita Y, Eguchi H, Doki Y, Yano M. 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 [PMID: 22123160 DOI: 10.1097/SLA.0b013e31823d813c]

30 **Bilici A**. Prognostic factors related with survival in patients with pancreatic adenocarcinoma. *World J Gastroenterol* 2014; **20**: 10802-10812 [PMID: 25152583 DOI: 10.3748/wjg.v20.i31.10802]

31 **Ansari D**, Bauden M, Bergström S, Rylance R, Marko-Varga G, Andersson R. Relationship between tumour size and outcome in pancreatic ductal adenocarcinoma. *Br J Surg* 2017; **104**: 600-607 [PMID: 28177521 DOI: 10.1002/bjs.10471]

32 **Marchegiani G**, Andrianello S, Malleo G, De Gregorio L, Scarpa A, Mino-Kenudson M, Maggino L, Ferrone CR, Lillemoe KD, Bassi C, Castillo CF, Salvia R. Does Size Matter in Pancreatic Cancer?: Reappraisal of Tumour Dimension as a Predictor of Outcome Beyond the TNM. *Ann Surg* 2017; **266**: 142-148 [PMID: 27322188 DOI: 10.1097/SLA.0000000000001837]

33 **Shimada K**, Sakamoto Y, Sano T, Kosuge T, Hiraoka N. Reappraisal of the clinical significance of tumor size in patients with pancreatic ductal carcinoma. *Pancreas* 2006; **33**: 233-239 [PMID: 17003643 DOI: 10.1097/01.mpa.0000232917.78890.01]

34 **Fortner JG**, Klimstra DS, Senie RT, Maclean BJ. Tumor size is the primary prognosticator for pancreatic cancer after regional pancreatectomy. *Ann Surg* 1996; **223**: 147-153 [PMID: 8597508 DOI: 10.1097/00000658-199602000-00006]

35 **Wasif N**, Ko CY, Farrell J, Wainberg Z, Hines OJ, Reber H, Tomlinson JS. Impact of tumor grade on prognosis in pancreatic cancer: should we include grade in AJCC staging? *Ann Surg Oncol* 2010; **17**: 2312-2320 [PMID: 20422460 DOI: 10.1245/s10434-010-1071-7]

36 **Hartwig W**, Hackert T, Hinz U, Gluth A, Bergmann F, Strobel O, Büchler MW, Werner J. Pancreatic cancer surgery in the new millennium: better prediction of outcome. *Ann Surg* 2011; **254**: 311-319 [PMID: 21606835 DOI: 10.1097/SLA.0b013e31821fd334]

37 **Crippa S**, Partelli S, Zamboni G, Barugola G, Capelli P, Inama M, Bassi C, Pederzoli P, Falconi M. Poorly differentiated resectable pancreatic cancer: is upfront resection worthwhile? *Surgery* 2012; **152**: S112-S119 [PMID: 22766365 DOI: 10.1016/j.surg.2012.05.017]

38 **Barugola G**, Partelli S, Marcucci S, Sartori N, Capelli P, Bassi C, Pederzoli P, Falconi M. Resectable pancreatic cancer: who really benefits from resection? *Ann Surg Oncol* 2009; **16**: 3316-3322 [PMID: 19707831 DOI: 10.1245/s10434-009-0670-7]

39 **Koprowski H**, Steplewski Z, Mitchell K, Herlyn M, Herlyn D, Fuhrer P. Colorectal carcinoma antigens detected by hybridoma antibodies. *Somatic Cell Genet* 1979; **5**: 957-971 [PMID: 94699 DOI: 10.1007/BF01542654]

40 **Neoptolemos JP**, Stocken DD, Bassi C, Ghaneh P, Cunningham D, Goldstein D, Padbury R, Moore MJ, Gallinger S, Mariette C, Wente MN, Izbicki JR, Friess H, Lerch MM, Dervenis C, Oláh A, Butturini G, Doi R, Lind PA, Smith D, Valle JW, Palmer DH, Buckels JA, Thompson J, McKay CJ, Rawcliffe CL, Büchler MW; European Study Group for Pancreatic Cancer. Adjuvant chemotherapy with fluorouracil plus folinic acid *vs* gemcitabine following pancreatic cancer resection: a randomized controlled trial. *JAMA* 2010; **304**: 1073-1081 [PMID: 20823433 DOI: 10.1001/jama.2010.1275]

41 **Oettle H**, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, Ridwelski K, Niedergethmann M, Zülke C, Fahlke J, Arning MB, Sinn M, Hinke A, Riess H. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. *JAMA* 2013; **310**: 1473-1481 [PMID: 24104372 DOI: 10.1001/jama.2013.279201]

42 **Sinn M**, Bahra M, Liersch T, Gellert K, Messmann H, Bechstein W, Waldschmidt D, Jacobasch L, Wilhelm M, Rau BM, Grützmann R, Weinmann A, Maschmeyer G, Pelzer U, Stieler JM, Striefler JK, Ghadimi M, Bischoff S, Dörken B, Oettle H, Riess H. CONKO-005: Adjuvant Chemotherapy With Gemcitabine Plus Erlotinib Versus Gemcitabine Alone in Patients After R0 Resection of Pancreatic Cancer: A Multicenter Randomized Phase III Trial. *J Clin Oncol* 2017; **35**: 3330-3337 [PMID: 28817370 DOI: 10.1200/JCO.2017.72.6463]

43 **Chikhladze S**, Lederer AK, Kousoulas L, Reinmuth M, Sick O, Fichtner-Feigl S, Wittel UA. Adjuvant chemotherapy after surgery for pancreatic ductal adenocarcinoma: retrospective real-life data. *World J Surg Oncol* 2019; **17**: 185 [PMID: 31706323 DOI: 10.1186/s12957-019-1732-3]

44 **Parikh AA**, Maiga A, Bentrem D, Squires MH 3rd, Kooby DA, Maithel SK, Weber SM, Cho CS, Katz M, Martin RC, Scoggins CR, Sutton J, Ahmad SA, Abbott DE, Carr J, Kim HJ, Yakoub D, Idrees K, Merchant N. Adjuvant Therapy in Pancreas Cancer: Does It Influence Patterns of Recurrence? *J Am Coll Surg* 2016; **222**: 448-456 [PMID: 26895735 DOI: 10.1016/j.jamcollsurg.2015.12.031]

**Footnotes**

**Institutional review board statement:** The study was reviewed and approved by the Institutional Review Board of Asan Medical Center, No. 2020-1540.

**Informed consent statement:** Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

**Conflict-of-interest statement:** No potential conflict of interest relevant to this article was reported.

**Data sharing statement:** No additional data are available.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Unsolicited manuscript

**Peer-review started:** May 3, 2021

**First decision:** May 27, 2021

**Article in press:** August 23, 2021

**Specialty type:** Surgery

**Country/Territory of origin:** South Korea

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): D

Grade E (Poor): 0

**P-Reviewer:** Ling Q, Ostwal V, Xie Q **S-Editor:**  Wu YXJ **L-Editor:** Filipodia **P-Editor:**  Wu RR

**Figure Legends**



**Figure 1 Flowchart of patient selection.** CA 19-9: Carbohydrate antigen 19-9; PDAC: Pancreatic ductal adenocarcinoma; TNM: Tumor-node-metastasis.



**Figure 2 Receiver operating characteristic curve of serum carbohydrate antigen 19-9.** A: Receiver operating characteristic (ROC) curve for carbohydrate antigen 19-9 (CA 19-9) values and early recurrence in tumor-node-metastasis (TNM) stage I patients who underwent pancreatic resection; B: ROC curve for tumor size and early recurrence in TNM stage I patients who underwent pancreatic resection. AUC: Area under the curve.

**Table 1 Patient demographics**

|  |  |
| --- | --- |
| **Characteristics** | **Patients, *n* = 407 (%)** |
| Age in yr, median (range) | 62 (30-88) |
| Sex, *n* (%) |
| Male | 225 (55.3) |
| Female | 182 (44.7) |
| BMI in kg/m2, median (range) | 23.2 (15.3-31.6) |
| Pre-op CA 19-9 in U/mL, *n* (%) |
| Normal | 167 (41) |
| Abnormal | 240 (59) |
| Tumor location, *n* (%) |
| Head/uncinate | 254 (62.4) |
| Neck/body/tail | 151 (37.1) |
| Head/body | 2 (0.5) |
| Tumor size, median, cm (range) | 2.5 (0.3-4.0) |
| Total number of harvested lymph nodes, median (range) | 14 (1-74) |
| Differentiation, *n* (%) |  |
| Well | 60 (14.9) |
| Poor | 288 (71.6) |
| Unknown | 54 (13.4) |
| Moderate | 5 (1.2) |
| Stage, *n* (%) |
| IA | 109 (26.8) |
| IB | 298 (73.2) |
| Adjuvant chemotherapy, *n* (%) |
| No | 154 (37.8) |
| Yes | 253 (62.2) |
| Recurrence within 6 mo, *n* (%) |
| No | 309 (75.9) |
| Yes | 98 (24.1) |

BMI: Body mass index; CA 19-9: Carbohydrate antigen 19-9.

**Table 2 Univariate and multivariate analyses of the factors associated with early recurrence**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Factors** | **Number of patients, *n* (%)** | **Univariate, *P* value** | **Odds ratio (95%CI)** | **Multivariate, *P* value** |
| Age in yr |  | 0.211 | ` |  |
| < 65 | 234 (57.5) |
| ≥ 65 | 173 (42.5) |
| Sex |  | 0.261 |  |  |
| Male | 225 (55.3) |  |  |  |
| Female | 182 (44.7) |  |  |  |
| Tumor size in cm |  | < 0.001 |  | 0.004 |
| < 2.85 | 244 (60.0) |  |  |  |
| ≥ 2.85 | 163 (40.0) |  | 2.039 (1.251-3.323) |  |
| RM |  | 0.555 |  | 0.638 |
| Negative | 348 (85.5) |  |  |  |
| Positive | 59 (14.5) |  | 1.177 (0.583-2.287) |  |
| Tumor location  |  | 0.394 |  |  |
| Head/uncinate | 254 (62.4) |  |  |  |
| Neck/body/tail | 151 (37.1) |  |  |  |
| Differentiation |  | 0.005 |  | 0.019 |
| Well | 60 (14.9) |  |  |  |
| Moderate | 288 (71.6) | 0.196 | 1.430 (0.652–3.133) | 0.372 |
| Poor | 54 (13.4) | 0.005 | 3.493 (1.377–8.858) | 0.008 |
| CA 19-9 in U/mL |  | < 0.001 |  | 0.006 |
| < 70 | 226 (55.5) |  |
| ≥ 70 | 181 (44.5) | 1.987 (1.217–3.243) |
| LVi |  | 0.126 |  | 0.372 |
| No | 263 (64.6) |  |
| Yes | 144 (35.4) | 1.270 (0.749–2.144) |
| PNi |  | 0.517 |  | 0.911 |
| No | 110 (27.0) |  |
| Yes | 297 (73.0) | 0.966 (0.535–1.780) |
| NLR |  | 0.768 |  |  |
| < 2  | 244 (60.0) |
| ≥ 2 | 163 (40.0) |
| Adj. CTx. |  | 0.059 |  | 0.025 |
| No | 154 (37.8) |  |
| Yes | 253 (62.2) | 0.573 (0.352–0.933) |

Adj. CTx.: Adjuvant chemotherapy; CA 19-9: Carbohydrate antigen 19-9; CI: Confidence interval; LVi: Lymphovascular invasion; NLR; Neutrophil-lymphocyte ratio; PNi; Perineural invasion; RM: Resection margin.

**Table 3 Comparisons between the early and non-early recurrence group**

|  |  |  |  |
| --- | --- | --- | --- |
| **Factors** | **Early recurrence, *n* (%)** | **Non-early recurrence, *n* (%)** | ***P* value** |
|  | ***N* = 98 (24.1%)** | ***N* = 309 (75.9%)** |  |
| Age in yr |  |  | 0.21 |
| <65 | 51 (52.0) | 183 (59.2) |  |
| ≥ 65 | 47 (48.0) | 126 (40.8) |  |
| Sex |  |  | 0.261 |
| Male | 59 (60.2) | 166 (53.7) |  |
| Female | 39 (39.8) | 143 (46.3) |  |
| Tumor size, median in cm |  |  | 0.001 |
| < 2.5 | 23 (23.5) | 129 (41.7) |  |
| ≥ 2.5 | 75 (76.5) | 180 (58.3) |  |
| RM |  |  | 0.555 |
| Negative | 82 (83.7) | 266 (86.1) |  |
| Positive | 16 (16.3) | 43 (13.9) |  |
| Tumor location |  |  | 0.712 |
| Head/uncinate | 63 (64.3) | 191 (62.2) |  |
| Neck/body/tail | 35 (35.7) | 116 (37.8) |  |
| Differentiation |  |  | 0.002 |
| Well | 9 (9.2) | 51 (16.5) |  |
| Moderate | 65 (66.3) | 223 (72.2) |  |
| Poor | 22 (22.4) | 32 (10.4) |  |
| Preoperative CA 19-9 in U/mL |  |  | 0.004 |
| Normal | 28 (28.6) | 139 (45.0) |  |
| Abnormal | 70 (71.4) | 170 (55.0) |  |
| LVi |  |  | 0.125 |
| No | 57 (58.2) | 206 (66.7) |  |
| Yes | 41 (41.8) | 103 (33.3) |  |
| PNi |  |  | 0.516 |
| No | 24 (24.5) | 86 (27.8) |  |
| Yes | 74 (75.5) | 223 (72.2) |  |
| NLR |  |  | 0.768 |
| < 2  | 60 (61.2) | 184 (59.5) |  |
| ≥ 2 | 38 (38.8) | 125 (40.5) |  |
| Adj. CTx. |  |  | 0.058 |
| No | 45 (45.9) | 109 (35.3) |  |
| Yes | 53 (54.1) | 200 (64.7) |  |
| Recurrence pattern |  |  | 0.121 |
| Local | 26 (26.5) | 73 (35.4) |  |
| Systemic | 72 (73.5) | 133 (64.6) |  |

Adj. CTx.: Adjuvant chemotherapy; CA 19-9: Carbohydrate antigen 19-9; LVi: Lymphovascular invasion; *N*: Total number of patients; NLR: Neutrophil-lymphocyte ratio; PNi: Perineural invasion; RM: Resection margin.



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** bpgoffice@wjgnet.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2021 Baishideng Publishing Group Inc. All rights reserved.**