

# METASTATIC LYMPH NODE RATIO, 6<sup>TH</sup> OR 7<sup>TH</sup> AJCC EDITION: WITCH IS THE BEST LYMPH NODE CLASSIFICATION FOR ESOPHAGEAL CANCER? PROGNOSIS FACTOR ANALYSIS IN 487 PATIENTS

*Índice de metástase linfonodal da 6ª ou 7ª edição do AJCC: qual é a melhor classificação linfonodal para o câncer de esôfago?  
 Uma análise de fatores prognósticos em 487 pacientes*

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**HEADINGS** - Esophageal cancer. Oncology. Lymph node. Lymphadenectomy. Esophagectomy.

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**DESCRIPTORES** - Câncer de esôfago. Oncologia. Linfonodo. Linfadenectomia. Esófagectomia.

**ABSTRACT - Background:** The esophageal cancer is one of the most common and aggressive worldwide. Recently, the AJCC changed the staging system, considering, among others, the important role of the lymph node metastasis on the prognosis. **Aim:** To discuss the applicability of different forms of lymph node staging in a western surgical center. **Methods:** Four hundred eighty seven patients with esophageal cancer were enrolled. Three staging systems were evaluated, the 6<sup>th</sup> and the 7<sup>th</sup> AJCC editions and the Lymph Node Metastatic Ratio. **Results:** The majority of the cases were squamous cell carcinoma. The mean lymph node sample was eight. Considering the survival, there was no significant difference between the patients when they were classified by the 7<sup>th</sup> AJCC edition. Analysis of the Lymph Node Metastatic Ratio, just on the group of patients with 0 to 25%, has shown significant difference ( $p=0,01$ ). The 6<sup>th</sup> AJCC edition shows the major significant difference between among the classifications evaluated. **Conclusion:** In this specific population, the 7<sup>th</sup> AJCC edition for esophageal cancer was not able to find differences in survival when just the lymph node analysis was considered.

**RESUMO - Racional:** O câncer de esôfago é um dos mais comuns e agressivos que existem. Recentemente o AJCC mudou o sistema de estadiamento, considerando, entre outros fatores, a importância da metástase linfonodal sobre o prognóstico. **Objetivo:** Discutir a aplicabilidade de diferentes formas de estadiamento linfonodal em um serviço de cirurgia ocidental. **Métodos:** Quatrocentos e oitenta e sete pacientes com câncer de esôfago foram arrolados. Três estadiamentos foram avaliados, a 6ª e a 7ª Edição do AJCC e o Índice de Metástase Linfonodal. **Resultados:** A maioria dos casos foi composta por carcinoma epidemóide. A média de amostra linfonodal foi de oito. Considerando a sobrevida, não houve diferença significativa entre os pacientes quando foram classificados pela 7ª Edição do AJCC. Analisando o Índice de Metástase linfonodal, apenas o grupo de pacientes com 0-25% mostrou diferença significativa ( $p=0,01$ ). A 6ª Edição do AJCC mostrou a maior diferença entre as classificações avaliadas. **Conclusão:** Considerando as características da amostra, a nova classificação do AJCC não foi capaz de evidenciar diferenças significativas na sobrevida dos pacientes, quando apenas o estadiamento linfonodal foi avaliado.

## INTRODUCTION

Esophageal cancer is the eighth most common cancer in the world. Recent estimative indicate 482,000 new cases a year with 407,000 deaths related to it<sup>17</sup>. Most of the patients affected tend to be men, between the sixth and seventh decades of age<sup>9,13</sup>. The overall survival rate around the world is between 10 to 15% in five years.<sup>1</sup> In specialized medical centers, with expert teams of surgeons and optimal lymph nodal sampling, survival rates can reach up to 40% in five years<sup>12</sup>. In order to improve these rates, prognostic factors such as the number of metastatic lymph nodes (MLN) and the metastatic lymph node ratio (MLR – the number of positive nodes among all retrieved) have been studied<sup>5,16</sup>.

Studies have demonstrated a direct relationship between the number of extracted lymph nodes and survival. Altorki et al.<sup>1</sup> observed a decrease in chances of death according to the harvested number of lymph nodes. It was reported a survival hazard ratio of 49%, when more than 40 nodes were dissected. Zhang et al.<sup>16</sup> studied 1.146 patients with squamous cell carcinoma and observed worst survival rates in patients with more MLN. The authors suggested that the stratification of these lymph nodes could influence the patients' prognosis. Another study carried out with 488 patients, did not show difference in survival rates when the lymph node was classified either as regional or as distant, but the authors founded statistical significance stratifying MLN<sup>5</sup>.

In 2010, Liu et al<sup>10</sup> found a significant improve in survival rates in their series 1.325 patients with squamous cell carcinoma, according to the MLR.

In the same year the American Joint Committee on Cancer (AJCC) released the new staging system tumor, node, metastasis (TNM) for esophageal cancer, subdividing regional lymph nodes by the number of involved lymph nodes<sup>14</sup>. Despite of it, the debates about the best method for lymph node evaluation persisted, so as the best surgical approach regarding to that.

The comparison between these staging systems, focusing on lymph node analysis has not yet been evaluated in South American population, specifically Southern Brazil. The socioeconomic characteristics of this region make the incidence and the pathology aspects of esophageal cancer similar to those founded in Eastern countries, while the major surgery procedures follows the Western parameters, which not provide the same radical lymph node dissection<sup>2,3,4,13</sup>.

The purpose of this study was to compare three lymph node analysis systems: the evaluation of MLR and the recommended by the 6<sup>th</sup> or 7<sup>th</sup> AJCC for esophageal cancer editions in a reference cancer center in Southern Brazil.

## METHODS

The protocol for this study was approved by the Ethics Committee of the Santa Casa Hospital (protocol n.3496/11), under the supervision of the Federal University of Health Sciences of Porto Alegre (protocol n.771/11).

The study was conducted analyzing the patient's files from January 2000 to June 2011, at Santa Casa Hospital, in Porto Alegre, RS, Southern Brazil. The variables studied were age, gender, alcohol and tobacco abuse, social conditions (inferred by the use of public or private health systems) as well as date of the diagnosis, histological type, tumor grade, site and staging according to Tumor Node Metastases (TNM) system. Were contemplated the number of harvested lymph nodes, metastatic lymph nodes (analyzed according to the 6<sup>th</sup> and 7<sup>th</sup> TNM AJCC editions), metastatic lymph node ratio (stratified in three groups: 0-0.25; 0.26-0.5; >0.5) and diameter (greater or lower than 5 cm). Surgical mortality and overall death rates were also investigated. To analyze overall survival, file results were matched with the Mortality Information System of the State of Rio Grande do Sul. For those whose information could not be found on the system, active search was carried out through phone calls.

An historic cohort study was conducted based on a sample calculation of the outcome of previous studies<sup>5,12</sup> for a significance level of 5%, power of 90% and minimal difference of 15% on survival probability in five years in patients with or not metastatic lymph node, leading to a minimal of 446 patients. The calculation was made by using the PEPI (Programs of Epidemiologists), version 4.0.

Statistical analysis was performed making use of the SPSS, 17.0 version. When normal distribution was observed, parametric tests were performed, including t student test and univariate analysis. As for categorical variables, the qui-square test was conducted. Survival curves were estimated by the Kaplan-Meier method and compared with the log-rank test. To control confounding factors, the multivariate analysis of Cox regression was applied. The measure of effect used was the odds ratio, with a confidence interval of 95%. P values under 0.05 were considered significant.

## RESULTS

Eight hundred and twenty nine patients were enrolled in the hospital system research during the period evaluated.

Among these, 342 cases did not have complete information in the medical files, or in the Mortality Information System. Thus, 487 patients were included in the analysis.

The average age was 61.04 (21 to 91) years. A higher prevalence of the disease was noticed amongst patients with more than 60 years of age (52.2%). Three hundred and sixty nine (75.8%) patients were men. Two hundred and thirty nine (86.6%) patients had history of tobacco abuse and 47.4% informed having abused of alcohol. Three hundred and ninety (80.1%) were diagnosed and treated by the Brazilian public health system. The most common tumor site was the middle third of the esophagus, which was found in 53.7% of the patients. Concerning to histological characteristics, 90.6% were squamous cell carcinoma and 54.3% of all tumors were moderately differentiated. As for overall survival rate, the index of death was 94.3% until the present date (Table 1).

**TABLE 1** - Demographics and clinical pathological characteristics

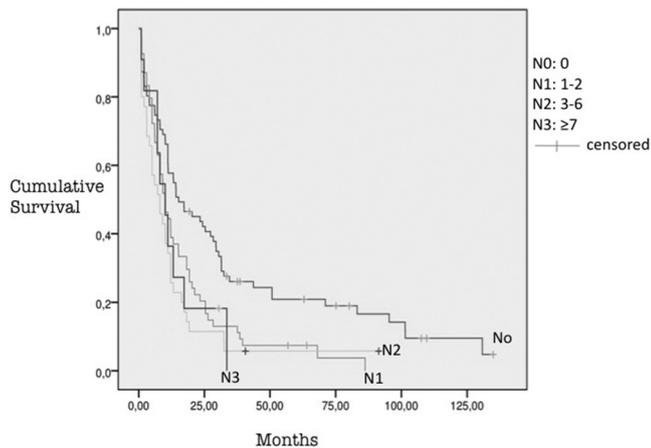
Variables	n=487
Age (years - mean ± SD)	61,0 ± 11,2
Gender - n (%)	
male	369 (75,8)
female	118 (24,2)
Tabacco abuse <sup>†</sup> - n (%)	
yes	239 (86,6)
no	37 (13,4)
Alcohol abuse <sup>‡</sup> - n (%)	
yes	128 (47,4)
no	142 (52,6)
T classification (invasiveness) § - n (%)	
T1	12 (3,6)
T2	49 (14,9)
T3	88 (26,7)
T4	44 (13,3)
Stage IVB	
Cell type - n (%)	
squamous cell	441 (90,6)
adenocarcinoma	46 (9,4)
Differentiation¶ - n (%)	
poorly differentiated	118 (37,9)
moderately differentiated	169 (54,3)
well differentiated	24 (7,7)
Tumor site <sup>**</sup> - n (%)	
upper third	33 (8,2)
middle third	217 (53,7)
lower third	146 (36,1)
gastroesophagic junction	8 (2)
Overall death- n (%)	
no	28 (5,7)
yes	459 (94,3)

<sup>†</sup> 211 files did not have data regarding tobacco abuse (43.3%); <sup>‡</sup> 217 files did not have data regarding alcohol abuse (44.6%); <sup>§</sup> 158 files did not have data regarding tumor (T) classification (32.4%); <sup>¶</sup> 176 files did not have data regarding tumor differentiation (36.1%); <sup>\*\*</sup> 83 files did not have data regarding tumor site (17%).

The median of overall survival was seven months (CI 95%: 6.2 to 8). Men had worse survival rates in five years: 5.5% versus 12.5% (p=0.005).

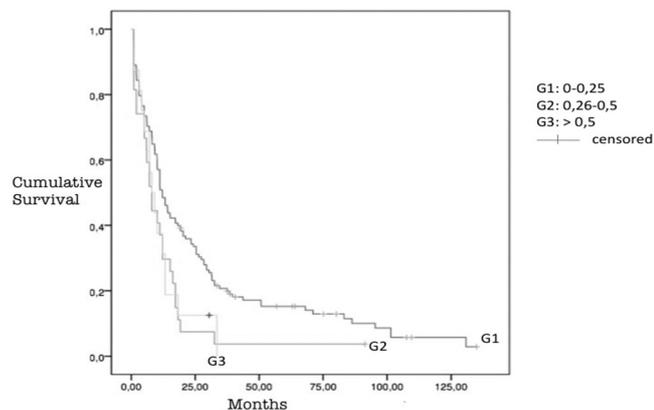
Out of the 487 patients with esophageal cancer, 200 (41.1%) were submitted to a surgical procedure to remove the tumor and could be analyzed in regard to lymph node assessment. In these patients, a median of eight lymph nodes was removed in each operation. Surgical mortality rate reached 14.5%.

According to the new AJCC revised stage system (7<sup>th</sup> Edition), 85 (42.5%) patients did not present metastatic lymph nodes, while 59 (29.5%), 43 (21.5%), 13 (6.5%) had, respectively, from 1 to 2 (N1), from 3 to 6 (N2) and 7 or more (N3) metastatic lymph nodes in the specimen. None significant differences in survival were found among the N1, N2 and N3 groups (Figure 1).



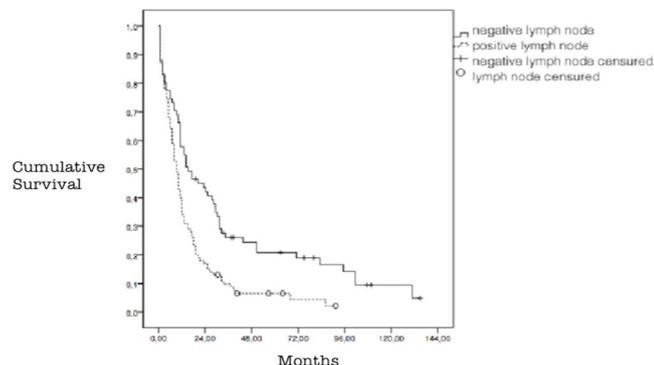
**FIGURE 1** - Cumulative survival curve according to the criteria of the 7<sup>th</sup> AJCC edition. N0=0; N=1-2; N2=3-6; N3<sup>37</sup> (p>0,05)

The mean metastatic lymph node ratio was 10%. The group of patients with 0 to 25% has shown significant difference in the survival curve when compared with the others groups (p=0,01). No significant differences were found between the others categories (Figure 2).



**FIGURE 2** - Cumulative survival curve according to Metastatic Lymph Node Ratio. 0-0,25 (p<0,01); 0,26-0,5; >0,5 (p>0,05)

Considering the 6<sup>th</sup> Edition of AJCC stage system, 57,5% of the patients had metastatic lymph nodes. The median survival of patients with metastatic lymph nodes was 9.2 months (CI 95%: 7.2 to 11.2) while the ones without evidence of lymph node metastasis presented a survival rate of 15.2 months (CI 95%: 6 to 24.5) (p<0.001) (Figure 3).



**FIGURE 3** - Cumulative survival curve according to the criteria of the 6<sup>th</sup> AJCC edition. Positive and negative (p<0,01)

Some others prognosis factors were analyzed. Considering the diameter of the tumor, 88.1% of the patients had tumors that were smaller than 5 cm. In this group of patients the mean of survival 13.2 months (CI 95%: 9.9 to 16.5) and 8.1 (CI 95%: 6.9 to 9.3) on those the tumor were bigger than 5 cm (p=0.004). Patients with tumors T1 e T2 had longer survival rates than the ones with T3, T4 and IVB classifications (p<0.001)

After multivariate model adjustment, there are still significant differences concerning factors such as gender (HR: 1.67; CI 95% 1.09 to 2.55; p=0.019), metastatic lymph nodes according to the 6<sup>th</sup> AJCC edition (HR: 1.63; CI 95% 1.13 to 2.36; p=0.010) and T3 staging in relation to group T1-T2 (HR: 1.52; CI 95% 1.04 to 2.23; p=0.032).

## DISCUSSION

The analysis of the data reveals common characteristic in patients who are diagnosed with esophageal cancer: lower social status, late diagnosis, advanced stage tumors and poor prognosis and survival.

In regards to epidemiological issues, was found a higher frequency rate of esophageal cancer patients who were between 60 and 70 years of age, with the majority of patients being men. Liu et al.<sup>10</sup> and Peyre et al. have shown similar results. Was observed, however, a sample from a lower social status than the one presented by western studies<sup>3,6</sup> and a very high frequency of squamous cell carcinoma (90% of the cases). Following this trend, this sample was similar to those presented by the eastern studies<sup>5,10,16</sup>, where middle third tumors are predominant.

Late diagnosis, whereas by delayed symptoms or by delayed public health care treatment, has lead us to the alarming number of only 40% of the patients being able to undergo surgical treatment. Among these surgical patients, only 18.5% had T1 or T2 tumors. This information is in agreement with the eastern studies of Liu et al.<sup>10</sup> and Zhang et al.<sup>10</sup> in which the majority of the patients presented T3 tumors.

In regards to the lymph nodal sampling, was found a median of eight lymph nodes harvested for each specimen, while Mariette et al.<sup>11</sup> suggest that this number should be, at least 15 lymph nodes and, Peyre et al.<sup>12</sup> recommend the dissection of 23 to 29 lymph nodes. The International Union Against Cancer and AJCC have proposed the retrieve of at least six lymph nodes<sup>7</sup>.

Whatever the number, is not well established if a larger sample can be responsible for an independent improve in the prognosis of the disease.

In the present study the classification of lymph nodes according to the AJCC 7<sup>th</sup> edition showed no effect in the patients' prognosis. These data differs from those founded by Talsma et al, which showed a significant difference in the prognosis when the groups (N0, N1, N2, N3) were compared<sup>15</sup>. The authors did a whole analysis of the 7<sup>th</sup> AJCC edition and have endorsed it as the best system to stratified the prognosis. These researchers found a mean of 11 lymph nodes. In this study it was observed a mean of eight lymph nodes and maybe this limited number could prevent the implementation of the TNM 7<sup>th</sup> edition.

An Oriental study aimed to determine the differences between the 7<sup>th</sup> edition of the AJCC staging system in relation to the staging system based on metastatic lymph node ratio<sup>8</sup>. This study focused only on elderly patients who underwent esophagectomy with extensive lymph node dissection (mean of 22 lymph nodes). The metastatic lymph node ratio was similar to that evidenced in the present study, although after logistic regression they found that both MLR and the classification of the 7<sup>th</sup> AJCC were independent prognostic factors. The authors recommend the AJCC system for more

accurate analysis.

In this study, only the group with metastatic lymph node ratio between 0 – 0,25 have shown a significant effect in the patients' prognosis, which was not sustained after logistic regression analysis. On the other hand, the analysis of the MLN (6<sup>th</sup> TNM edition) in agreement with other studies<sup>1,11,16</sup> could predict survival even after multivariate analysis. According to Mariette et al.<sup>11</sup> MLR is considered a good prognostic parameter in conservative operations, although, it is considered a more reliable one. This statement could be even more suitable for Brazilian population.

This is a retrospective study and vulnerable to biases inherent biases. It is believed that this is the first Brazilian study to evaluate the method of lymph node staging in patients with esophageal cancer. The importance of this analysis is due to the peculiarity of this sample, especially as regards the prevalence of advanced cases, where 40% not even could undergo surgery, which limits the application of the 7<sup>th</sup> TNM Stage System.

## CONCLUSIONS

In a population of southern Brazil, regarding to the lymph node staging, just the 6<sup>th</sup> AJCC edition system was able to be an independent prognostic factor for patients with esophageal carcinoma. It is believed that this result is the reflection of a reduced lymph node sampling. The others classifications evaluated are more specific and probably a significant difference will be evident only in populations with extensive lymph node resection, as performed in eastern centers. The rate of positive lymph nodes should be considered an important tool in this population.

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