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ORIGINAL ARTICLE

The Role of Log Odds of Positive Lymph Nodes in Predicting the Survival after Resection for Ampullary Adenocarcinoma

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Abstract

Lymph node metastasis is a important factor on survival in ampullary adenocarcinoma. Log odds of positive lymph nodes (LODDS) is a novel prognostic indicator on lymph node status. We aimed to evaluate the prognostic impact of LODDS for the patients with ampullary adenocarcinoma who underwent R0 pancreaticoduodenectomy. The study includes 42 patients.. LODDS was calculated as "log (number of metastatic lymph nodes+0.5)/(number of total harvested nodes - metastatic lymph nodes+0.5)". LODDS subgroups were created based on their LODDS value: LODDS1(LODDS≤ − 1.5), LODDS2(−1.5 < LODDS≤ − 1.0), LODDS3(−1.0 < LODDS≤ − 0.5), LODDS4(LODDS> − 0.5). The mean survival time was 72.7 ± 7.82 months. Survival rates for 1, 3 and 5 years were 93%, 65% and 45%, respectively. The mean LODDS value was −1.0466 ± 0.51. LODDS subgroups show strong correlation with Overall Survival(OS). The mean survival were 114.8, 81.8, 56.6 and 25.6 months in LODDS subgroups 1, 2, 3 and 4, respectively (Log-rank; $p = 0.002$), in addition LOODS values shows correlation with perineural invasion and micro vascular invasion ($p = 0.015$ and $p = 0.001$ respectively). Findings in our patient group support the hypothesis that LODDS subgroups correlate with OS, and that value of LODDS has considerable role in prediction of OS as well.

Keywords Log odds of positive lymph nodes · Ampullary adenocarcinoma · LODDS · Microvascular invasion · Perineural invasion

Introduction

Primary ampullary carcinoma is known to be associated with longer overall survival rates compared to other periampullary region cancers; the incidence is reported as 4–6 cases per a million population [1, 2]. Survival depends on various factors after surgical treatment of ampullary adenocarcinoma such as extent of local invasion, status of surgical margins and presence or absence of lymph node (LN) metastasis [2–4]. Currently, the most commonly used staging system for ampullary adenocarcinoma is the tumor-node-metastasis (TNM) classification defined by (the) American Joint Committee on Cancer (AJCC) [5] According to this staging system; patients with lymph node (LN) metastasis are classified as N1 regardless of the number of metastatic lymph nodes. However recent studies have shown that, total number of metastatic LN, number of harvested LN and the ratio of metastatic LN count to total harvested LN count (LNR), also have prognostic importance [6–9]. According the literature, AJCC manual has been

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updated very recently and defined 1–3 LN metastasis as N1 and 4 or more LN metastasis as N2 [10].

Log odds of positive lymph nodes (LODDS), which is a novel prognostic indicator, was defined in the last decade. First studies assessed the efficiency of LODDS in colon and gastric cancer [11, 12], subsequently studies on breast cancer, rectal cancer and pancreatic cancer were published [13–15] LODDS is calculated as "log (number of metastatic lymph nodes + 0.5) / (number of total harvested nodes - metastatic lymph nodes + 0.5)".

In our study, we aimed to evaluate the prognostic impact of LODDS for patients with ampullary adenocarcinoma who were treated with R0 pancreaticoduodenectomy (± adjuvant chemo/radiotherapy) in a single center.

Material and Methods

Our study includes retrospective data about patients who underwent margin negative pancreaticoduodenectomy for pathologically proven primary ampullary adenocarcinoma between 2002 and 2015. It includes complete follow up data and excludes patients who died in perioperative period (0–90 days) and/or cases with positive surgical margins. We obtained patients informed consent and approval of the local ethical committee for this study (date: July 17, 2017; decision no: 2017/19–41).

Standard pancreaticoduodenectomy and standard LN dissection (LN regions 3, 4, 5, 6, 8a, 12b1, 12b2, 12c, 13a, 13b, 14a, 14b,17a, and 17b) were performed for all cases [16, 17]. Histopathologic examinations of specimens were performed by experienced pathologists. Details (demographics of the patients, presentation symptoms, operation histopathological features of tumors, status of surgical margins, harvested total LN count, metastatic LN count, perioperative morbidity and mortality, and oncological follow up) were analyzed from the prospectively collected database of our institution and pathology reports. Survival status and death dates of the patients were obtained from the national population registry system and the hospital registry system. Complications were classified according to Clavien–Dindo (C-D) classification system [18], pancreatic fistulas were classified according to the international study group (ISGPF) definition [19]. Mortality that occurred during the postoperative hospital stay or the time between 0 and 90 days after operation was recorded as perioperative mortality.

All patients were discussed both preoperatively and postoperatively and their adjuvant therapies were planned in the multidisciplinary tumor board.

None of the patients had neoadjuvant therapy, for completely resected stage IA ampullary carcinomas, only observation is preferred. In cases between stage IB to stage III, we prefer to apply sandwich therapy with 6 cycles of Gemcitabine, 5-fluorouracil and leucovorin (GEMFUFOL) followed by 5-FU based chemoradiotherapy and followed by 6 cycles GEMFUFOL [20]. Adjuvant concomitant radiotherapy was administered to patients with pathological T3 or T4 disease and/or positive lymph nodes. All patients were simulated with computed tomography and had either volumetric arc treatment (VMAT) or conformal radiotherapy plans. The clinical target volume (CTV) included the tumor bed, the pancreatic remnant, the hepaticojejunostomy, the pancreaticojejunostomy, the celiac axis, the superior mesenteric artery, and the paraaortic lymph nodes between the upper and lower slices of the CTVs defined, using the RTOG guideline [21]. Also the medulla spinalis, liver, kidneys, and the bowel bag were contoured as critical structures. Radiotherapy was given using high- energy photons and three or four fields and in conformal planned cases, and image guided radiotherapy (IGRT) tecnique was used in the VMAT case. In conformal planning cases, radiotherapy was given by using high-energy photons in three or four fields. In the VMAT case, image guided radiotherapy (IGRT) technique was employed. A total of 45 Gray dose was delivered in 25 fractions.

Patients were examined routinely during the first postoperative two years at 3-month intervals, during the third to fifth years at 6-month intervals, and at least annually thereafter until their death. Follow-up evaluation included physical examination, blood chemistry, cancer antigen 19–9 (CA 19–9) and carcinoembryonic antigen (CEA) levels, and thoracoabdominal computed tomography scan. We performed magnetic resonance imaging (MRI) and positron emission tomography (PET) if necessary.

LODDS was calculated as described in previous studies [12, 22]; "log (number of metastatic lymph nodes + 0.5)/ (number of total harvested nodes - metastatic lymph nodes + 0.5)" 0.5 is added to both numerator and denominator to avoid singularity. LODDS subgroups were created as previous studies according to LODDS value. LODDS1 ($LODDS \leq -1.5$), LODDS2 ($-1.5 < LODDS \leq -1.0$), LODDS3 ($-1.0 < LODDS \leq -0.5$), LODDS4 ($LODDS > -0.5$) [11, 15].

In our study, we investigated the impact of the two following factors on overall survival (OS): Log odds of positive lymph nodes and presence of LN metastasis.

All statistical analyses were performed with using SPSS 16.0 statistical package (SPSS, Chicago, Ill); OS was calculated as elapsed time from the operation date to time of death. Kaplan – Meier (K-M) estimator was used to calculate the OS rates; Log – rank test was used to compare differences between survival curves. Independent samples T-test was used for comparing normally distributed continuous variables, non-normally distributed variables was compared with using Mann–Whitney U test. Chi-square test was used for comparison of categorical data. $p < 0.05$ was considered significant.

Results

Between 2002 and 2015; 53 consecutive patients underwent pancreaticoduodenectomy for ampullary adenocarcinoma. Six patients (11%) follow-up data are not complete, 2 (3.7%) patients died during perioperative period (0–90 days); and on 4 (7.5%) patients' pathological specimens positive surgical margin was detected. The data of these 11 patients were not included in our statistical analyses. The causes of perioperative mortality were pulmonary embolism in first patient, acute myocardial infarction in second patient.

The median age of the patients was 62 ± 8.85 (range; 45–77). Twenty four patients were male (57%) and 18 patients were female (43%). The mean Body Mass Index (BMI) was 24.7 ± 10.1 and 26.2 ± 9.9 in male and female group respectively. 5 patients (12%) had coronary arterial disease, 7 patients (16%) had pulmonary comorbidities (4 patients had chronic pulmonary obstructive disease and 3 patients had asthma), 11 patients (26%) had diabetes mellitus type 2.

Patients' demographic characteristics are summarized in Table 1.

During the evaluation of the morbidity results of our series, we observed one Grade III B, 4 Grade III A, and 2 Grade II complications according to C-D classification. Only one patient required reoperation for abdominal hemorrhage. 5 patients (12%) developed pancreatic fistula, (2 grade A (5%); 3 grade B (7%)), one of them was re-operated for gastro-duodenal artery stump hemorrhage; all patients who had pancreatic fistulas were treated with non-operative procedures. Four patients (9.5%) had surgical site infection treated by intravenous wide spectrum antibiotics and/or negative pressure wound management.

The mean metastatic LN count was 1.8 ± 2.33 (range; 0–8) and the mean harvested LN count was 19.6 ± 11.49 (range; 6–45), 20 patients (48%) had only reactive lymph nodes, whereas 22 patients (52%) had one or more metastatic LN. According the latest TNM classification 10 patients (24%) were evaluated as N1 and 12 patients (28%) were evaluated as N2. Microvascular invasion and perineural invasion were detected in 26 (62%) and 7 (17%) patients, respectively (Table 1).

The mean LODDS value was −1.0466 ± 0.51. When we divide the patients into subgroups by their LODDS value; 8 patients (19%) were classified into LODDS 1, 18 patients (43%) into LODDS 2, 10 patients (24%) into LODDS 3, and 8 patients (14%) into LODDS 4 group (Table 2).

The mean survival time was 72.7 ± 7.82 months. Survival rates for 1, 3 and 5 years were 93%, 65% and 45%, respectively.

Recurrences were observed in 11 (26%) patients. 3 (7%) patients had local recurrence and 8 (19%) patients had metastasis (3 hepatic, 2 peritoneal, 2 lung). The mean disease-free survival time was 70.1 ± 8.12 months. Disease-free survival rates for 1, 3 and 5 years were 90%, 63% and 43%, respectively.

The OS of patients with LN metastasis was significantly shorter than non-metastatic patients (log – rank; $p = 0.005$); the median survival of metastatic LN and non – metastatic LN groups were 95.2 and 52.8 months. 5-year survival rates of patients with LN metastasis and without LN metastasis were 31% and 68% respectively (Fig. 1), but there was no survival difference between N1 and N2 groups; The median survival of N1 and N2 groups were 53.4 months and 51.9 months respectively.

When we grouped the patients according to presence of <2 AJCC and ≥ 2 metastatic lymph nodes Log-rank; $p = 0.008$) and < 3 and ≥ 3 metastatic lymph nodes (Log-rank; $p = 0.016$), we found significant difference in OS rates, However, there was no statistically significant difference when we selected the cut-off point as 4 or more for metastatic LN (Log-rank; $p = 0.077$). In non-parametric tests, LOODS values shows

Table 1 Demographical and histopathological features of patients

Median Age (range)	62 (45–77)
Gender	
Male	24 (57%)
Female	18 (43%)
BMI *	
Male	24.7 ± 10.1
Female	26.2 ± 9.9
Comorbidities	
Coronary Arterial Disease,	5 (12%)
Chronic Pulmonary Obstructive Disease Asthma	4 (10%)
Diabetes Mellitus Type 2	3
	11(26%)
Lymph Node Status	
No Metastatic Lymph Node	20 (48%)
≥ 1 Metastatic Lymph Node	22 (52%)
Mean Metastatic Lymph Node Count (range)	1.8 (0–8)
Mean Harvested Lymph Node Count (range)	19.6 (6–45)
T stage **	
pT1	5 (12%)
pT2	17 (40%)
pT3	16 (38%)
pT4	4 (10%)
Microvascular invasion	
Absent	16 (38%)
Present	26 (62%)
Perineural invasion	
Absent	35 (83%)
Present	7 (17%)

BMI Body Mass Index

**T stage* the size and extent of the main tumor

Table 2 Mean survival times and patient numbers in LODDS groups

LODDS	Patients number (ratio)	Median survival time (months)
LODDS 1 *(LODDS ≤ −1.5)*	8; (19%)	114.81 ± 17.01
LODDS 2 *(−1.5 < LODDS ≤ −1.0)*	18 (43%)	81.8 ± 11.12
LODDS 3 *(−1.0 < LODDS ≤ −0.5)*	10 (24%)	56.6 ± 14.03
LODDS 4 *(LODDS > −0.5)*	8 (14%)	29.8 ± 10.63

*LODDS: Log odds of positive lymph nodes

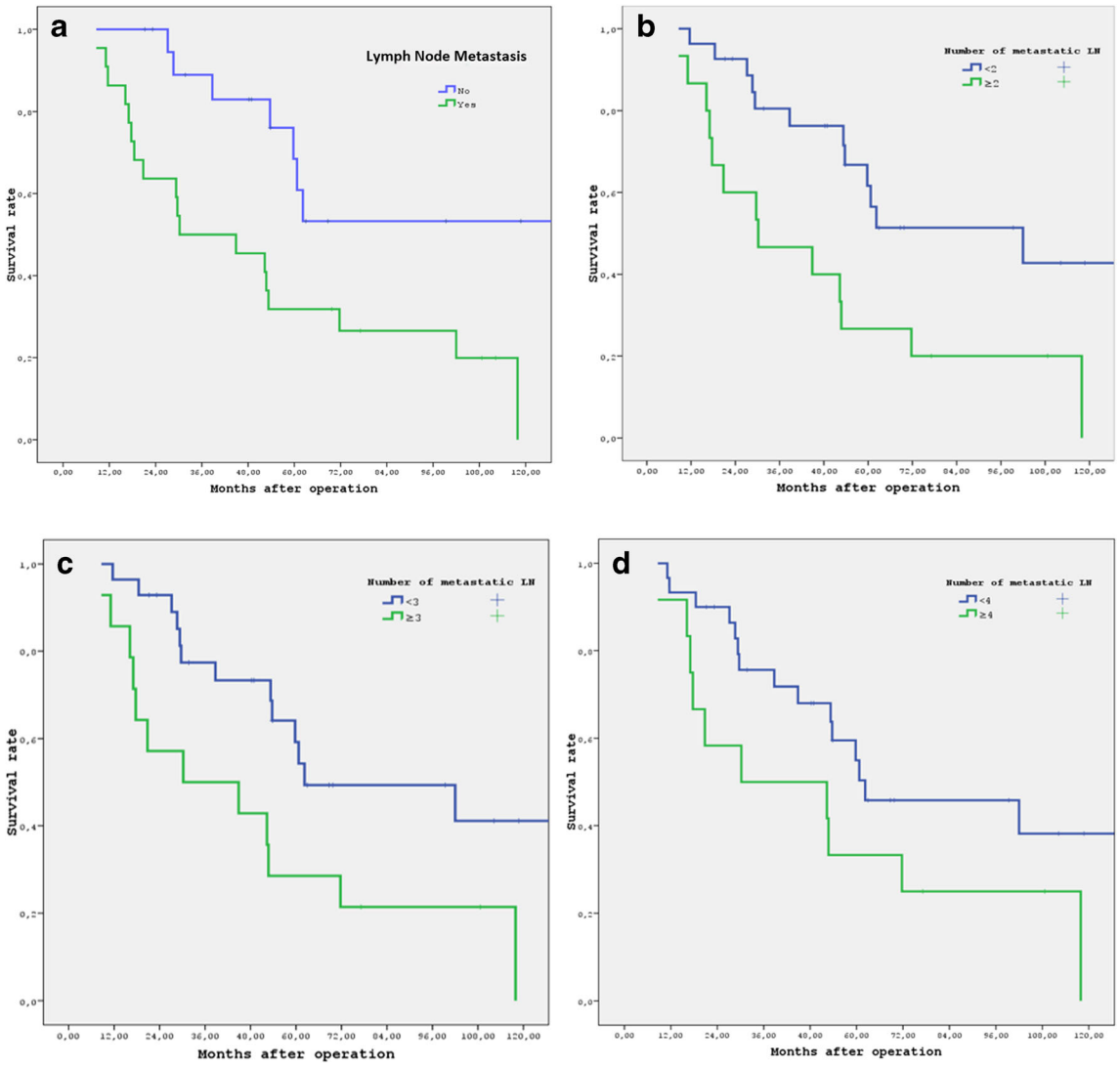

Fig. 1 Kaplan-Meier curves for the R0 Ampullary adenocarcinoma patients according to presence of lymhp node metastasis and number(s) of metastatic lymph nodes. **a** Kaplan-Meier curves for the R0 Ampullary adenocarcinoma patients, stratified by Lymph Node (LN) metastasis; $p = 0.005$. **b** Kaplan-Meier curves for the R0 Ampullary adenocarcinoma patients, stratified by number of Lymph Node (LN) metastasis <2, or ≥ 2; $p = 0.008$. **c** Kaplan-Meier curves for the R0 Ampullary adenocarcinoma patients, stratified by number of Lymph Node (LN) metastasis <3, or ≥ 3; $p = 0.016$. **d** Kaplan-Meier curves for the R0 Ampullary adenocarcinoma patients, stratified by number of Lymph Node (LN) metastasis <4, or ≥ 4; $p = 0.077$

correlation with perineural invasion and micro vascular invasion (Mann-Whitney U; $p = 0.015$ and $p = 0.001$ respectively).

LODDS subgroups show strong correlation with OS. The mean survival were 114.8, 81.8, 56.6 and 25.6 months in LODDS subgroups 1, 2, 3 and 4, respectively (Log-rank; $p = 0.002$) (Table 2, Fig. 2). On the other hand, we did not find statistically significant difference between LODDS subgroups and disease free survival (Log-rank; $p = 0.54$).

Harvested total LN count (< 12 or ≥ 12); (< 14 or ≥ 14); (< 16 or ≥ 16) and (< 19 or ≥ 19) were not associated with OS (Log-rank; $p = 0.667$, $p = 0.65$, $p = 0.48$, $p = 0.39$ respectively).

Discussion

Ampullary carcinomas are associated with longer survival and relatively earlier diagnosis than other periampullary region cancers. After margin negative resection for ampullary carcinoma, reported rate of 5-year survival rate is more than 35% [8, 23]. Since our institution has substantial experience in hepatopancreatobiliary region diseases, only specialized surgeons performed pancreatobiliary surgery and pathological examinations were performed by experienced pathologists, the OS rates in our series are similar to those in high volume centers.

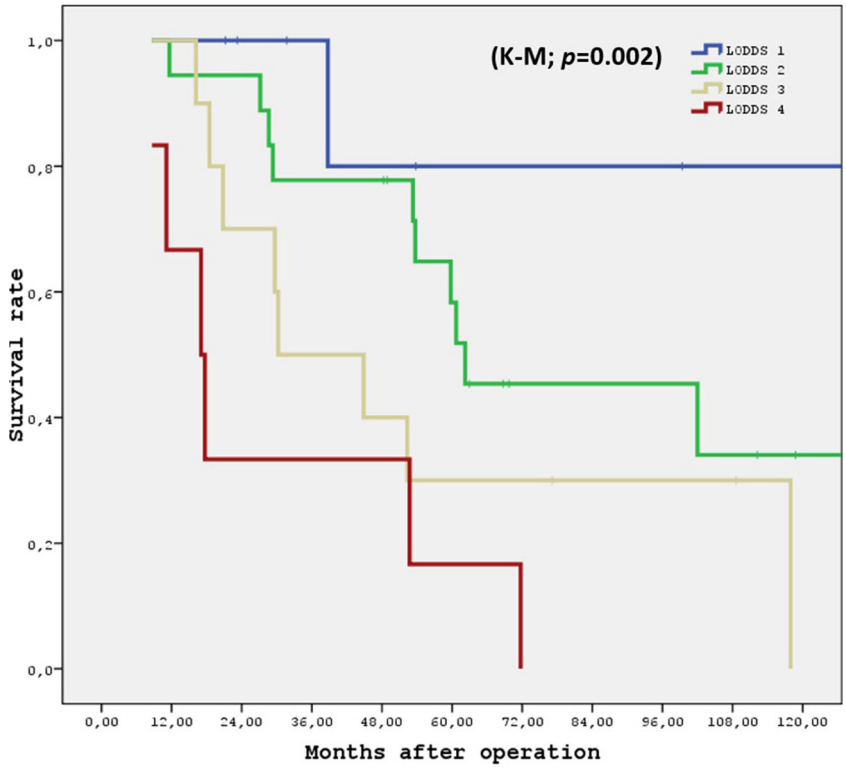

Fig. 2 Kaplan-Meier curves for the R0 Ampullary adenocarcinoma patients, stratified by LODDS subgroups; $p = 0.002$. *LODDS: Log odds of positive lymph nodes

Several factors such as histopathologic grade, presence of LN metastasis, perineural invasion, margin negative surgical resection affect the survival in ampullary carcinomas [1, 9].

Various studies have found that most important prognostic factor in ampullary carcinoma is the presence of LN metastasis [5, 6, 9, 23–27]. 5 years survival rates in patients with and without LN metastasis are 45% and 31% respectively [1]. The present study revealed similar results too. Patients with LN metastasis had significantly shorter OS compared to patients with no LN metastasis.

The most commonly used staging system world-wide for ampullary carcinomas is the AJCC classification system. Until the last update, patients with ≥1 LN metastases are classified as N1 regardless of the number of metastatic lymph nodes in the AJCC system [5]. Several studies have been published in recent years in order to evaluate the prognostic significance of the total number of metastatic LNs, totally harvested number of LNs, metastatic/total LN ratios [6–9, 23, 25, 26, 28–31].

In parallel to the increasing experience of the surgical and pathology team, the total number of harvested lymph nodes increased as well. The number of totally harvested LN might demonstrate the radicality of lymphadenectomy. The 7th edition of the AJCC cancer staging manual recommends harvesting minimum 12 LNs for accurate staging. Falconi et al. [6) reported the dissection of ≥16 lymph nodes whereas Chen et al. [23) reported the dissection of ≥14 lymph nodes as an independent prognostic factor for ampullary adenocarcinoma.

In this study, no significant relationship was found between OS and totally harvested LN counts ≥12, ≥14, ≥16 or ≥ 19 (which is the mean number of harvested LN count in our cases).

Several studies have found the number of metastatic LN as a prognostic factor for ampullary adenocarcinoma [7, 9, 26, 28, 30–32]. Choi et al. [28] claimed that the presence of ≥2 LN metastases was associated with poor prognosis, Sierzega et al. [7], Sakata et al. [30] and Sommerville et al. [31] reported that the presence of ≥4 metastatic LNs was affiliated with short OS. Additionally, Lee et al. [32] and Kang et al. [9] found that presence of ≥3 LN metastases is an important prognostic factor in ampullary carcinomas. Moreover, Kang et al. [9] have proposed a new nodal classification system as node-negative (N0), 1–2 LN's positive (N1), and ≥ 3 LN's positive (N2), in their Surveillance, Epidemiology, and End Results (SEER) data-based studies which includes 1057 cases and novel version of AJCC cancer staging manual defined N1 and N2 groups as 1–3 positive LN's and ≥ 4 LN's respectively [10].

The prognosis is expected to get worse as the number of metastatic LNs increases. Also our study demonstrates that patients with LN metastasis had worse outcomes. We found significantly shorter OS when the cutoff value in LN metastasis was determined as ≥2 and ≥ 3. However, there was no statistically significant difference when cut off value was ≥4. The count of metastatic LNs might be affected by the total number of harvested LN. If the total number of LNs obtained is limited, tumor staging may result in down-staging [26]. Inspired by this condition, several studies have aimed to assess the importance of metastatic LNs and totally harvested LNs ratio in ampullary carcinoma [6, 7, 30, 33]. The limitations of these studies are the use of different cut-off values and limited number of cases.

Major limitations of our study are the nature of study (retrospective analyses of data), limited number of patients and experience of single center.

In addition to the above-mentioned parameters, a new method, called "LODDS", has been described in recent years to evaluate the prognostic significance of LN metastasis. This method has some theoretical advantages over LNR. In LNR evaluation, patients without LN metastasis are defined as "LNR 0", regardless of the total number of harvested LNs. Even if the patients have different numbers of metastatic LNs and total number of harvested LNs, they get the same ratio results (e.g. 2/4 or 5/10). The LODDS method ensures the distinguishing in these situations.

Lahat et al. [15] have included all N0 patients in the LODDS1 subgroup, regardless the logarithmic calculation results in their studies on early stage pancreatic ductal adenocarcinomas. In our study, patients were divided into the appropriate LODDS subgroups based on logarithmic calculation results.

Sun et al. [11] and LaTorre et al. [34] designed 5 LODDS subgroups in their studies; Arslan et al. [22] and Huang et al. [14] used different cut-off values and designed 3 and 5 LODDS groups, respectively. In our patient group, none of the patients had LODDS value >0. As we did not have a LODDS 5 subgroup, we designed 4 LODDS subgroups similar to the study of Lahat et al. [15].

The findings in our series also show that LODDS is an effective method for predicting OS. Furthermore, LODDS values also correlated with other prognostic factors, perineural invasion and microvascular invasion. These correlations have never been mentioned in previous studies on LODDS.

In the literature, several studies show that LODDS is an effective method that correlates with prognosis in gastric, colon, rectum, pancreas and many other malignancies [11, 12, 14, 22, 34]. Only one study evaluated the efficiency of LODDS in ampullary carcinomas, Kwon et al. [35] found that LODDS is a prognostic factor for locoregional disease free survival, but one should kept in mind that only two LODDS subgroups were created in Kwon et al. [35] study.

In conclusion findings in our patient group support the hypothesis that LODDS subgroups show correlation with OS, and LODDS has a strong value in prediction of OS. For widespread use of the LODDS classification, larger prospective randomized studies are needed. Also the value ranges and cut-off points of the LODDS subgroups need to be clearly defined for each malignancy.

Compliance with Ethical Standards

Conflict of Interest All authors declare that there is no potential and real conflict of interest.

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