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ORIGINAL ARTICLE

Prognostic Value of Metastatic Lymph Node Ratio in Pancreatic Cancer

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Abstract

Lymph node involvement in pancreatic adenocancer is one of the strongest predictors of prognosis. However, the extent of lymph node dissection is still a matter of debate and number of dissected nodes varies widely among patients. In order to homogenize this diverse group of patients and more accurately predict their prognosis, we aimed to analyze the effect of metastatic lymph node ratio as an independent prognostic factor. We retrospectively analyzed medical recordings of 326 patients with pancreatic cancer who were treated in a tertiary medical oncology center over a 10-year period. Both in univariate and multivariate analyses, metastatic lymph node ratio proved to be a strong predictor of prognosis which was unaffected from heterogeneity of our patient population and can be used to facilitate predict prognosis of patients who underwent lymph node dissection to various extents and with future studies it can emerge as a successful tool for creating prognostic subgroups of the disease.

Keywords Prognostic value · Metastatic lymph node ratio · Pancreatic cancer

Introduction

Pancreatic cancer (PC) is one of the most aggressive cancers and with 200,000 annual new cases, it is the fourth most common cause of cancer-related deaths worldwide [1, 2]. It has a very poor prognosis with reported overall 5-year survival rates between 1 and 5% that increases up to 15–25% with radical resection [1–3]. Despite advances in chemotherapeutics, surgery maintains its major role in treatment and more radical surgical approaches are being offered in the literature [4, 5].

Lymph node metastasis (LNM) being a major prognostic determinant even in the setting of radical resection [6–8], literature still lacks a generally applicable rule on the extent of lymph node dissection [9]. There is limited number of randomized controlled trials on the subject which all failed to show any survival benefit of extended lymph node dissection [10–13]. A recent consensus statement by International Study Group on Pancreatic Surgery (ISGPS) concluded that extended lymphadenectomy is not recommendable and suggested resection of standardized lymph node stations [14].

Prognostic value of the ratio of metastatic lymph nodes to the resected nodes has been studied for different kinds of cancer with some significant results. A good example of this is gastric cancer and accumulating data on the topic suggests that the metastatic lymph node ratio (MLR) is emerging as an independent prognostic factor [15, 16]. However, prognostic significance of MLR in PC is still controversial and recent research suggests its significance similar to the patterns in gastric cancer [17].

Using ratio, rather than the number of metastatic lymph nodes for predicting prognosis, may help to standardize this heterogeneous group of patients who undergo lymph node dissection to various extents. This study aims to evaluate the prognostic value of MLR in PC with a brief review of the literature.

Material and Methods

Medical recordings of patients who were admitted to a tertiary medical oncology center for a span of 10 years were retrospectively searched based on International Classification of Diseases-10 (ICD-10) codes. A total of 427 patients labeled with a diagnosis of pancreatic adeno cancer were enrolled in

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the study and their recordings were further analyzed. Recordings of 90 patients that lacked proper histopathologic results were immediately discarded and a further 11 patients who were labeled as adeno cancer but actually had different types of pancreatic malignancies also were excluded. Thus, data from a net total of 326 patients with pancreatic adeno cancer were statistically analyzed.

Qualitative Properties of the Patient Population

The database that the patients were recorded belonged to a tertiary medical oncology center that served to all western region of Turkey. High volume and large geographic coverage of the center provided advantages of a multicenter study. However, this heterogeneity made it impossible to analyze some prognostic parameters suggested by the literature such as extent of lymph node dissection and topographic mapping of the metastases.

Quantitative Analysis of the Data

A receiver operating characteristic (ROC) analysis failed to define a cut off value for MLR in our population (area under the curve was 0.605, $p = 0.275$). Thus, we tested 5, 10, and 15% cutoff values which were determined by previous large studies [18–22].

Results

Descriptive Analysis of the Patients

Average age of the population was 59.3 ± 10.4 ranging from 21 to 87. Majority of the patients were male (68.7% $n = 224$) and 38.3% ($n = 125$) patients were operated. Only 16 patients were alive at the time the study was conducted and 45 patients were lost to follow-up. Overall 5-year survival from the time of diagnosis was 4.4% and average survival time was 458 days. However, 5-year survival rate for the patients who underwent surgery was 7.9% with an average survival time of 651 days. Estimated survival times for the whole patient population and the operated group were 500 and 805 days respectively.

Majority of the tumors were located in the head of the pancreas (60.4%, $n = 197$) followed by body (27%, $n = 88$) and tail (12.6%, $n = 41$). The distribution of the surgical procedure types was consistent with tumor location distribution. Whipple's procedure was the most common type of operation (60%, $n = 75$) followed by pylorus protective pancreaticoduodenectomy (PPPD) (18.4%, $n = 23$), distal pancreatectomy (20%, $n = 25$), and total pancreatectomy (1.6%, $n = 2$).

Of the 125 patients who were operated on, there was microscopic evidence of tumor on the resection border (R1 resection) in 23 patients (18.4%).

Average number of dissected lymph nodes was 12.6 ± 7.4 ranging from one to 44.

Majority of the tumors were moderately differentiated (61.4%) in the whole patient population. This was also valid for the operated patient group in which 54.3% of the tumors were moderately differentiated. Table 1 summarizes descriptive statistics for the patient population and the group of operated patients.

Survival Analysis

A logistic regression analysis was employed to test the effect of, tumor size, resection status, number of resected and metastatic lymph nodes, histologic differentiation and the presence of vascular and local invasion on survival. Among these variables, tumor size being larger than 4 cm, poor histologic differentiation and presence of vascular invasion had significant effect on survival (p values 0.03, 0.01 and 0.01 respectively). Interestingly, positive surgical margins (R1 resection) ($p = 0.081$) and presence of local invasion ($p = 0.097$) did not significantly altered survival.

As a proven negative prognostic factor, LNM was observed 69% of the operated patients and this proved to be a strong predictor of survival ($p = 0.008$).

Number of dissected lymph nodes varied widely among the patients ranging from one to 44 suggesting an inhomogeneity in the extent of lymph node dissection among different surgeons.

We tested the cut of values of 5, 10, and 15% for MLR separately, using tumor size as a covariant as it was the only significant prognostic factor for the operated group.

All these cutoff values proved significant for predicting survival. Among the tested MLR, there was a correlation between the percentage of involved lymph nodes and life expectancy. The less percent of involved nodes was associated with more estimated survival time.

For example, life expectancy for the patients with less than 5 % MLR was 1090 days. However, estimated survival for the patients with more than 5 % MLR was 665 days. The p value for this difference in 95% confidence interval was 0.01 and having less than 5 % MLR was found to be a strong predictor of survival (Fig. 1).

Similar results were found for the patients with less than 10 % MLR. Estimated survival time dropped from 975 to 649 days for the patients having more than 10 % MLR ($p = 0.016$). As an independent prognostic factor, tumor size being more than 4 cm did not did not alter prognostic relevance of 10 % MLR when tested as a covariate ($p = 0.007$).

Lastly, life expectancy for the patients with less than 15% MLR was 912, which was significantly longer when compared to 616 days for the patients with more than 15% MLR ($p = 0.04$).

Table 1 Descriptive statistics of the patients

	Population	Operated group
Age (average)	59.3	57.6
Sex		
Male	224 (68.7%)	84 (67.2%)
Female	102 (31.3%)	41 (32.8%)
Tumor location		
Head	197 (60.4%)	99 (79.2%)
Body	88 (27%)	17 (13.6%)
Tail	41 (12.6%)	9 (7.2%)
Tumor differentiation		
Poor	60 (18.6%)	18 (14.7%)
Moderate	201 (61.4%)	68 (54.3%)
Well	65 (20%)	39 (31%)
5-year survival (%)	4.4%	7.9%
Average time of survival (days)	458	651
Type of surgery		
Whipple	NA	75 (60%)
PPPD	NA	23 (18.4%)
Distal Pancreatectomy	NA	25 (20%)
Total Pancreatectomy	NA	2 (1.6%)
Resection accuracy		
R0	NA	102
R1	NA	23
Number of dissected lymph nodes	NA	12.6 ± 7.4 (range 1–44)

NA, not applicable

Discussion

Pancreatic cancer is one of the deadliest type of cancers with reported 5-year survival rates between 1 and 5% [2]. Radical surgery remains the best treatment option, rising five-year survival rates up to 15–25% in some series [1, 3].

The literature almost agrees on the important effect of LNM on prognosis [23, 24]. Despite our failure to demonstrate significance of some other classic prognostic

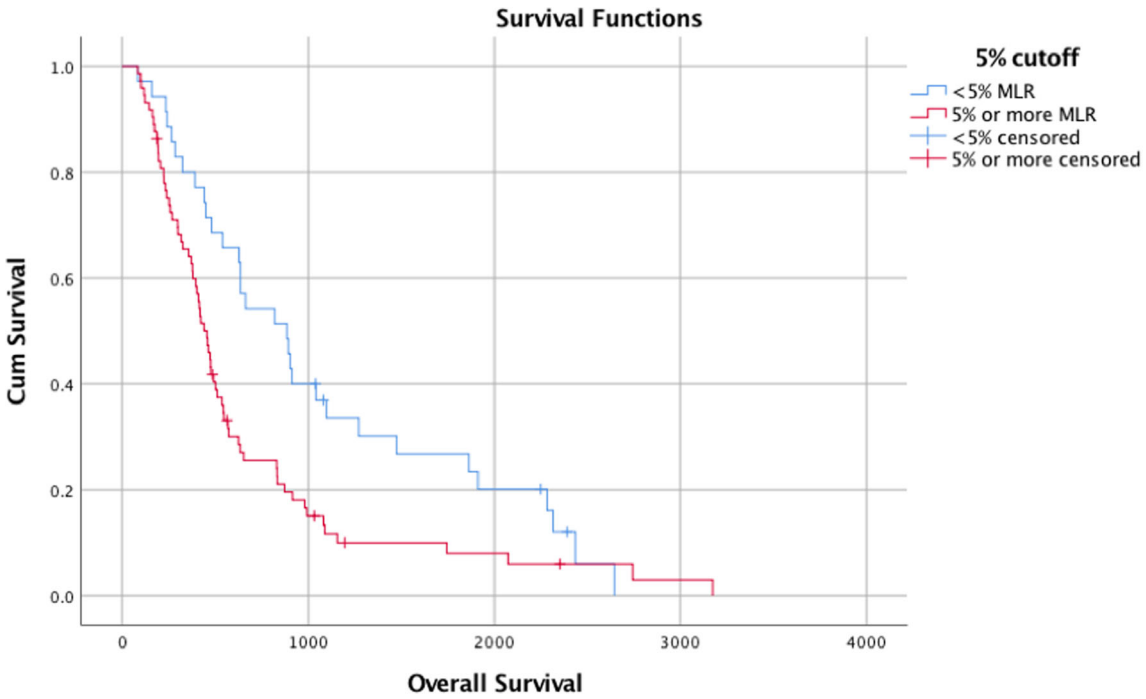

Fig. 1 Survival plot for 5% cutoff for MLR

markers of PC in our patient population, LNM still proved a strong predictor of survival.

Extent of lymph node dissection is very well established for some malignancies such as gastric and rectal cancer [25, 26]. However, there are only few randomized prospective studies evaluating the effect of extended lymph node dissection on the prognosis of PC and even these studies lack some qualities such as covering only periampullary region tumors or having limited number of patients to accurately show survival advantage [4, 10, 11]. Moreover, it is postulated that very large number of cohorts are needed to determine subgroups that would benefit from extended dissection [27].

The number of evaluated lymph nodes is shown to be associated with improved survival by multiple studies [28–30]. Current opinion in the literature suggests the removal of at least 10 lymph nodes to avoid under staging. Concordantly, having less than 10 nodes removed was associated with poor prognosis in our patient group ($p < 0.005$). However, MLR proved to be a significant predictor of survival even in this subgroup of patients. Nevertheless, this should not be interpreted as a discouragement for proper lymph node dissection but rather taken as an opportunity to more accurately predict the prognosis of patients with low number of dissected nodes. Additionally, MLR provides the opportunity to homogenize the adjuvant treatment of PC patients operated by a heterogeneous group of surgeons coming from diverse disciplines.

Another factor that could have affected prognosis of our patients is adjuvant chemotherapy. Since all the data was collected from the archives of a medical oncology center, all the patients received adjuvant therapies. However, those therapies were not homogenous neither by means of regiment nor duration. This probably have some effect on our results but we expect this effect to be minimal because, despite our failure to demonstrate the effect of even classical prognostic factors of PC in our population, LNM and MLR proved to be strong predictors of prognosis even for our heterogeneous group of patients.

In conclusion, MLR offers a feasible solution for homogeneously predicting prognosis of PC patients who underwent heterogeneous lymph node dissection procedures and with future studies, it can emerge as a successful tool for creating prognostic subgroups of the disease.

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