

Streszczenie w języku angielskim

Background

Lymph node status in non-small cell lung cancer is one of the most important prognostic factors. However, many controversies and discussions persist regarding this aspect. For this reason, we decided to explore the following issues regarding lymphadenectomy in lung cancer:

- I. narrative review of alternative methods of lymph node classification in TNM classification of lung cancer
- II. clinical relevance, impact of 3A prevascular lymph node resection on overall survival in right-sided lung cancer
- III. clinical relevance and the effect of zero lymph node retrieval (pNx) phenomenon on overall survival in lung cancer.

Material and Methods

- I. We reviewed the PubMed database based on the following lymph node classifications: ongoing TNM classification, number of positive lymph nodes, number of negative lymph nodes, number of lymph nodes retrieved, lymph node ratio, mathematical modification of this ratio by logarithm, lymph node chains, lymph node zones, and number of lymph node stations. We also included combinations of these classifications.
- II. We analyzed the data from the Polish Lung Cancer Group database on 6348 patients who underwent lung resection between 2005 and 2015. 3A node resection was performed in 221 patients (3ALN+), while 6217 patients did not undergo such resection (3ALN-). We performed Propensity score matching to minimize selection bias and to increase statistical significance of the study. We paired 221 patients from the 3ALN+ group and 221 from the 3ALN- group.
- III. We performed a retrospective analysis of the Polish Lung Cancer Group database. The pNx phenomenon was defined as zero lymph nodes retrieved. We included 17192 patients.

Results

- I. Review of literature has shown that the current classification of lymph nodes may lead to inaccurate staging of patients. Classifications based on the number of positive lymph nodes, lymph node ratio or its mathematical modifications are the most studied in numerous papers.

For this reason, based on these numerous data, they should be considered first as potential additional factors in the classification of the N feature in TNM classification.

II. The incidence of 3a lymph node metastasis was 8% and it increased with pT stages. A significant increase in frequency was noted between pT1c and pT2a, which was doubled from 4% to 9%. For pT4, the frequency was as high as 15%. The highest frequency was noted among patients undergoing pneumonectomy (10%) and in the N2b1 and N2b2 subgroups (33% and 64%, respectively). In univariable analysis, we found no significant difference in 5-year overall survival between the 3ALN+ and 3ALN- groups (51% vs 51%, $p=0.74$). But metastatic lymph nodes and non-metastatic lymph nodes of 3ALN+ differed significantly ($p<0.0001$). The pN2 subgroups (pN2a1, pN2a2, pN2b1 and pN2b2) were not significantly different in terms of survival after Propensity Score Matching analysis. 3A lymph node metastasis was not an independent prognostic factor in multivariable analysis in the entire group after Propensity Score Matching as well as in the pN2 subgroups. 12

III. In 1080 patients (6%), no lymph nodes were resected (pNx). Patients in this group were more likely to be younger, more likely to be female, had a different distribution of pT stages, were more likely to have squamous cell carcinoma, were more likely to have undergone thoracotomy, were more likely to have been operated on in non-academic centers, and had a lower rate of certain comorbidities. Patients with pNx were more often cN0 than other patients with pN1 and pN2 but less often than patients with pN0 ($p<0.001$). Patients with pNx underwent invasive diagnostics of mediastinal nodes less frequently than patients with pN1 and pN2 but more frequently than patients with pN0 ($p<0.001$). Overall, 5-year survival was 64% for pN0, 45% for pN1, 32% for pN2, and 50% for pNx. In the pairwise comparison of pN subgroups, all pN pairs were significantly different from each other (all $p<0.0001$ except pNx vs pN1 $p=0.016$). The location of the survival curve and overall, 5-year survival of patients with pNx depended on histopathological diagnosis, surgical approach and pT stage. In multivariable analysis, pNx was an independent risk factor for death (HR=1.37, 95%CI: 1.23-1.51, $p<0.01$).

Conclusions

- I. Based on the literature reviewed, it seems that, next editions of the N feature in the TNM classification may benefit from adding a quantitative factor. In addition, there should be a consensus on minimal lymphadenectomy in lung cancer, as this increases the quality of staging. However, the introduction of such new classifications requires international prospective validation studies to establish appropriate cutoff values and prognostic groups and to decide which quantitative classification should be used.
- II. Although lymph nodes of station 3A were not an independent prognostic factor in our cohort, the frequency of metastasis in this station increases significantly in more advanced stages of cancer. The rate of metastasis in this station is comparable to other, more routine lymph node stations. Hence, including this lymph node station in lymphadenectomy may be beneficial for patients with advanced right-sided lung cancer.
- III. Lymph node resection in lung cancer remains a key step in surgical treatment. The survival of the pNx subgroup is comparable to the pN1 subgroup. The survival of pNx patients depends on other factors which may be useful in daily practice and clinical decisions.