UDC: 616.24-006

ZH.ZH. ZHOLDYBAY[1,2], G.R. AKHMETOVA[1], ZH.K. ZHAKENOVA[2]

[1]Kazakh Institute of Oncology and Radiology, Almaty, the Republic of Kazakhstan
[2]Asfendiyarov Kazakh National Medical University, Almaty, the Republic of Kazakhstan

Modern lung cancer staging criteria – TNM classification, 8th edition. Problems of X-ray diagnostics

Materials. *This article presents the 8th edition of lung cancer TNM-staging and analyses the changes in classification vs. edition 7.*

Results. *The fundamental changes included in TNM-8 include: modifications in T classification based on 1 cm differences in tumour size – new T-categories were included, and the existing T-categories were reconfigured; the grouping of lung cancer that results in partial or complete atelectasis or pneumonitis; the grouping of tumours involving the main bronchus regardless of the distance from the carina; revision of diaphragmatic invasion from the point of T- classification; removal of mediastinal pleural invasion from the T-classification; subdivision of M-classification into different descriptors on the basis of the number and location of extra-thoracic metastases. It also provides recommendations on the classification of diseases that lead to multiple lesions of the lungs including primarily multiple malignant lung diseases.*

Conclusion. *The revised lung cancer TNM classification is important in everyday practice of every oncologist. The changes in lung cancer TNM-staging presented in the 8th edition are necessary and important for X-ray diagnosticians who make an integral part of a large multidisciplinary team.*

Keywords: *TNM, staging, lung cancer.*

Introduction. Lung cancer is a common cancer. It remains the most common cause of death from cancer in the world [1,2]. In the Republic of Kazakhstan, lung cancer is leading in the structure of cancer mortality for several decades, with a share of 16.5% in 2015 [3]. An accurate determination of lung cancer stage is necessary to develop an effective treatment strategy and optimize the treatment outcome. Understanding of the key changes introduced into the TNM classification ed. 8 will help the radiologists to make the correct staging of lung cancer and optimize therapy for that pathology.

Aim of the study is to review the lung cancer TNM-staging ed. 8 and analyse the changes introduced in TNM classification ed. 7. Work on TNM classification ed. 8 started immediately after the publication of ed. 7 in 2009. The revised TNM classification (TNM-8) is based on the detailed analysis of new major international database of lung cancer cases collected by the International Association for the Study of Lung Cancer (IASLC). To prepare TNM-8, the members of IASLC and their partners from the Cancer Research and Biostatistics (CRAB) have chosen 77,156 cases for final analysis. Those cases included 70,967 cases of non-small cell lung cancer and 6,189 cases of small cell lung cancer. The analysis of obtained data allowed formulating and proposing changes in the definitions of T, N and M category and the resulting TNM staging for lung cancer [4-6]. IASLC was the main source of recommendations for lung cancer treatment acknowledged by the Union for International Cancer Control (UICC) [7].

The analysis of changes introduced into the TNM-8 classification. The descriptors, internationally used in TNM-system (tumour-lymph node-metastasis) for staging of various cancer types, include the size and extent of the primary tumour locoregional invasion (T), degree of regional lymph node involvement (N), and also presence or absence of intrathoracic or distant metastases (M). This classification is aimed at provision of assistance to clinicians in planning of treatment, defining of prognosis, assessment of treatment outcomes and facilitation in information exchange between physicians.

An updated lung cancer TNM classification ed. 8 is presented in Table1.

Table 1 – Criteria for determination of T, N, M categories in lung cancer staging

• **Tx –**	primary tumour cannot be assessed or the tumour was verified by detection of malignant cells in sputum or lavage, while the tumour was not visualized by bronchoscopy
• **T0 –**	no visibility of primary tumour
• **Tis –**	carcinoma in situ (Tis (AIS) for adenocarcinoma, Tis (SCIS) for squamous cell carcinoma)
• **T1 –**	tumour reaches 30 mm in diameter or less in the largest measurement, surrounded by a pulmonary parenchyma or visceral pleura, in bronchoscopy no signs of invasion of proximal of lobar bronchus (this means that the tumour is not located in the main bronchus)[a]
° **T1(mi) –**	**minimally invasive adenocarcinoma[b]**
° **T1a –**	**tumour 10 to 20 mm in diameter in the largest measurement[a]**
° **T1b –**	**tumour 20 to 30 mm in diameter in the largest measurement[a]**
° **T1c –**	**tumour from 20 to 30 mm in diameter in the largest measurement[a]**

• **T2 –**	tumour **31 to 50 mm** in diameter in the largest measurement, or the tumour in combination:
° **–**	with involvement of main bronchus, regardless of the distance to carina, but without its lesions
° **–**	with involvement of visceral pleura
° –	with atelectasis or obstructive pneumonitis which is located in perihilar sections and involves a part of the lung or the whole lung
° **T2a –**	**tumour 31 to 40 mm in diameter in the largest measurement,** or size cannot be identified (for example, when the tumour is inseparable from atelectasis)
° **T2b –**	**tumour 41 to 50 mm in diameter in the largest measurement**
• **T3 –**	**tumour 51 to 70 mm in diameter in the largest measurement,** or direct invasion of:
° –	chest wall (including the parietal pleura and tumour of the upper sulcus)
° –	phrenic nerve
° –	parietal pericardium
° –	metastatic tumour nodes (node) of the same lobe
• **T4 –**	**tumour 70 mm in diameter in the largest measurement,** or lesions of:
° –	diaphragm
° –	mediastinum
° –	heart
° –	large vessels
° –	trachea
° –	recurrent laryngeal nerve
° –	oesophagus
° –	vertebral body
° –	trachea bifurcation
° –	visceral pericardium
° –	metastatic nodules (node) in other ipsilateral lobes
N –	**regional lymph nodes involvement**
• **Nx –**	lymph nodes assessment is not possible to perform
• **N0 –**	no regional lymph nodes metastasis
• **N1 –**	metastasis in ipsilateral peribronchial and/or ipsilateral root lymph nodes, or metastases in intrapulmonary lymph nodes, including direct lesion of lymph nodes: :
° **N1a –**	lesions of lymph nodes of one N1 collector
° **N1b –**	lesions of lymph nodes of several N1 collectors
• **N2 –**	metastases in ipsilateral mediastinal and/or subcarinal lymph nodes
° **N2a1 –**	lesions of lymph nodes of one N2 collector without involvement of lymph nodes of N1 collector (skip-metastasis)
° **N2a2 –**	lesions of lymph nodes of one N2 collector with involvement of lymph nodes of N1 collector
° **N2b –**	multiple involvement of lymph nodes of N2 collector
• **N3 –**	metastases in contralateral mediastinal, chylar, any scalene or supraclavicular lymph nodes
M –	distant metastases
• **M0 –**	no distant metastases found
• **M1 –**	distant metastases found
° **M1a –**	tumour nodes in the contralateral lung, tumour nodular pleural lesion, metastatic pleural or pericardial effusion (PE)[d]
° **M1b –**	single distant tumour node[e]
° **M1c –**	multiple extra-pulmonary metastases in one or more organs

Notes:

a – quiet a rare option of detection of a superficially located tumour any size, when the invasion limited to the bronchus wall, and the tumour can be located proximal to the main bronchus - the process is also classified as T1a

b – solitary adenocarcinoma less than or equal to 30 mm in diameter, with a predominant «lepidic»-pattern and invasion of any tumour focus at the site equal to or less than 5 mm

c– T2 tumours are classified as T2a if their diameter is up to 40 mm in the largest measurement, or the size cannot be identified (for example, when the tumour is inseparable from atelectasis), and T2b if the tumour is 41 to 50 mm in diameter in the largest measurement

d – majority of pleural (pericardial) effusions have the tumour origin. However, in some patients the multiple microscopy of pleural (pericardial) fluid does not prove the tumour origin, effusion does not contain blood and is not an exudate

e – understood as the lesion may include one remote (non-regional) lymph node

T – primary tumour

Size T remains an important and basic criterion for differentiation of all categories from T1 to T4, inclusive. In comparison to ed. 7, the values of staging dimensions by T-determinant have been extended: the values of 2 cm, 3 cm, 5 cm and 7 cm remained the same, but the new ones have been added - 1 cm (for T1) and 4 cm (for T2). Each centimetre of the tumour node in the range from 1 cm to 5 cm is attributed to the worsening of survival. The tumour nodes from 5 cm to 7 cm are staged as T3, and the tumours over 7 cm are staged as T4.

Thus, the new T-categories have been introduced, and the existing T-categories have been reconfigured.

As of now, the T2 category includes tumours with involvement of main bronchus, with that tumours are located at the distance less than 2 cm from the cari-

na, but without its invasion. Besides, the tumours complicated by atelectasis and obstructive pneumonitis spread to part of the lung or the whole lung have been down-graded to T2 level [8,10]. The tumours invading the diaphragm have been reclassified as T4. In practice the mediastinal pleural invasion has been rarely used for staging, thus that criterion has been excluded from the new version [9,10].

The authors of the review draw attention to the following postulates:

1) The invasion of the anatomical structure by metastatic regional lymph node does not affect the T criterion (for example, the lesion of recurrent nerve by the aorto-pulmonary window lymph node metastasis).

2) The involvement of the pulmonary hilum cellular tissue is classified as T2a, the lesion of the mediastinal cellular tissue – as T4, the lesion of the parietal pericardium – as T3 (the lesion of the cellular tissue, surrounding the pericardium, should not be classified as T4).

3) T-category of tumour is established by the worst criterion.

4) The Pancost tumour is classified as T4 if it affects the spinal roots C8 and above, brachial plexus, subclavian vessels, vertebral bodies, arch laminae or prolapses into the spinal canal. The tumour is classified as T3 if it affects only Th1-Th2 spinal roots.

In 2011, the following variants of adenocarcinoma have been separated: adenocarcinoma in situ, minimally invasive adenocarcinoma and adenocarcinoma with predominantly "lepidic"-pattern (so-called lateral-spreading growth type), with followed introduction to the lung cancer classification by WHO members [10, 12, 13]. Consequently, these changes have been reflected in the new staging system, where the categories of Tis - adenocarcinoma in situ and Tis - squamous cell carcinoma in situ have been introduced. The minimally invasive adenocarcinoma was classified as T1mi.

Staging of sub-solid nodes and minimally invasive tumours. The breakdown of small forms of lung cancer (minimally invasive carcinoma, "lepidic"-forms especially when it dominates, growth in situ) refers to certain difficulties in clinical and radiological assessment of T-parameter. According to UICC recommendations, only the invasive size of the tumour should be considered to assign the T-value. In clinical staging, for partially solid nodes, assumed to be a non-mucinous adenocarcinoma, for clinical staging of (c) T, the size of solid component in the pulmonary window on a high-resolution computed tomogram is taken into account. Since potentially the volume of the tumour "lepidic"-component could be significantly underestimated, a relevant reassessment of pathomorphological material and diligent analysis of correspondence between the microscopic and radiographic data might be required [9, 10]. Given the limitations of radiological assessment and in line with UICC recommendations, in case of discrepancies between the clinically (radiologically) assessed tumour size and actually found in pathomorphological examination, the clinically identified dimensions should be used in addition for determination of pathomorphological T – (p) T criterion [11].

N – involvement of regional lymph nodes. Anatomical mapping of lymph nodes is still determined in accordance with the IASLC lymph node map: the detailed and convenient tool for identification of the lymph nodes groups, which was continuously applied since its publication in 2009 [12]. As in ed. 7, N0 - N3 stages consistently breakdown patients into prognostically diverse groups, and this division remained unchanged in the new 8th edition. Additional work has been carried out on further breakdown of: N1 into N1a (one lymph nodes group), the group N1 - subgroup b (with involvement of several groups of lymph nodes); N2 into N2a1 (involvement of the group of nodes without implication of lymph nodes of N1 level, so-called skip-metastases), N2 with involvement of one group of lymph nodes with engagement of N1 (N2a2) nodes, and N2 with engagement of multiple groups of lymph nodes (N2b). Despite the different survival rates determined for these detailed subgroups, the data were obtained on the basis of pathomorphological staging and were not clinically assessed. Nevertheless, the data of pathomorphological staging shall be recorded them in the medical protocols for prognostic purposes [4, 12, 13].

Lung cancer staging by N criterion is presented in the below table.

Table 2 – Lung cancer staging by N criterion: involvement of regional lymph nodes *

N	Characteristics of N criteria
Nx –	impossible to assess the regional lymph nodes;
N0 –	no metastasis in the regional lymph nodes;
N1 –	metastasis in ipsilateral peribronchial and/or ipsilateral root lymph nodes, or metastases in intrapulmonary lymph nodes, including direct lesion of lymph nodes;
N1a –	lesions of lymph nodes of one N1 collector;
N1b –	lesions of lymph nodes of several N1 collectors;
N2 –	metastases in ipsilateral mediastinal and/or sub-carinal lymph nodes;
N2a1 –	lesions of lymph nodes of one N2 collector without involvement of lymph nodes of N1 collector (skip-metastasis)
N2a2 –	lesions of lymph nodes of one N2 collector with involvement of lymph nodes of N1 collector
N2b –	multiple involvement of lymph nodes of N2 collector
N3 –	metastases in contralateral mediastinal, root, any scalene or supraclavicular lymph nodes.

Notes:

* – No changes vs. ed. 7 classification

M – Distant metastases.

No significant differences in survival of M1a group of patients (metastases within the thoracic cage) were found; therefore, that category remained unchanged in comparison to ed. 7. However, in the M1b group (distant metastases outside the thoracic cage), the survival differences were found for patients with one metastasis in one organ compared to the patients with multiple metastases in one or more organs. Hence, the group of M1b category in current 8th edition has been set aside for describing the group of extremely limited "oligo-metastatic" cases, when one metastasis was detected in one remote organ.

Also, the M1c category has been reclassified in order to describe the cases with multiple metastases in one or more distant organs/tissues. Supposedly, that type of differentiation will be the first step towards the rational definition of oligo-metastatic disease [5, 6, 14].

Resulting TNM staging. Summary data on determination of cancer stage based on TNM-8 classification is presented in the Table 3.

Table 3 – Resulting TNM staging based on ed. 8 classification

Stage	TNM equivalent	5-year survival
0 stage	Tis, N0 ,M0	Up to 92%
Ia stage	T1a , N0, M0	
Ib stage	T2a, N0, M0	68%
IIa stage	T2b, N0, M0	60%
IIb stage	T1-T2, N1, M0 or T3, N0, M0	53%
IIIa stage	T1-T2, N2, M0 or T3-T4, N1, M0 or T4, N0, M0	36%
IIIb stage	T1-T2 , N3, M0 or T3-T4, N2, M0	26%
IIIc stage	T3-T4, N3, M0	13%
IVa stage	any T, any N, c M1a/M1b	10%
IVb stage	any T, any N, with M1c	0%

The staging of patients with primary-multiple synchronous lung cancer. The frequency of primary-multiple lung cancer is growing, and the existing classification rules remain ambiguous. In the ed. 8, these types of tumours are divided into two main groups according to the disease pattern. Specific recommendations have been developed to facilitate the staging of such a multiple process. Thus, each tumour is staged separately in case of two separate primary lung cancers. For individual tumour nodes (intrapulmonary metastases), no changes were made to ed. 7 of TNM classification: T3 - for ipsilateral individual cancer nodes in the same lobe, T4 for ipsilateral lymph nodes localized in other lobes, and M1a - for node (s) in contralateral lobe (lobes).

However, a complimentary breakdown was added to distinguish the following:

1) Single primary lung cancer visualized mostly in the form of "ground-glass" consolidation with typical features of non-mucinous adenocarcinoma and with dominant "lepidic"-pattern in pathomorphological study;

2) The pneumonia-like type of cancer, detected at visualization, commonly corresponds with pathomorphologically determined invasive mucinous adenocarcinoma. The staging of this type of lesion remains most controversial. This question is left open for continued data collection and further decision-making on staging. According to previously adopted rules, the highest T-category is assigned (for the largest focus) followed by the number of lesions (or "m" for multiple forms in parentheses). After that, the general N and M categories are assigned for the entire process.

The recommendations for staging of primary-multiple lung cancer are provided in Table 4.

Table 4 – Principles of staging of synchronous primary-multiple lung cancer

Characteristics	Tumour node of second localization	Multiple "ground-glass" densities	Pneumonia-like type of adenocarcinoma	Secondary pulmonary nodes
Visualization	Two or more tumours with radiation characteristics of primary lung cancer	Multiple partially solid or "ground-glass" nodules	Parts of consolidation and/or "ground-glass"	Lung cancer with secondary solitary nodules
Pathomorphological characteristics	Disparate histotype and disparate morphology within the complex histological assessment	Adenocarcinoma with predominant "lepidic"-component	Identical histology (most commonly an invasive mucinous type adenocarcinoma)	Same histotype and nodes morphology within the complex histological assessment
TNM-classification	Each tumour is staged separately clinically and pathomorphologically	T-category – for nodule with the largest T, N and M - general categories	T – based on the size: T3 – in one lobe localization; T4 or M1a – if in diverse ipsilateral and contralateral lobes N and M - general categories	Disposition of separate nodes as related to primary tumour is defined as T3, T4, or M1a; N and M - general categories integrally for the whole process
Comments	Non-connected tumours	Independent tumours with similar morphology	One tumour, diffuse lung involvement	One tumour with intrapulmonary metastases

The criteria used to clarify the clinical (cTNM) and pathomorphological (pTNM) staging of four variants of lung cancer presented in Table 4 are based on the best currently available evidence [4, 14-17].

Thus, the fundamental changes of TNM-8 classification include: the modifications in T classification based on 1-cm differences in tumour size; the grouping of lung cancer resulting in partial or complete atelectasis or pneumonitis; the grouping of tumours involving the main bronchus regardless of the distance from the carina; the revision of diaphragmatic invasion from the point of T-classification; the removal of mediastinal pleural invasion from the T-classification; the subdivision of M-classification into different descriptors on the basis of the number and location of extra-thoracic metastases. It also includes recommendations on classification of dis-

eases leading to multiple lesions of the lungs including primarily multiple malignant lung diseases.

Conclusion. The revised lung cancer TNM classification is important in everyday practice of every oncologist. The changes in lung cancer TNM-staging presented in ed. 8 reflect the results of continued clinical and pathomorphological studies aimed at improving the quality of diagnostics and treatment of this category of patients. Knowledge of modern staging is essential for radiologists who make an integral part of a large multidisciplinary team.

References:

1. Ozkan E., West A., Dedelow J.A. et. al. CT Gray-Level Texture Analysis as a Quantitative Imaging Biomarker of Epidermal Growth Factor Receptor Mutation Status in Adenocarcinoma of the Lung // AJR. – 2015. – Vol. 205. – P. 1016–1025

2. Kligerman S., Abbott G.. A Radiologic Review of the New TNM Classification for Lung Cancer. // AJR – 2010. – Vol. 194. – P. 562–573

3. Pokazateli onkologicheskoy sluzhby Respubliki Kazakhstan za 2015 god [Indicators of the cancer service of the Republic of Kazakhstan for 2015]. - Almaty, 2015. – C. 156-157.

4. Goldstraw P., Chansky K., Crowley J., Rami-Porta R., Asamura H., Eberhardt W.E., Nicholson A.G., Groome P., Mitchell A., Bolejack V. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer // Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer. – Vol. 11 (1). – P. 39-51. doi:10.1016/j. jtho.2015.09.009

5. Rami-Porta R., Bolejack V., Crowley J. et al. The IASLC Lung Cancer Staging Project: proposalsfortherevisionsofthe Tdescriptors in the forthcoming eighth edition of the TNM classification for lung cancer // J Thorac Oncol. -2015. – Vol. 10(7). – P. 990–1003. doi:10.1097/JTO.0000000000000559

6. Nicholson A.G., Ming S. Tsao, Travis W. D., Patil D. T., Galateau-Salle F., Mirella Marino, Dacic S., Beasley M. B., Butnor K. J., Yatabe Y., Pass H.I., Rusch V. W., Detterbeck F. C., Asamura H., Rice T. W., Rami-Porta R. Eighth Edition Staging of Thoracic Malignancies: Implications for the Reporting Pathologist // Arch Pathol Lab Med. – 2018 Feb 26. doi: 10.5858/arpa.2017-0245-RA

7. Carter B.W., Lichtenberger J.P. et al. Revisions to the TNM Staging of Lung Cancer: Rationale, Significance, and Clinical Application // RadioGraphics. – 2018. – Vol. 38. – P. 374-391.

8. Travis W.D., Brambilla E., Noguchi M. et al. International Association for the Study of Lung Cancer/American Thoracic Society / European Respiratory Society international multidisciplinary classification of lung adenocarcinoma // J Thorac Oncol. – 2011. – Vol. 6 (2). – P. 244-285.

9. Travis W.D., Brambilla E., Burke A.P., Marx A., Nicholson A.G., eds. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. 4th ed. –Lyon, France: International Agency for Research on Cancer (IARC), 2015. WHO Classification of Tumours; vol. 7.

10. Travis W.D., Asamura H., Bankier A.A. et al. The IASLC Lung Cancer Staging Project: proposals for coding T categories for subsolid nodules and assessment of tumour size in part-solid tumours in the forthcoming eighth edition of the TNM classification of lung cancer // J Thorac Oncol. – 2016. – Vol. 11 (8). – P. 1204-1223.

11. Union for International Cancer Control TNM Supplement: A Commentary on Uniform Use. 4th ed. – Oxford, United Kingdom: Wiley-Blackwell, 2012.

12. Rusch V.W., Asamura H., Watanabe H. et al. The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer.// J Thorac Oncol. – 2009. – Vol. 4(5). – P. 568-577.

13. Asamura H., Chansky K., Crowley J. et al. The International Association for the Study of Lung Cancer – Lung Cancer Staging Project: proposals for the revision of the N descriptors in the forthcoming 8th edition of the TNM classification for lung cancer. // J Thorac Oncol. – 2015. – Vol. 10(12). – P. 1675-1684.

14. Eberhardt W.E., Mitchell A., Crowley J. et al. The IASLC Lung Cancer Staging Project: proposalsfortherevisionofthe Mdescriptors in the forthcoming eighth edition of the TNM classification of lung cancer // J Thorac Oncol. – 2015. – Vol. 10(11). – P. 1515-1522.

15. Detterbeck F.C., Franklin W.A., Nicholson A.G. et al. The IASLC Lung Cancer Staging Project: backgrounddataandproposedcriteria to distinguish separate primary lung cancers from metastatic foci in patients with two lung tumours in the forthcoming eighth edition of the TNM classification for lung cancer. // J Thorac Oncol. – 2016. - Vol. 11 (5). – P. 651-665.

16. Detterbeck F.C., Nicholson A.G., Franklin W.A. et al. The IASLC Lung Cancer Staging Project: summary of proposals for revisions of the classification of lung cancers with multiple pulmonary sites of involvement in the forthcoming eighth edition of the TNM classification. // J Thorac Oncol. – 2016.- Vol. 11(5). – P. 639-650.

17. Detterbeck F.C., Marom E.M., Arenberg D.A. et al. The IASLC Lung Cancer Staging Project: background data and proposals for the application of TNM staging rules to lung cancer presenting as multiple nodules with ground glass or lepidic features or a pneumonic-type of involvement in the forthcoming eighth edition of the TNM classification. // J Thorac Oncol. – 2016. – Vol. 11(5). – P. 666-680.