

“N” STATUS EVALUATION IN PATIENTS WITH LUNG CANCER. PROBLEMS AND SOLUTIONS.

(review)

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Summary: Staging of Non-small cell lung cancer remains an important question of modern oncology. Correct N-status of patients one of the unsolved problem. There are invasive and non-invasive methods for detection N-status. CT or CT/PET one of the most frequently used methods. But, this methods unable to assessed stage of disease carefully. There are lots of methods in a literature that described detection of micromethastasis in visually intact lymph nodes: simple pathomorphologic assessment, immunohistochemical assessment with cytokeratines in combination with p53, lymphoscintigraphy, immunomagnetic separation, flowcythometry, polymerase chain reaction. Unfortunately there are no any methods than satisfied for all oncologists. That's why lots of problem needs for solving. First of all adequate diagnostic of micromethastasis in lymph nodes. Than separation of factors that influence for methastasing. Third, investigation of survival prognosis in patients with metastatic involvement of lymph nodes. After that necessary to define ways of treatment for each patient.

Key words: micrometastasis, lymphdissection, prognosis, survival, lung cance

Accurate establishing of the disease state of patients with non-small cell lung cancer (NSCLC) permits to get information as to prognosis and to select the most “correct” therapeutic approach [19]. Casalia and co-author. (2005) distinguish a number of factors which influence prognosis of patients with NSCLC – N-status (N0-1 or N2); N2 topography of lesion, number of affected lymph nodes (LNs), number of removed LNs during the lymph node dissection, presence of latent/unrecognized metastases [9]. Presence of micrometastases or isolated tumor cells in the LNs is associated with distant metastases of patients with early stage of NSCLC [31]. Thus, detection of the regional and distant metastases is the most important task for prognostication of survivability of patients with NSCLC [4,6,19].

In order to estimate lymphatic status at the stage of non-invasive diagnostic a helical computed tomography (CT) with contrast enhancement is used. The LNs with diameter of more than 1cm along the short axis usually are considered as standard criterion of the metastatic LNs. However clinical currency of the present method doesn't meet requirements of the modern oncology because in 20% of cases the LNs with diameter of up to 1cm can contain cancer metastases at the same time the “larger” LNs can be benign [19]. During multiple factor analysis the LNs with size of >1cm which had been revealed during CT didn't obtain static significance in prognostication of the latent N2 metastases. However in literature there are other data showing clear correlation between location of micrometastases and size of the LNs [7]. In accordance with data of Tanakaa and co-author. (2004) the latent metastases in N2 LNs, which are considered intact according to the pre-surgical CT examination, are revealed in 10.4% of patients. The latent metastases in the LNs of N1/N2 category are revealed in 8.8% of patients [30]. Generalized data present 57% of CT sensitivity, 82% of specificity, 56% of positive prognostic value and 83% of negative prognostic value [19].

Some authors recommend PET-scanning as one of the most precise non-invasive diagnostic methods. Many researchers show that during PET-diagnostics the latent N2 metastases are revealed in 16% of patients, clinically estimated as N0 or N1 [7,11]. Bille and co-author. (2005) indicate that sensitivity of CT/PET in detection of the cancerous lesion makes 32.4% in the LNs of <10mm and 85.3% - in the LNs of 10mm and more [8]. However during morphological examination the latent metastases in the LNs were revealed in 16% of patients with NSCLC, who according to CT/PET data were intact in relation to metastases in the LNs. The most frequently the latent metastases were revealed in 4 and 7 harvesters of the LNs [11].

The standard of the diagnostics of patients who ill with NSCLC is a detection of pathomorphological status of removed LNs. Right diagnostics of the LNs metastatic lesion shall be possible only if lymph node dissection is made correctly and material subject to the

pathohistological examination is marked in a right way [1]. However systematic mediastinal lymph node dissection (SMD) is not made in 42.2% of patients.

Systematic lymph dissection in patients with lung cancer was proposed in the middle XX centuries at first [5, 12]. N.Martini in 1995 year detalized dissection of the next anatomical zone: right upper mediastinum, lift sub aortic zone, bifurcation zone and lower mediastinum. He described aim of lymph dissection – removing mediastinal lymph nodes with surrounding fat tissue in one block [25]. Than technique was called full systematic or radical mediastinal lymph node dissection. In the right side limph node dissection must include removing all paratracheal lymph nodes from subclavicular vessels to tracheobronhial angle, all bifurcation and paratracheal nodes, that located between main bronchus, pericardium, esophagus and vena cava inferior also lymph nodes ligamentum pulmonare inferior. In the left side, as proposed by N.Martini, lymph dissection must include removing lymph nodes aortic window, bifurcation lymph nodes, paratracheal lymph nodes and lymph nodes ligamentum pulmonare inferior [25]. Wu et al. (2008) described lymph node dissection of the three parts of mediastinum. Upper part - 1-4 collectors, middle part - 7-8 collectors, lower part – 9-th collector. Front border of the upper part of mediastinum – vena cava superior, back - trachea, lower border – pulmonare artery, upper – angle between vena brahiocephalica and trachea. For middle part of mediastinum resection must begin from upper part of vena cava inferior, trough the pericard and esophagus and after main bronchus and carina. Lymph nodes and fat of the ligamentun pulmonare inferior removing called as lymph dissection of lower part of mediastinum [42, 44].

In table described lymph nodes dissection due to location of the primary tumor (Proposed International lung cancer study society) [1].

Table.

Minimal volume of mediastinal lymph nodes dissection in patient with lung cancer due to primary tumor location

primary tumor location	volume of mediastinal lymph nodes dissection
Upper and middle lobe of right lung	Para and pre-tracheal, bifurcation lymph nodes
Lower lobe of right lung	bifurcation, lower paratracheal, paraesophageal and lymph nodes of the ligamentum pulmonare inferior
Upper lobe of left lung	Subaortic, bifurcation and frontal mediastinal lymph nodes
Lower lobe of left lung	bifurcation, paraesophageal and lymph nodes lower pulmonare ligament

There is partial/selective mediastinal lymph node dissection except complete dissection.

For extended operation possible to performed bilateral dissection of mediastinum. Three and five year survival for patients after extended operation were 80,3% and 70%, and for patient after typical operation - 60% and 19% [9].

Bilateral dissection may conducted through right thoracotomy. Bilateral dissection through the left side is not standard procedures but its possible to do with out crossing ductus arteriosus and mobilization aorta in patients with lower lobe cancer and metastases in 7 group lymph nodes. Also in patients with upper lobes cancer and metastases in 5-6 groups lymph nodes [38].

Selective mediastinal lymph node dissection – dissection some of collector in depends of tumor location. For example: for upper lobe cancer recommended upper mediastinal dissection. For lower lobes cancer- lower mediastinal dissection. [29].

Mediastinal dissection possible to conduct as for open surgery as for thoracoscopic. There are no significant differences in efficacy and safety procedure [14]

Despite improving surgical technique, more than 50% patients after radical operations due to lung cancer have progression of disease. It is related with occult metastases in lymph nodes.

As a consequence a correct staging of patients with NSCLC and prescription of the proper treatment become impossible [33]. The result is a relatively high level of tumor recurrence development even in case of stage I of NSCLC. It is connected with presence of the latent metastases in the LNs. The latent metastases (skipped metastases, micro-metastases, unforeseen N2 lesion) are usually called cases of metastatic lesion which are not detected by ordinary tool methods of examination (CT, PET) and are only revealed during post-surgical morphological examination. In accord with data of different authors the latent metastases are revealed in 4% - 70.5% of patients with NSCLC [2, 3, 6, 18, 20, 28, 29]. At that, during Ia stage of NSCLC the latent metastases are revealed in 19-28% of patients (5-year survival rate of the present group makes 70%) while in case of Ib stage – in 29-38% and 5-year survival rate makes 57% [16, 24, 28].

At the present moment in international literature there is no a clear agreement as to relationship between clinical and morphological factors (sex, age, size and localization of the primary tumor, T-status, size of the LNs during CT/PET, histological type, differentiation of neoplasms, proliferative index) and risk of development of micro-metastases in case of the lung cancer [12, 25, 28]. So, Passlick_1996 indicates that localization of the primary tumor and size of the LNs of more than 1cm during CT/PET are significantly related with the level of micrometastases in the LNs (P=0.006) [25]. Many researchers clearly detect T-status as predictor of micrometastases. In 2002 Osaki and others demonstrated that cases of micrometastases in the

LN's rise from T1 to T2 during the primary NSCLC without correlation with histological subtype of the tumor. With immunohistochemical techniques Rena and co-author. (2007) showed that the latent metastases are more frequently revealed in patients with pulmonary adenocarcinoma (26.3%) than in patients with other histological grades of NSCLC ($p=0.04$). Also relation between risk of development of metastases depending on the primary tumor size is mentioned. Thus, if the tumor size is more than 2cm the latent metastatic lesion of the LN is registered in 15.4% of cases [28]. At the same time other authors indicate that pT criterion and histological structure of the primary tumor are not related with the level of micro-metastases detected with Ber-Ep4 marker [12, 25].

Different authors propose various methods of the metastasis identification. At present a routine histological examination of the LN's is widely used [17, 31]. However many researchers indicate a significant underestimation of the lymphatic status using this method [13, 25]. Often false-negative results are received because of impossibility of identification of metastases in four and sometimes less sections which are made during routine pathomorphological examination of the LN's of patients with NSCLC after surgery [23]. Therefore it is recommended to make more sections of the LN's. These additional sections can increase the pathologist workload but simultaneously can help to stage NSCLC in patients more precisely due to detection of metastases. Besides the pathologist's report should include description of number of the lymph nodes which were removed and which of them were studied, general number of the metastatic LN's in each group and the LN capsule state [18].

As the "gold standard" of morphological studies for detection of micro metastases, immunohistochemical staining (INC) of lymphadens with cytokeratins is recommended [2, 3, 6, 9, 10, 12, 16, 28]. To improve the delicacy of this method using Gu (Geriatric Unit) and et al. (2002), a combination of cytokeratins was used and p53.

This technology allowed to detect micro metastases in lymphadens in 44,9% of cases with pN0, meanwhile 18,4% of patients were subsequently restaged in N1 and 26,5% of patients in N2 [12]. IHC has fewer false-positive results than non-morphological research methods, such as flow cytometry or polymerase chain reaction (PCR) [14].

Nosotti et al. (2005) showed that the PCR diagnostic micro metastases are detected in 36.3% of patients with stage I NSCLC whereas the IHC method detects micro metastases in 19.04% of patients with histological "negative" lymphadens [22, 26].

Hashimoto et al. (2000) suggested to use the diagnostic PCR procedure, called "genetic method, gN», to identify micro metastases of patients with DR NSCLC. According to the research, this method showed high accuracy. Micro metastases were detected in 30% of patients

with histologically negative lymphadens. Patients with g-N1 and g-N2 had a lower survival rate than those ones with g-N0 ($P = 0,042$ and $P = 0,001$, respectively). The five-year survival rate was 100% for patients with gN 0, 75% of the g-N1, and 42.9% for the g-N2 patients. These results indicate a high sensitivity and specificity of this method [13]. The search of new genetic markers for PCR diagnostic is continued. Recent work by a number of researchers have shown that TACSTD1 (KS1 / 4) is a good marker for the PCR identification of mediastinal metastases in lymphadens of patients with NSCLC. TACSTD1 is proved to be the most promising detached affect marker for patients with NSCLC in their lymphadens [21, 32, 34].

Recently, new methods are offered, demonstrating the high sensitivity of the detection of micro metastases, such as lymphoscintigraphy, immunomagnetic separation, flow cytometry [5, 18, 15]. According to Lardinois, metastases missed during lymphoscintigraphy, were found in 25% of cases. Also, lymphoscintigraphy of cytokeratin-positive cells is widely-recognized. A comparative analysis of the micro metastases detection efficiency by IHC and flow cytometry revealed efficiency of 33% and 38% respectively. The authors point out that in order to prevent false-positive results, one should remove the lymph node capsule [18, 15].

All of the above methods and work aimed at solving one of the most important issues - the dependence of the prognosis of patients with NSCLC from micro metastases in lymphadens. This is especially real time data for those patients with early-staged disease [9]. Multivariate analysis showed that patients with stage I NSCLC after radical surgery, the presence of micro metastases in lymphadens are an independent factor of poor prognosis, with more significance than the T-status. Thus, Gu et al. (2002) note that the 5-year survival of patients with stage Ia after surgery without the presence of micro metastases in lymphadens was 90%, while with the presence of micro metastases in lymphadens - 50% ($p = 0.057$). Among patients with stage Ib, the overall 5-year survival rate of patients with and without micro metastases was 21.4% and 76.0%, respectively ($p = 0.0016$) [12]. Other authors have noted as well that poor prognosis among patients with NSCLC with the presence of CEA mRNA in the studied lymphadens, which are markers of micro metastases ($p < 0.021$) [22, 26].

According to various authors disease-free survival among patients with stage Ia ranges from 34.8 to 41.1 months, and for the Ib patients (presence of micro metastases in lymphadens) - 18,0-29,0 months ($p = 0,0081$). Besides, the size of the micro metastases does not matter for the prognosis, what matters is its presence only.

Survival among patients with micro metastasis detected by immunohistochemistry is not better than that of patients with metastases detected by conventional lymphadens histological examination [15].

The above data demonstrates that even a minimal tumor lesion in lymphadens is associated with a poor prognosis and is an independent prognostic factor. It is generally effective for patients with localized (pT1-3 pN0), and common (pT1-3 pN1-2) NSCLC form [25]. If lymphadens mediastinal was not examined properly, the oncologists' prognosis towards every individual patient with NSCLC will be unclear. However, the prognosis of patients depends not only on the presence of N2-destruction of lymphadens, it is also important what kind of basin is affected, the number of "positive" lymphadens in each basin, the size of lymphadens affected by metastasis.

Thus, to improve the quality of care for patients with NSCLC is necessary to solve a number of important tasks: conducting an adequate diagnosis of micro metastasis in lymphadens, the allocation of factors predisposing to metastasize, to study the survivability in dependence on the presence of micro metastases in lymphadens as well as the determination of subsequent treatment of patients with detection of micro metastases.

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