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The new recommendations of the 7th edition of the TNM classification for Lung Cancer in pathologic assessment (pTNM)

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The paper entitled "Nowa klasyfikacja TNM w raku płuca" *(The new TNM classification for lung cancer)* by Anna Wrona and Jacek Jassem [1] provides an extremely clear and exhaustive presentation of the latest recommendations of the 7th edition of the TNM (tumour, node, metastasis) classification adopted in 2009. The paper deserves particular recognition for the fact that the authors have managed to write such an ample discussion in Polish so shortly after the publication of the lung cancer staging classification, which is bound to generate considerable interest among doctors dealing with lung cancer patients, including both surgeons, pulmonologists and oncologists.

The paper has inspired me to write a longer comment on the issues related to the pathologic assessment of lung cancer postoperative material, the aim of which was to draw attention to significant changes and recommendations that have been made and must be taken into account in histopathology reports.

The seventh edition of the TNM classification for lung cancer is the result of an analysis of a large group of patients from all over the world with a diagnosis of non-small cell lung carcinoma (NSCLC) and small cell lung carcinoma (SCLC) managed with various modalities: surgery, chemotherapy, radiotherapy, or a combination of these [2]. The changes concern not only the TNM descriptors, but — which seems extremely important — involve the inclusion of small-cell lung cancers, divided into localised and disseminated forms so far, and carcinoid tumours, which were previously not included in any classification and were therefore not staged [2–5]. The inclusion of SCLC in the TNM system allows doctors to better identify prognostic groups compared to the previous classification [2, 4], while the inclusion of carcinoid tumours raises them to an equal position with NSCLC and SCLC, emphasising their malignant potential despite a better prognosis compared to the other epithelial lung tumours [2, 3].

Changes in the pT descriptor (tumour size, pleural infiltration, satellite nodules)

The new edition primarily focused on the differentiation of the tumour size [2], as the previous classification raised many controversies, mainly due to the placement of lung cancers infiltrating the pleura in the same group irrespective of the primary tumour size [6]. In the previous edition the basic threshold value used in the classification of lung cancers was exclusively the diameter of 3 cm. The current classification provides 5 prognostic groups that differ in terms of survival likelihood. The classification is based on 4 principal tumour sizes, namely 2, 3, 5, and 7 cm. The differentiation in the tumour size resulted in the identification of two subgroups within the principal groups, namely the pT1a and pT1b subgroups within the pT1 category with the primary tumour sizes of ≤ 2 cm

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and > 2–3 cm, respectively, and pT2a and pT2b subgroups within the pT2 category with the primary tumour sizes of ≤ 5 cm and > 5–7 cm, respectively; and pT3 for tumours exceeding 7 cm in size [2, 7].

For several years it has been proposed that pleural infiltration be identified as a separate descriptor, PL, including four categories: PL0, PL1, PL2, and PL3. PL0 refers to tumours which do not infiltrate the pleura or infiltrate it only very superficially without extending beyond the pleural elastica. PL1 and PL2 refer to tumours invading the pleura with PL1 signifying extension beyond the pleural elastica and PL2 extending to the surface of the pleura with the potential to extend beyond it. PL3 refers to tumours invading the parietal pleura [6, 8].

The new edition does not identify the PL descriptor as a separate category, although pleural involvement corresponding to PL1 and PL2 has been included in the pT2 group (depending on the tumour size: pT2a for tumours of ≤ 5 cm in diameter and pT2b for tumours of > 5 cm in diameter but < 7 cm). Tumours invading the parietal pleura (PL3), irrespective of size, are classified as pT3 tumours [2, 5].

In view of the above, a thorough microscopic evaluation of the pleura is extremely important for the correct classification of peripheral lung cancers. The new TNM system provides a more precise morphological definition of pleural involvement as extension of the tumour infiltrates beyond the pleural elastica [2]. This evaluation is not always easy, as the response to the tumour may take the form of a thickening, fibrosis, or hyalinisation of the pleura overlying the tumour, which in the standard H + E staining can make it difficult or even impossible to investigate the layer of elastic fibres within the pleura and therefore to identify pleural invasion, if any [5, 6, 8]. According to the recommendations of the adopted classification, in each case of a subpleural tumour the standard histologic diagnosis should include the EVG (elastic van Gieson) stain, which allows the pathologist to assess the integrity of the pleural elastica and makes it easier to identify pleural invasion by the tumour and to determine the pathologic stage of the disease [2, 5, 8].

The classification provides a clear and precise categorisation of tumour spread to the pleura and infiltration of the interlobar pleura. Previously these features caused a great deal of controversy and it was not clear how they should be classified. Currently the discovery of tumour nodules in the pleura is considered a metastasis and classified as pM1a, while the infiltration of the pulmonary lobes through the interlobar fissure is qualified as pT2a [2].

Cases with a macroscopically discovered and microscopically confirmed additional tumour focus, the so-called satellite nodule, located in the same lobe as the primary tumour and exhibiting the same histology, now fall within the pT3 rather than pT4 group, as previously, while cases localised ipsilaterally but in other lobes than the primary tumour are now included in the pT4 rather than pM1 category [2, 7]. The discovery of satellite nodules requires specification of their number and the size of the largest nodule in the pathology report [5, 9].

Synchronous tumours with different histologies should be treated as separate primary tumours and separately staged [2, 5].

The new classification solves the problem with categorising tumours infiltrating the mediastinal adipose tissue. Previous ambiguities first of all concerned tumours located in the tissues within the pulmonary hilum. Currently, cases in which infiltration of the adipose tissue of the hilum is discovered are classified as pT2a or pT2b, depending on the tumour size, while mediastinal adipose tissue involvement outside the hilum now falls within the pT4 group [2].

The correct classification of the pathologic stage of a cancer depends on the procedure type, and in doubtful cases consultation with the surgeon performing the procedure is recommended to confirm the extent of the procedure and the surgical assessment of intraoperative margins [9].

Changes concerning the lymph nodes (the pN descriptor)

The current edition introduces the concept of nodal zones, thereby unifying the classifications used previously [2], although it still does not reflect the necessity to specify the number of examined lymph nodes and lymph nodes with metastases within a zone, despite the significant differences in the prognosis observed with the involvement of one lymph node or several lymph nodes within a group. The differences primarily concern the N1 and N2 stations. In view of the above it seems necessary to include in the pathology report information about the number of examined lymph nodes and lymph nodes with metastases in the individual zones. For the sake of simplicity a two-letter system has been proposed with pN1a referring to cases where metastases are discovered in a single N1 station lymph node and pN1b referring to cases where more lymph nodes reveal metastatic involvement. Similarly, it is recommended that cases concerning the N2 zone be classified as pN2a and pN2b [2, 10]. The usefulness of this classifi-

cation requires further prospective studies, which will be taken into account before the next edition is published.

In the histological examination of the lymph nodes, not only the identification of metastases is important but also establishing their extent, identification of the so-called micrometastases, isolated tumour cells or clusters of tumour cells and, if possible, the assessment of the preservation of the connective tissue capsule [10].

Micrometastases are defined as tumour foci of no more than 0.2 cm in size, described in the pathology report by the "mi" descriptor, pN(mi). Isolated tumour cells or their small clusters, on the other hand, that do not exceed 0.2 mm, which may be detected by standard H & E staining, immunohistochemical (IHC) methods, other specialist methods, such as flow cytometry, or molecular methods, are referred to as the so-called isolated tumour cells (ITC). These foci do not show the morphological features typical of metastatic activity. First of all, no stromal reaction is observed in the form of fibrosis, the so-called desmoplastic response, increased proliferation of the tumour cells, or infiltration of the blood and lymphatic vessel walls. They should therefore be classified as pN0. Similarly, ITC foci in distant organs are treated as pM0 [2].

Both groups, pN(mi) and ITC, require further prospective studies to define more precisely their significance for prognosis and patient management [2, 6]. In light of the observations made so far it seems that they are not prticularly relevant for the course of the disease [6].

The microscopic examination of the lymph nodes must also include an assessment of the connective tissue capsule, as its invasion by the neoplastic infiltrate means that the surgery has not been radical and it is referred to as R1. Examination of the capsule integrity is not always possible, as the local conditions may not allow for a complete excision of the lymph node. In situations where it is extensive, the neoplastic infiltrate visible in the margins of lymph node fragments should be classified as R1, despite the lack of capsule [9].

Lung cancers, especially those with central location, extensively infiltrating the pulmonary parenchyma may directly invade the neighbouring lymph nodes. Previously there were no unequivocal morphologic criteria that would facilitate the isolation of invaded lymph nodes form the tumour mass, which on numerous occasions made the establishment of the correct stage of the cancer difficult.

The new TNM edition proposes that cases with well-delineated nodules within the neoplastic infiltrate that are found in locations that might correspond to lymph nodes should be considered pN1-positive lymph nodes with metastases [2, 9].

Direct infiltration of a lymph node and metastases are both classified similarly, as no difference in the prognosis has been observed between the two means of nodal involvement [2, 9].

Changes in the pM descriptor

The M descriptor in the new edition has been expanded. The pM1 group has been subclassified into pM1a and pM1b. The pM1a subgroup includes cases with separate nodules or a nodule in the contralateral lung and cases with nodules in the pleura or pleural, or pericardial effusion with cytologically confirmed tumour cells. Cases with confirmed distant lesions, confirmed by histopathology, have been classified as pM1b [2, 5, 11].

Changes concerning additional features not included in the pTNM classification

Some microscopic features have not been included in the pTNM classification, although their inclusion is necessary in the pathology report due to their prognostic significance and influence on the decision whether to offer the patient adjuvant treatment.

The assessment of the radicality of the surgery is of paramount importance as well as the evaluation of the presence of emboli in the blood and lymphatic vessels.

Assessment of the radicality of treatment (R, residual tumour)

The surgery radicality recommendation applies to each surgical resection margin, first of all in the bronchi and vessels, the margin of resected lymph nodes, pleural or pericardial effusion with cytologically confirmed tumour cells, or neoplastic nodules in the pleura or pericardium. The radicality of the surgery is designated by the R descriptor, with R0 referring to a margin that is free from the cancerous infiltrate, R1 to neoplastic infiltrates detected by microscopy, and R2 to an infiltrate identified in gross examination [2, 6].

The invasion of the surgical margin of the bronchus has important prognostic and predictive implications. Carcinoma in situ has a better prognosis than direct infiltration of the bronchial mucosa, tumour emboli in the lymphatic and capillary vessels of the bronchial mucosa, or peribronchial infiltration [6]. The result of the microscopic assessment of the surgical margin of the bron-

chus should, therefore, include information about the way in which the tumour infiltrate spreads and about the length of the tumour-free surgical margin.

The current edition proposes expanding the R descriptor to include the R1(is) category, emphasising the existence of carcinoma in situ, and the R1(cy+) category to describe cases of radical resection with confirmed tumour cells in the pleural fluid [2].

Resection of the chest wall with ribs requires microscopic evaluation of the radicality of the surgery, taking into account the depth of the neoplastic infiltrate. The new edition of the TNM system proposes using three categories within the pT3 descriptor: pT3a for infiltrates invading the parietal pleura, pT3b for infiltrates invading the intrathoracic fascia, and pT3c for infiltrates invading a rib and/or soft tissues [2].

The depth of the infiltrate is prognostically significant, and the collected information will be used in the preparation of the next edition.

Tumour emboli in blood vessels (V) and lymphatic vessels (L)

The presence of emboli in lymphatic and blood vessels does not result in pTNM reclassification but may be important for the course of the disease and the selection of management, and is a significant prognostic factor.

The new edition takes into account the necessity to include information about blood vessels (pV) in the pathology report, where pV0 refers to the absence of emboli, pV1 to emboli detected by microscopy, and pV2 to macroscopic infiltration of the vascular wall or the presence of tumour emboli inside the vascular lumen [2].

The current TNM system does not treat emboli in lymphatic vessels (pL) as an important feature that requires inclusion in the pathology report [2]. It has been emphasised that the detection of emboli in lymphatic vessels is important as it is associated with earlier formation of metastases in the lymph nodes and correlates with the N descriptor [6]. It is, on the other hand, less significant in the case of pre-existent lymph node metastases. In view of the above, it seems that especially in pN-negative cases the information about emboli in lymphatic vessels should be included in the microscopic findings section of the pathology report.

Significance of histologic examination for pTNM evaluation

The final description of the pathology report concerning the stage of the cancer should include principal pTNM features and the data which do not affect the staging but are recognised prognostic factors and may affect the course of the disease and the decision to offer the patient adjuvant treatment. The final characteristics should be described with the pTNMLVR or ypTNMLVR symbols for cancers previously managed with neoadjuvant treatment or radiotherapy, and with rpTNMLVR for recurrent tumours [2].

The changes introduced by the most recent TNM classification have fulfilled many expectations by focussing, for instance, on subclassifying tumour sizes, on providing more precise definitions of pleural infiltration, and on unifying the lymph node classification. They have allowed certain inconsistencies to be rectified which interfered with the correct pathologic categorisation of lung cancer.

The correct pathologic staging requires a very thorough and skilful microscopic examination and in some cases a joint clinical and pathologic assessment.

References

1. Wrona A., Jassem J. Nowa klasyfikacja TNM w raku płuca. Onkol. Prak. Klin. 2009; 5: 250–260.
2. Goldstraw P. International Association for The Study of Lung Cancer Staging Manual in Thoracic Oncology. Orange Park, Editorial Rx Press 2009.
3. Travis W.D., Giroux D.J., Chansky K. et al. The IASLC Lung Cancer Staging Project: proposals for the inclusion of carcinoid tumours in the forthcoming (seventh) edition of the TNM Classification for Lung Cancer. J. Thorac. Oncol. 2008; 3: 1213–1223.
4. Shepherd F.A., Crowley J., Van Houtte P. et al. The IASLC Lung Cancer Staging Project: proposals regarding the clinical staging of small-cell lung cancer in the forthcoming (seventh) edition of the TNM Classification for Lung Cancer. J. Thorac. Oncol. 2007; 2: 1067–1077.
5. Travis W.D. Reporting lung cancer pathology specimens. Impact of the anticipated 7th Edition TNM Classification based on recommendations of the IASlC Staging Committee. Histopathology 2009; 53: 3–11.
6. Marchevsky A.M. Problems in pathologic staging of lung cancer. Arch. Pathol. Lab. Med. 2006; 130: 292–302.
7. Rami-Porta R., Ball D., Crowley J. et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the T descriptors in the forthcoming (seventh) edition of the TNM Classification for Lung Cancer. J. Thorac. Oncol. 2007; 2: 593–602.
8. Travis W.D., Brambilla E., Rami-Porta R. et al. Visceral pleural invasion: pathologic criteria and use of elastic stains: proposals for the 7th edition of the TNM classification for lung cancer. J. Thorac. Oncol. 2008; 3: 1384–1390.
9. AJCC Cancer Staging Handbook. Seventh edition. Lung. Springer 2009; 299–323.
10. Rusch V.W., Crowley J., Giroux D.J. et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the N descriptors in the forthcoming seventh edition of the TNM Classification for Lung Cancer. J. Thorac. Oncol. 2007; 2: 603–612.
11. Postmus P.E., Brambilla E., Chansky K. et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the M descriptors in the forthcoming (seventh) edition of the TNM Classification for Lung Cancer. J. Thorac. Oncol. 2007; 2: 686–693.