

Relationship Between Serum CA 19-9 Levels and Lymphovascular and Perineural Invasion of the Tumor and Lymph Node Metastasis in Patients Operated due to Pancreatic Carcinoma

Pankreas Karsinomu Nedeniyle Ameliyat Edilen Hastalarda Serum CA 19-9 Düzeyleri ile Tümörün Lenfovasküler ve Perinöral Invazyonu ve Lenf Nodu Metastazı Arasındaki İlişki

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Abstract

Objectives: The aim of this study was to determine the relationship between serum CA 19-9 levels and lymphovascular and perineural invasion and lymph node metastasis in patients operated due to pancreatic cancer.

Materials and Methods: A total of 32 patients underwent pancreaticoduodenectomy or distal pancreatectomy at Sivas Cumhuriyet University Department of Surgical Oncology. CA 19-9 values were evaluated by retrospectively examining the data of the patients. By examining the pathology reports, the presence of lymphovascular and perineural invasion and lymph node metastasis was evaluated.

Results: The mean serum CA 19-9 level in patients with lymphovascular invasion was 242.38 U/mL, and the mean serum CA 19-9 level in patients without lymphovascular invasion was 31.73 U/mL. The mean serum CA 19-9 level was 220.93 U/mL in patients with perineural invasion and 15.23 U/mL in patients without perineural invasion. The mean serum CA 19-9 level was 238.52 U/mL in patients with lymph node metastasis and 35.16 U/mL in patients without lymph node metastasis. A value of 16.25 U/mL of serum CA 19-9 gives a positive result of 84.7% for lymphovascular invasion and 91.8% for perineural invasion. A value of 27.06 U/mL of serum CA 19-9 gives a positive result of 85.9% for lymph node metastasis.

Conclusion: Lymphovascular invasion was detected in 94.44% and perineural invasion was detected in 90.48% of our patients with serum CA19-9 values above 16.25 U/mL. Lymph node metastasis was detected in 80.7% of our patients with serum CA19-9 values above 27.06 U/mL. Before surgery, it is important to predict the probability of lymphovascular and perineural invasion of the tumor and lymph node metastasis, and to make the decision to perform broader surgery and perform adjuvant, neoadjuvant therapy and serum CA19-9 levels are of great benefit in this regard.

Key Words: Pancreatic Cancer, CA 19-9, Lymphovascular And Perineural Invasion

Öz

Amaç: Bu çalışmanın amacı pankreas kanseri nedeniyle ameliyat edilen hastalarda serum CA 19-9 düzeyleri ile lenfovasküler ve perinöral invazyon ve lenf nodu metastazı arasındaki ilişkiyi belirlemektir.

Gereç ve Yöntem: Sivas Cumhuriyet Üniversitesi Cerrahi Onkoloji Kliniği'nde, pankreatikoduodenektomi veya distal pankreatektomi uygulanan 32 hastanın verileri, CA 19-9 düzeyleri retrospektif olarak incelendi. Patoloji raporları incelenerek lenfovasküler ve perinöral invazyon varlığı, lenf nodu metastazı değerlendirildi.

Bulgular: Lenfovasküler invazyonu olan hastalarda ortalama serum CA 19-9 seviyeleri 242,38 U/mL, olmayan hastalarda ortalama serum CA19-9 seviyeleri 31,73 U/mL idi. Perinöral invazyonu olan hastalarda ortalama serum CA19-9 seviyeleri 220,93 U/mL idi, olmayan hastalarda ortalama serum CA 19-9 seviyeleri 15,23 U/mL idi. Lenf nodu metastazı olan hastalarda ortalama serum CA19-9 seviyeleri 238,52 U/mL, lenf nodu metastazı

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Received/Geliş Tarihi: 14.09.2021 Accepted/Kabul Tarihi: 22.10.2021

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Journal of Ankara University Faculty of Medicine is published by Galenos Publishing House.

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olmayan hastalarda ortalama serum CA 19-9 seviyeleri 35,16 U/mL idi. Serum CA19-9 değeri 16,25 U/ml lenfovasküler invazyon için %84,7 ve perinöral invazyon için %91,8 pozitif sonuç verir. Serum CA19-9 değeri, 27,06 U/mL lenf nodu metastazı için %85,9'luk bir pozitif sonuç vermektedir.

Sonuç: Serum CA 19-9 değerleri 16,25 U/mL'nin üzerinde olan hastalarımızın %94,44'ünde lenfovasküler invazyon, %90,48'inde perinöral invazyon saptandı. Serum CA 19-9 değerleri 27,06 U/mL'nin üzerinde olan hastalarımızın %80,7'sinde lenf nodu metastazı saptandı. Ameliyattan önce, tümörün lenfovasküler ve perinöral invazyon olasılığını, lenf nodu metastazını tahmin etmek, daha geniş bir ameliyat yapma ve adjuvan, neoadjuvan tedavi yapma kararını vermek önemlidir ve serum CA 19-9 düzeyi bu konuda büyük fayda sağlamaktadır.

Anahtar Kelimeler: Pankreas Kanseri, CA 19-9, Endovasküler Ve Perinöral İnvazyon

Introduction

Pancreatic cancer is shown as the 4th deadliest cancer in the world among all cancer types (1). At the time of diagnosis, 52% of the patients have diffuse disease, 26% of them have regional spread, and only 15-20% of the patients have the tumor in the surgical removal stage (2). While the one-year overall survival rate of pancreatic cancer is 26%, the five-year survival rate is 6% (3). The size, location, differentiation level, and lymph node relationship of the tumor have been associated with clinical outcomes. In addition, pancreatic cancer incidence and mortality rate increase with advancing age (4,5).

Cancer antigen (CA) 19-9 is a marker that can be seen at high levels in malignant tumors such as bile duct, colon, stomach, ovarian, hepatocellular, esophagus and pancreatic cancers. It is used for differential diagnosis of conditions that will be confused with pancreatic cancer and again for the evaluation of response to treatment and relapse in pancreatic cancer (6). High levels of CA 19-9 can also occur in benign conditions such as biliary tract obstruction, cholangitis, inflammatory bowel disease, acute or chronic pancreatitis, cirrhosis of the liver, cystic fibrosis, and thyroid diseases (7). Serum CA19-9 value after resection is an independent indicator of recurrence and life expectancy, and CA19-9 level is correlated with tumor spread and metastatic disease (8,9).

Lymphovascular invasion is the invasion of tumor cells into blood vessels or lymphatic vessels. Lymphovascular invasion is significant in affecting local recurrence, lymph node metastasis, distant metastasis, and disease-free life expectancy, so it is considered an important prognostic indicator. Although lymphatic and blood vessel invasion, lymph node metastasis and micrometastases to lymph nodes are prognostic criteria that determine survival and recurrence in ampulla cancer, it is also a determinant of postoperative liver metastasis according to some researchers (10,11). In pancreatic cancer, the rate of lymphovascular invasion in tumors less than 2 cm is 86%; in tumors of 4-6 cm, it is 100%. Lymph vessel invasion rates are high even in patients without lymph node metastasis (12). Lymph node metastasis and total lymph node metastatic lymph node rate in pancreatic cancer are also markers found by researchers to be prognostically significant (13,14).

Perineural invasion is the appearance of cancer cells in the medial part of the perineurium. Perineural invasion is one of the important pathways involved in the spread of pancreatic cancer (15). Plexus invasion is observed more frequently in pancreatic cancer located in the pancreatic head than distal bile duct cancer and vater papilla carcinoma (16). The fact that perineural invasion is in various spreading patterns, does not always follow lymph node metastasis, occurs both before and after lymph node metastasis and peritoneal spread, requiring a closer examination of perineural invasion in order to perform curative treatment and improve prognosis in patients with pancreatic cancer (16).

The aim of this study was to determine the relationship between serum CA 19-9 levels and lymphovascular and perineural invasion and lymph node metastasis in patients operated due to pancreatic cancer. The low number of patients and the single-center of the study were restrictive aspects of this study.

Materials and Methods

Ethics Committee Approval

Ethics committee approval of the study was obtained from Sivas Cumhuriyet University Clinical Research Ethics Committee with the decision numbered 2020-10/34. The study was also carried out in accordance with the Helsinki Declaration of Principles. We have received verbal consent from patients.

Study Population

A total of 32 patients with a pre-diagnosis of pancreatic cancer underwent pancreaticoduodenectomy or distal pancreatectomy at Sivas Cumhuriyet University Department of Surgical Oncology, between February 2015 and December 2019. The exclusion criteria of the study; the presence of another malignancy, metastatic disease, bile duct obstruction, cholangitis, inflammatory bowel disease, acute or chronic pancreatitis, liver cirrhosis.

Study Design

The data of the patients were analyzed retrospectively, and their demographic findings, CA 19-9 values, and stage of the disease were evaluated. The presence of lymphovascular and perineural invasion, lymph node metastasis, and tumor diameter

were evaluated by examining the pathology reports. Serum CA19-9 reference range is 0-37 U/mL.

Statistical Analysis

The data was recorded in the SPSS 25.0 software program (IBM Corp, Armonk, NY, USA). ChiSquare and Mann-Whitney U tests were used for statistical evaluation, and cases where the p value was below 0.05 were considered statistically significant. Receiver operator characteristic (ROC) curve analysis was used to determine over which limit CA19-9 was associated with perineural invasion.

Results

Of the patients, 14 (43.7%) were female and 18 (56.2%) were male. The mean age of the patients was 62.4 ± 6.1 (21-82). Pathology results of patients; there were 26 ductal adenocarcinoma, 4 neuroendocrine tumor, 2 intraductal papillary mucinous neoplasia. Of the patients, 21 (65.6%) had pancreaticoduodenectomy, and 11 (34.3%) had distal pancreatectomy. In 8 cases (25.0%), the tumor was found to be a good degree, in 21 (65.6%) to be a moderate degree, and in 3 (9.3%) to be a bad degree differential. The mean tumor diameter of the patients was 4.6 ± 2.1 cm. Lymphovascular invasion was detected in 18 (56.2%) of patients, perineural invasion in 21 (65.6%), lymph node metastasis in 26 (81.2%), CA 19-9 elevation in 19 (59.3%) (Table 1).

While lymphovascular invasion was detected in 3 (23.0%) of the patients with serum CA19-9 level below 37 U/mL, lymphovascular invasion was not detected in 10 (76.9%) of them. While lymphovascular invasion was detected in 15 (78.9%) of the patients whose CA19-9 level was above 37 U/mL, lymphovascular invasion was not detected in 4 (21.0%) of them. The CA19-9 level given in Table 2 was found to be statistically significant in lymphovascular invasion ($p < 0.001$).

While perineural invasion was detected in 4 (30.7%) of the patients with a CA 19-9 level below 37 U/mL, 9 (69.2%) of them did not have perineural invasion. While perineural invasion was detected in 17 (89.4%) of the patients whose CA19-9 level was above 37 U/mL, perineural invasion was not detected in 2 (10.5%) of them. CA19-9 level was found to be in a statistically significant relationship with perineural invasion ($p < 0.001$) (Table 2).

Lymph node metastasis was detected in 5 (38.4%) of the patients with a CA19-9 level below 37 U/mL, as shown in Table 2, while lymph node metastasis was not detected in 8 (61.5%). Lymph node metastasis was detected in 18 (94.7%) of the patients whose CA19-9 level was above 37 U/mL, while lymph node metastasis was not detected in 1 (5.2%). CA19-9 level was found to be in a statistically significant relationship with lymph node metastasis ($p < 0.001$).

Mean serum CA 19-9 levels in patients with lymphovascular invasion were 242.38 U/mL, and mean serum CA19-9 levels in patients without lymphovascular invasion were 31.73 U/mL. Mean serum CA19-9 levels in patients with perineural invasion were 220.93 U/mL, and mean serum CA 19-9 levels in patients without perineural invasion were 15.23 U/mL. Mean serum CA 19-9 levels in patients with lymph node metastasis were 238.52 U/mL, and mean serum CA19-9 levels in patients without lymph node metastasis were 35.16 U/mL (Table 3).

As a result of the ROC analysis performed to determine above which value the serum CA19-9 level increased the frequency of lymphovascular invasion, it was determined that the lymphovascular invasion rate increased significantly in CA19-9 values above 16.25 U/mL (Figure 1). A value of 16.25 U/mL of CA19-9 gives a positive result of 84.7% for lymphovascular invasion. As a result of the analysis, the positive predictive value of CA19-9 in predicting lymphovascular invasion is 94.44%. As a result of the ROC analysis, it was determined that the perineural invasion rate increased significantly at the values of CA19-9 above 16.25 U/mL (Figure 2). A value of 16.25 U/mL of CA19-9 gives a 91.8% positive result for perineural invasion. As a result of the analysis, the positive predictive value of CA19-9 in predicting perineural invasion is 90.48%. Similarly, looking at

Table 1: Demographic and clinicopathological characteristics of cases

| Cases of pancreatic cancer | Cases |
|---|------------|
| Age | 62.4±6.1 |
| Gender n (%) | |
| Female | 14 (43.7%) |
| Male | 18 (56.2%) |
| Performed surgery n (%) | |
| Pancreaticoduodenectomy | 21 (65.6%) |
| Distal pancreatectomy | 11 (34.3%) |
| Tumor grade n (%) | |
| 1 | 8 (25.0%) |
| 2 | 21 (65.6%) |
| 3 | 3 (9.3%) |
| Tumor diameter (cm) (mean ± SD*) | 4.6±2.1 |
| Lymphovascular invasion n (%) | |
| Yes | 18 (56.2%) |
| No | 14 (43.7%) |
| Perineural invasion n (%) | |
| Yes | 21 (65.6%) |
| No | 11 (34.3%) |
| Lymph node metastasis n (%) | |
| Yes | 26 (81.2%) |
| No | 6 (18.7%) |
| High level of CA 19-9 n (%) | |
| Yes | 19 (59.3%) |
| No | 13 (40.6%) |

SD*: Standard deviation

the results of ROC analysis to determine which value of CA19-9 level increased the frequency of lymph node metastasis, it was determined that the rate of lymph node metastasis increased significantly at values of CA19-9 above 27.06 U/mL (Figure 3). A value of 27.06 U/mL of CA19-9 gives a positive result of 85.9% for lymph node metastasis. As a result of the analysis, the positive predictive value of CA19-9 in predicting lymph node metastasis is 80.77%.

Discussion

Pancreatic cancer ranks 13th among the most common types of cancer in the world (17). Despite standard curative surgery, pancreatic cancer treatment results are still poor. One of the possible reasons for this is local recurrence as a result of perineural and lymphovascular invasion (16). There are many studies investigating a wide range of treatment options such as wider surgeries, neoadjuvant, adjuvant chemoradiotherapy, intraoperative radiation therapy with the aim of reducing or preventing local recurrence in pancreatic cancer (18,19). 80%

of pancreatic cancer cases are between the ages of 60-80, very rare under the age of 40 (20). While pancreatic cancer that occurs at a younger age is 3 times more common in men than in women, the difference between men and women disappears in advanced ages and the incidence is equalized (21). Similarly, 18 of the cases of our study were male patients, and the average age of all the cases taken in the study was 62.4 ± 6.1 .

CA 19-9, an important indicator for pancreatic carcinoma, can be caused by both normal and tumor-containing epithelial cells of the pancreas. It is used for differential diagnosis of diseases that will be confused with pancreatic cancer and again for the evaluation of response to treatment and relapse in pancreatic cancer (22). High CA 19-9 (>1,000 U/mL) levels often indicate an advanced tumor with no chance of resection, even if they are not sufficient to be considered a preoperative inoperability criterion (22). A decrease in the postoperative CA 19-9 level is correlated with good survival. Conversely, postoperative high levels are also correlated with short survival and high recurrence rate (22). In this study, the association between serum CA19-9 and height

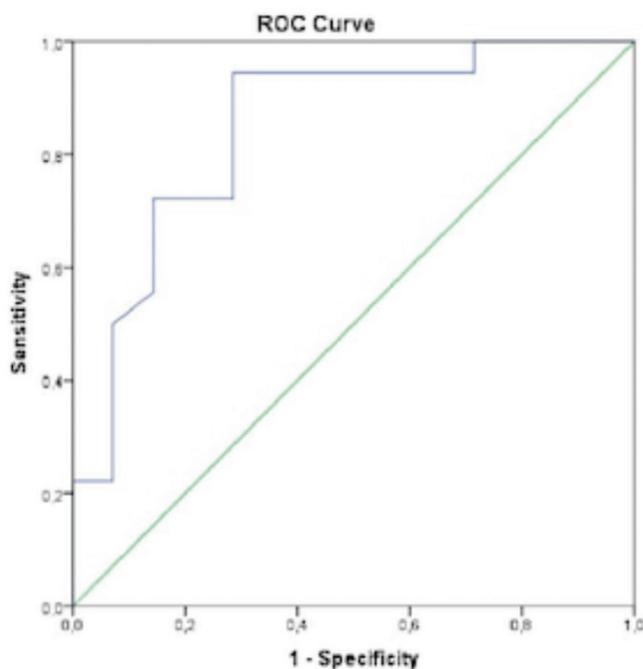


Figure 1: Lymphovascular invasion ROC analysis

ROC: Receiver operator characteristic

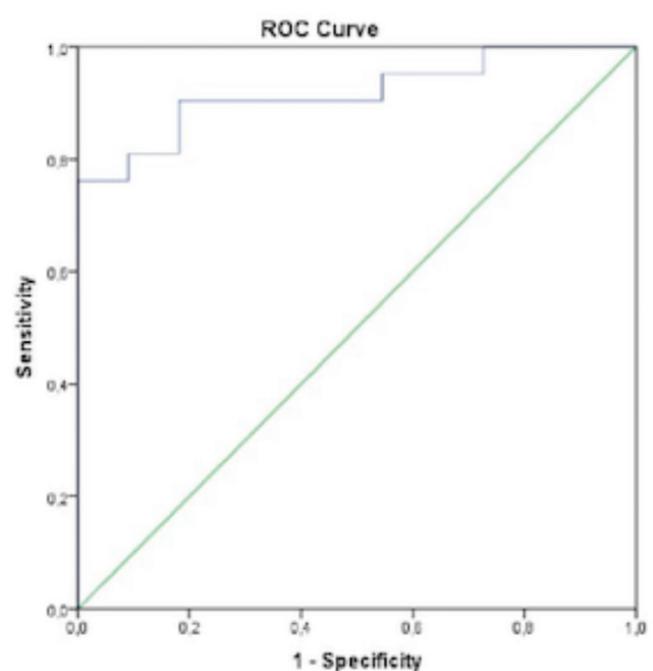


Figure 2: Perineural invasion ROC analysis

ROC: Receiver operator characteristic

Table 2: Comparison of Serum CA 19-9 levels with lymphovascular invasion, perineural invasion, and lymph node metastasis

| CA 19-9 | Normal (<37 U/mL) | | High (>37 U/mL) | | p-value |
|-------------------------|-------------------|-------------|-----------------|-------------|---------|
| | Yes n (%) | No n (%) | Yes n (%) | No n (%) | |
| Lymphovascular invasion | 3 (23.0) | 10 (76.9) | 15 (78.9) | 4 (21.0) | <0.001 |
| Perineural invasion | 4 (30.7) | 9 (69.2) | 17 (89.4) | 2 (10.5) | <0.001 |
| Lymph node metastasis | 5 (38.4) | 8 (61.5) | 18 (94.7) | 1 (5.2) | <0.001 |

and the incidence of lymphovascular and perineural invasion and lymph node metastasis was found to be significant. High levels of lymphovascular, perineural invasion and lymph node metastasis were detected in patients with Serum CA19-9 values above 37 U/mL. As a result of the ROC Curve analysis, serum CA19-9 values above 16.25 U/mL were statistically strongly correlated with lymphovascular and perineural invasion, and values above 27.06 U/mL were statistically strongly correlated with lymph node metastasis.

Lymphovascular and perineural invasion, common in pancreatic cancer, limits curative resection and causes abdominal pain, retropancreatic tumor spread, and poor prognosis (23). Pour et al. (24) in their study, they found that in pancreatic cancer (88%), 89% perineural invasion in intrapancreatic allograft followed by lymphatic invasion (33%) and vascular invasion (2%). In our study, 26 (81.2%) of the 32 patients who underwent pancreatectomy had lymph node metastasis,

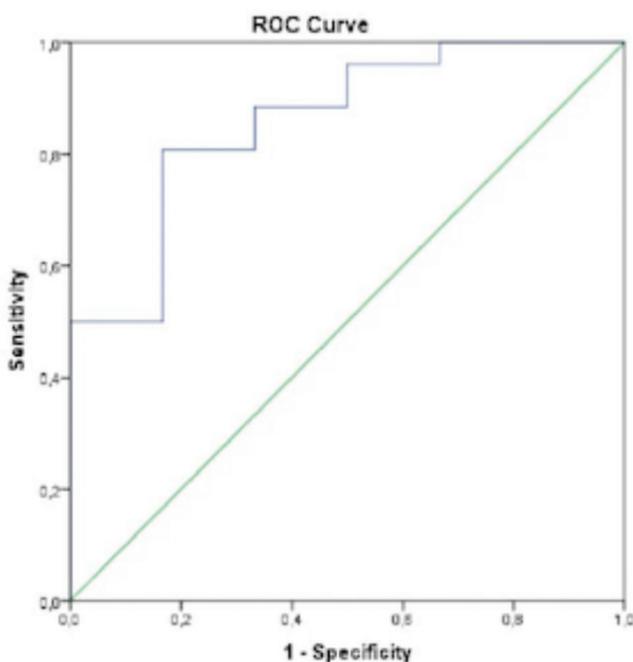


Figure 3: ROC analysis of lymph node metastasis

ROC: Receiver operator characteristic

Table 3: Comparison of CA 19-9 levels with lymphovascular invasion, perineural invasion and lymph node metastasis

| Min-Max | | Serum CA 19-9 (U/mL) | | |
|-------------------------|-----|----------------------|---------------------|--------|
| | | Mean \pm SD* | p-value | |
| Lymphovascular invasion | Yes | 6.70-1899.70 | 242.38 \pm 453.36 | <0.001 |
| | No | 1.20-171.30 | 31.73 \pm 47.06 | |
| Perineural invasion | Yes | 5.20-1899.70 | 220.93 \pm 422.14 | <0.001 |
| | No | 1.20-54.80 | 15.23 \pm 16.88 | |
| Lymph node metastasis | Yes | 5.80-1605.40 | 238.52 \pm 435.54 | <0.001 |
| | No | 2.20-162.00 | 35.16 \pm 36.01 | |

21 (65.6%) had perineural invasion, and 18 (56.2%) had lymphovascular invasion. Mean tumor size was 4.1 \pm 2.2 cm. In our study, no significant association was found between tumor size and lymphovascular and perineural invasion ($p>0.05$).

Perineural invasion can also be monitored without lymphatic or vascular invasion and is the only way of metastatic spread in some tumors (25). It is important to know in advance what conditions pancreatic tumors perform perineural and lymphovascular invasion and therefore require extended dissection, and to make the surgical plan according to this information in terms of determining the width of the surgery. Numerous studies are available with the use of tumor markers, especially CA19-9, along with radiological and endoscopic examinations from existing diagnostic methods to predict TNM staging of pancreatic carcinoma (26,27). Studies investigating the relationship between serum CA19-9 levels in patients with pancreatic carcinoma and lymphovascular invasion and perineural invasion of the tumor are very limited.

Early tumor invasion in pancreatic cancer is generally associated with aggressive spread, advanced vascularization and innervation, retroperitoneal settlement, and multifaceted lymphatic drainage. Lymph node status is generally accepted, prognosis is the determining factor. In studies, it was reported that 50-80% of patients had lymph node metastasis during surgery (28,29). For our study, this rate is 81.2%.

Lymphovascular and perineural invasion are not yet proven independent prognostic factors. As a result, lymphovascular invasion is observed in 70-80% of all R0 specialties, and perineural invasion in 50-100%, regardless of tumor size and lymph node status.

Wider, comparative studies are needed to tell whether the 16.25 U/mL limit value of serum CA19-9 found in our study can be used to make decisions such as making a broader dissection plan before surgery, applying adjuvant chemoradiotherapy to the patient in the case of curative resection, or applying neoadjuvant therapy.

Conclusion

It is known that the only curative treatment for pancreatic cancer is surgery. Despite standard curative surgery, it has been proven by studies that recurrence rates are high and that the causes of recurrence are lymphovascular and perineural invasion. Lymphovascular invasion was detected in 94.44% and perineural invasion was detected in 90.48% of our patients with Serum CA19-9 values above 16.25 U/mL. Predicting the likelihood of lymphovascular and perineural invasion of the tumor before surgery is important to decide whether to perform a larger surgery and to apply adjuvant and neoadjuvant therapy.

In order to use the CA19-9 limit value for this purpose, we need more extensive and prospective comparative studies.

Ethics

Ethics Committee Approval: Ethics committee approval of the study was obtained from Sivas Cumhuriyet University Clinical Research Ethics Committee with the decision numbered 2020-10/34.

Informed Consent: We have received verbal consent from patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.E.B., M.C.M., K.K., Concept: M.E.B., M.C.M., K.K., Design: M.E.B., M.C.M., K.K., Data Collection or Processing: M.E.B., M.C.M., K.K., Analysis or Interpretation: M.E.B., M.C.M., K.K., Literature Search: M.E.B., M.C.M., K.K., Writing: M.E.B., M.C.M., K.K.

Conflict of Interest: We declare that there is no conflicts of interest associated with this publication.

Financial Disclosure: We declare that we have not received any financial support to perform this study.

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