JBR–BTR, 2013, 96: 118-122.

UPDATE IN NON SMALL-CELL LUNG CANCER STAGING*

R.A. Salgado, A. Snoeckx, M. Spinhoven, B. Op de Beeck, B. Corthouts, P.M. Parizel[1]

Significant progress has been made with the introduction of the TNM-7 staging system for non-small cell lung cancer (NSCLC). Constituting the first major revision in 12 years, the seventh edition of NSCLC TNM (TNM-7) is based on the recommendations from the International Association for the Study of Lung Cancer (IASLC) Lung Cancer Staging Project of 2007. This new TNM iteration includes a subset analysis on SCLC and carcinoid tumors.
A thorough understanding of its principles by the radiologist is helpful to increase efficiency and to improve communication with the referring clinicians.

Key-word: Lung neoplasms, staging.

Lung cancer is a well-known devastating disease, representing the most common cancer-related death in males, and responsible for more than 1.4 million deaths in 2008 (1). With almost all subtypes expressing a significant initial clinically silent period, only 25% of the patients are eventually considered potential surgical candidates at the time of diagnosis (2). In order to provide the best standard of care for each individual patient, a correct disease staging at the time of diagnosis remains the best predictor of survival. Essentially, a staging system is needed to group different patients according to their disease progression, establish a comprehensive evaluation for a standardized treatment strategy for a particular disease stage, and provide guidance on prognosis and further disease evolution.

In order for staging systems to be practically implementable, they must be accurate, uncomplicated and easy reproducible. The best-known and widely implemented staging system for non-small cell lung cancer (NSCLC) is the TNM-system, based on information regarding the primary tumor (T), nodal status (N) and the characteristics of metastatic disease (M). Using different disease prescriptors, patients are grouped according to the biological behavior of the tumor, and stratified accordingly along different treatment lines. The TNM staging system provides as such a standardized nomenclature for exchange of information in both a clinical and research setting.

TNM 1-6 staging system: history and contemporary criticism

The initial steps to set up a clinically implementable staging system were taken by Pierre Denoix in 1942 and 1952. The TNM lung cancer staging system originates from proposals made by Mountain et al. in 1973 (3). Ever since its introduction, the TNM system has been continuously refined with up to six editions until 2009 by the TNM Prognostic Factors Project of the International Union Against Cancer (IUAC) as more data became available. While these iterations of the TNM staging system have proven to be an excellent tool in clinical practice and scientific research, they are not without their criticism on different levels.

The data used as a foundation in the TNM system was mostly collected from a single center (M.D. Anderson Cancer center, Houston, Texas, USA), and consisted of 2155 cases of histologically proven adenocarcinoma. This relatively small database, acquired from surgically staged patients, resulted in some cases in TNM data subsets containing too few cases for proper analysis (4). Furthermore, while there was some internal validation, the TNM data was not subjected to any external validation.

Another more pointing criticism was that the grouping of patients in different disease stages, based on the implementation of the existing descriptors, was far from perfect in earlier editions of the TNM system. In an ideal system, the stratification of patients according to their disease stage would create different groups who are strictly discriminated from each other by their specific prognosis and survival rates (Fig. 1A). As such, each stage group has its specific disease progression properties, allowing optimization of different treatment plans targeted to a specific disease stage. Unfortunately, it has been shown that significant overlap in cumulative survival exists between groups, often complicating a comparison between different disease stages (Fig. 1B) (5-7). More specifically, little difference in survival was encountered between disease stage IB and IIA, IIA and IIB and between IIIB and IV (6).

The prevalence of the different histological subtypes of NSCLC has also changed over time (8). In the original TNM staging database, 30% of the contained cases were adenocarcinoma, 58% of squamous cell carcinoma and 12% of unspecified subtypes. However, a more recent survey by the Surveillance, Epidemiology and End Results (SEER) program based on data collected between 2002 and 2006 showed a changing prevalence of the different subtypes: the presence of adenocarcinoma increased to 43%, with a decrease to 23% of squamous cell carcinoma and 34% share of unspecified subtypes. Therefore, the stage grouping and prognostic information derived from the original TNM database had now an outdated histologic disease distribution. Furthermore, the rising incidence of lung cancer in females has just recently started to reach a plateau phase after two decades of rise (9), reflecting a changing sex distribution which was yet unaccounted for.

New diagnostic imaging techniques have also an increasing impact on the accuracy of staging. More specifically, the introduction of 2(fluorine-18) fluoro-2-deoxy-D-glucose positron emission tomography (PET) and PET-CT systems in clinical practice have added a metabolic dimension to the previously solely morphological detection of tumoral presence and spread using CT and plain chest film (Fig. 2 A,B), consequently often upstaging disease. Furthermore, advances in conventional CT technology with an ever increasing spatial resolution and multiplanar capabilities have further contributed to an improved overall evaluation. Finally, contemporary

*Meeting "Lung Cancer Imaging in 2012: Updates and innovations", Tervuren, 10.11.2012.
1. Dept. of Radiology, Antwerp University Hospital, Edegem, Belgium.

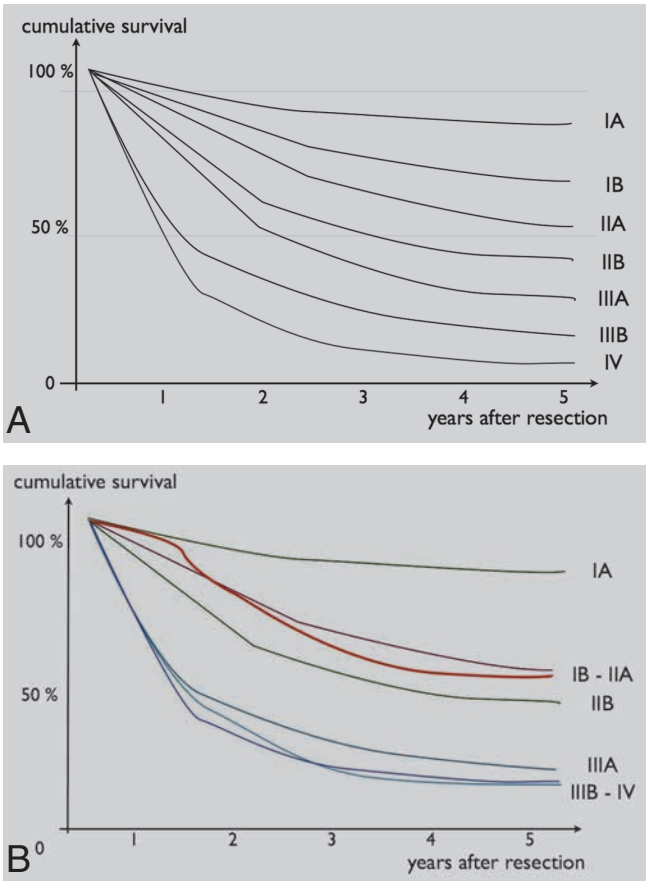

Fig. 1. — In an ideal staging system, patients would be according to their disease stage grouped in several disease stages, which do not overlap with each other in terms of treatment plans, prognosis and overall survival (A). However, this stratification proved imperfect in previous editions of the TNM-system, with several groups having overlapping survival curves (B). Adapted from reference (4).

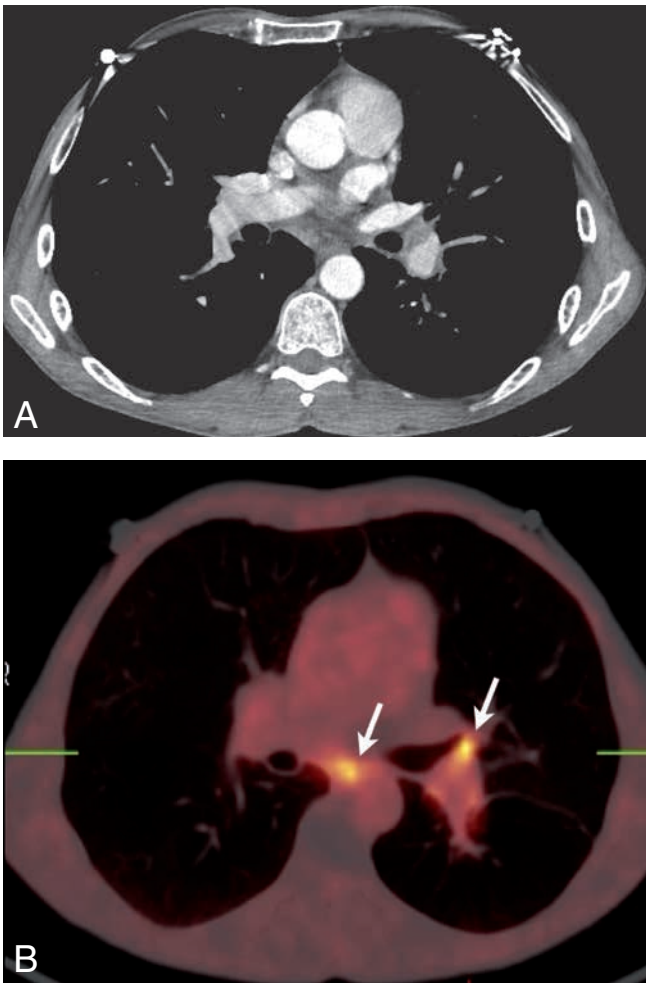

Fig. 2. — A patient with a primary lung carcinoma in the right lung (not shown). The axial CT view shows no morphologically abnormal lymph nodes (A). However, the PET examination (B) reveals at the same anatomic level abnormal uptake in two lymphnodes (arrows), indicating mediastinal and hilar adenopathy and as such upstaging the stage of disease.

staging tools like endoscopic ultrasonography (US), endo-bronchial US, endoscopic US-guided fine needle aspiration and endobronchial US-guided transbronchial needle aspiration have further pushed minimally invasive tumor staging to new frontiers (10) .

As such, these new staging techniques often lead to better accuracy of the initial staging, frequently upstaging patients as compared with older imaging techniques and consequently leading to stage migration in a significant number of patients (1). This is especially true in patients who have clinically silent advanced disease. When these patients consequently migrate from an early disease stage to a more advanced disease group, this can lead to an improved survival rate in both groups. This well-known effect has been termed the "Will Rogers"-phenomenon, and its existence must always be considered when evaluating and interpreting results from staging systems (11).

Up to TNM-6, only one size cut-off of 3 cm was used to distinguish between T1 and T2 tumors. However, different survival rates in tumor of various sizes have been reported (12-15). This is more specifically the case for tumors smaller than 2 cm and for tumors larger than 5-7 cm. This implicates that by using only a single size threshold for stratification of patients based on tumor size, the resulting discrimination will not take into account the different possible survival rates.

Finally, advances in (surgical) treatment techniques have led to more potentially resectable tumors. If adaptations to the staging system are not made to reflect this improved treatment options, in some cases this can potentially lead to unnecessarily 'upstaging' of potentially resectable tumors (16, 17).

TNM-7

In order to address these mentioned and other shortcomings, a major revision on the TNM system was introduced in 2009. Constituting the first major revision in 12 years, the seventh edition of NSCLC TNM (TNM-7) was based on the recommendations from the International Association for the Study of Lung

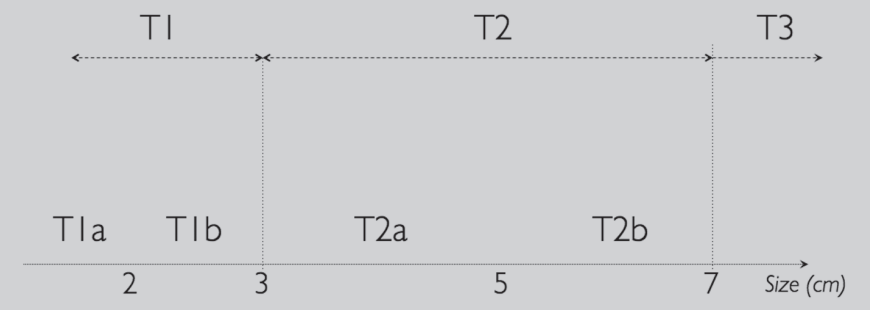

Fig. 3. — The size prescriptor has been further refined to better indicate the different survival characteristics of tumors of different sizes. Note that the 3 cm size cut-off remains the discriminating factor between T1 and T2, and that tumors larger than 7 cm are now considered T3 tumors.

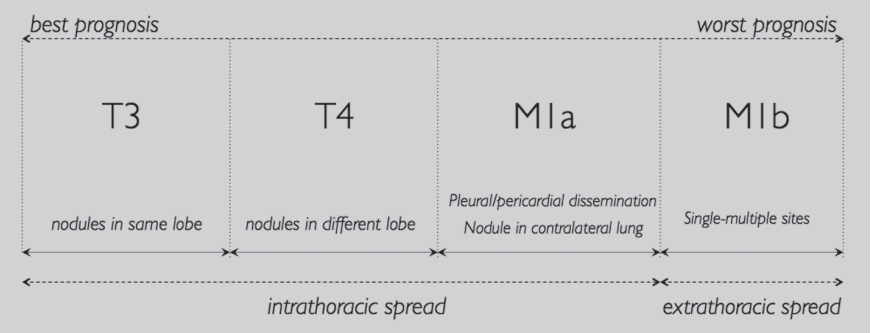

Fig. 4. — TNM-7, a distinction is made whether tumoral nodules are within the same or different lobe as the primary tumor. Furthermore, metastatic disease has been further refined into introthoracic or extrathoracic spread, the latter having the worst prognosis.

Cancer (IASLC) Lung Cancer Staging Project of 2007. This new TNM iteration also includes a subset analysis on SCLC and carcinoid tumors (18-20).

The gathered database encompasses initially more than 100.000 cases assembled during 1990-2000 in a multicentric, international fashion. A stable staging algorithm was used, with both internal and external validation (21). While the data was predominantly acquired from surgical staging information, contribution of non-surgical treatment modalities like radio- and chemotherapy was also included.

One of the main goals of this new TNM system was to achieve better grouping of patients according to their disease stage in order to provide a better stratified prognosis. To accomplish this, more accurate TNM prescriptors and stage groups were introduced. The changes mostly affected the descriptors for size and location of the primary tumor (T) and the classification of metastatic disease (M).

To better reflect different survival rates between tumors of different sizes, additional size cut-offs were introduced (2, 20). While the 3 cm threshold remains the discriminating factor to distinguish between a T1 and T2 tumor, both these prescriptors were further refined to include tumors of more specific size-ranges (Fig. 3). Further data analysis also indicated that tumors with a size equal or larger than 7 cm had a survival comparable with T3 tumors, and were consequently reclassified as T3. As such, it became the first time that size was used as a discriminator between T2 en T3.

As previously stated, evolving treatment practices allow to extend the range of potentially resectable tumors compared with previous generations. While a tumor invading the great vessels or mediastinum remains a T4 tumor, recent data has shown that a primary lung tumor with adjacent nodules in the same lobe has a more favorable prognosis similar to a T3 tumor. Therefore, this type of tumor presentation has been reclassified as T3, providing another example of better stratification between tumors that were considered before as similar (Fig. 4).

When further exploring the impact of concomitant lung nodules outside the primary tumor, it becomes clear that patients with ipsilateral nodules in a different lobe than the primary lesion have a better prognosis that patients with nodules in the contralateral lung. Consequently, these patients are now reclassified as T4 instead of M1 (Fig. 4).

The characterization of metastatic disease has also been further refined. One of the new key concepts is the distinction between intra- or extrathoracic metastatic disease. A T4 tumor with nodules in the ipsilateral lung but outside the lobe of the primary lesion has a median survival of 13 months. Even so, this is still more favorable than the presence of a malignant pleural/pericardial dissemination or nodules in the contralateral lung, both which are associated with a median survival of 8 months. Metastatic disease outside the lung has the worst prognosis with a median survival of 5 months. To make the distinction between intra- or extrathoracic disease, the M prescriptor has been further divided in M1a and M1b indicating intra- or extrathoracic metastatic disease (Fig. 4) (21). No further distinction is made between single or multiple sites of involvement. M-stage still precludes surgery.

The modification of the nodal stage (N) prescriptor has been more modest, with no major changes. The validity of the existing prescriptors has been further confirmed. Efforts also have been centered at the reconciliation of the Naruke and MD-ATS nodal map. TNM-7 introduces in this respect six nodal zones, with the hilar and peripheral zone indicating N1 status with the others zones corresponding to N2 disease. A new international lymph node map is current being developed, but has not yet been presented at the time of this writing (22). Finally, while there appears to be small differences in tumoral behavior in the presence of skip metastases, data subsets are still too small to make formal recommendations in this respect.

Consequences of TNM-7

TNM-7 does not introduce new subcategories to the current stage divisions. However, the effects of changed T and M prescriptors, and the impact of the new T1 and T2 subclassifications have led to a changed survival profile in some cases. As an example, a T2N1M0 disease corresponded with a IIB stage in previous

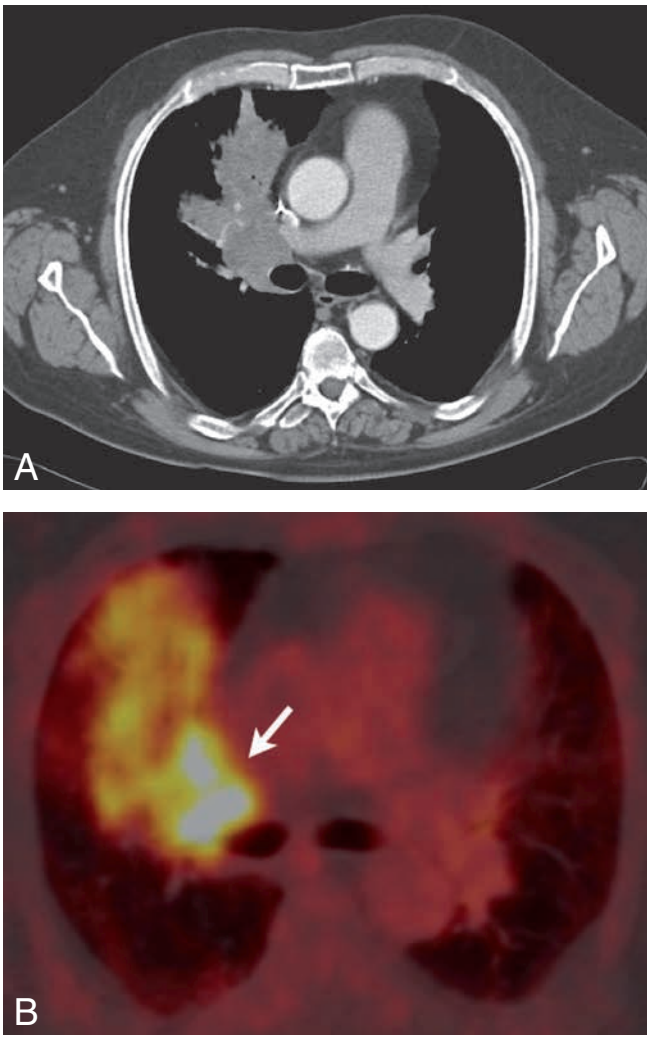

Fig. 5. — The conventional CT image shows a large heterogeneous mass extending anteriorly from the right hilus (A). Based on this image, it is unclear which part of this mass represents tumoral tissue, and which mass component is solely retro-obstructive atelectasis or other associated non-neoplastic changes. The PET image at the same level (B) additionally reveals an extensive uptake in the right hilus, indicating the site of the primary tumor (arrow). However, this type of image is yet no validated for exact tumor measurement to be used in staging systems.

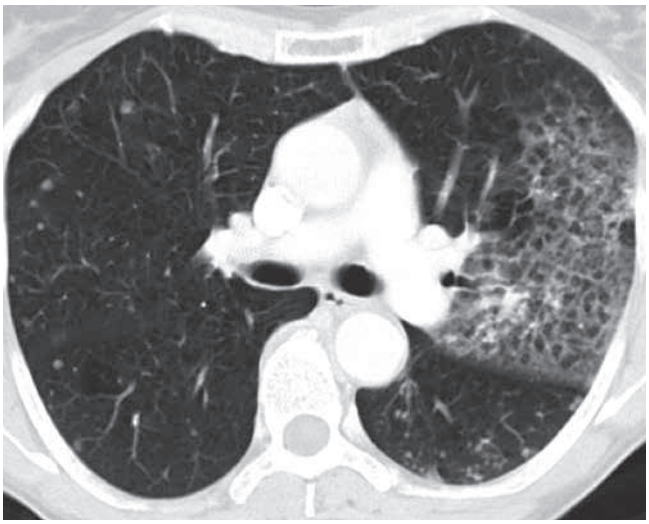

Fig. 6. — Slow growing tumor in de left lung with multiple bilateral small nodules, formerly known as mucinous bronchioloalveolar carcinoma. This rare type of tumor exhibits a much slower growth than a classical invasive adenocarcinoma. As such, they often have different survival rates than other tumors included in the TNM-database, the question remaining to what extend traditional results are applicable to this rare subtype of lung cancer.

staging systems. In TNM-7, this has now to be further refined using the mentioned subclassifications. As such, a patient with a previously determined IIB stage will, depending on the T2 subclassification status, migrate to a lesser stage IIA (T2aN1M0), or will stay at IIB if the criteria for a T2b prescriptor are met. The end result of stage migration secondary to the changed TNM prescriptors is that 10 subsets have been downstaged, and conversely 7 stages are upstaged (9). The clinical significance is that, since the boundary for surgery is set around stage IIA-B, the number of patients with potentially resectable tumors changes.

Issues or limitations

Despite the advances made in TNM-7, many limitations and restrictions remain. While it is not the aim of this overview to provide a complete coverage of this topic, some important remarks deserve to be mentioned.

Despite the significant advances in CT technology, it remains an imaging modality which is not often optimal for discrimination between different tissues. This is especially an issue when tumoral tissue is surrounded by atelectasis or other tissues with similar density, making the primary tumor indistinguishable from non-tumoral tissues (Fig. 5A). Consequently, the determination of tumor size is not always straightforward and sometimes performed with a significant margin of error. While PET-CT has a clear advantage in this respect, it has not been yet validated to serve as a tool for exact tumor sizing (Fig. 5B).

Furthermore, the impact of the multiplanar capabilities of modern CT systems allowing measurements in a different plane than the standard axial view has not yet included in any staging database.

Finally, questions remain on how to correctly approach infiltrative tumors with no clear boundaries, and/or tumor subtypes with a slow growing nature which probably have a more favorable prognosis (Fig. 6). It is also unclear if the number of contralateral or extrathoracic metastasis has an objective impact on survival.

Conclusion

It is evident that a significant progress has been made with the introduction of the TNM-7 staging system for NSCLC. While some questions remain, it remains the principal keystone for lung cancer staging. A thorough understanding of its principles and implication by the radiologist will increase its participation in the staging process, and improve the communication with referring clinicians.

References

1. Mirsadraee S., Oswal D., Alizadeh Y., Caulo A., van Beek E., Jr.: The 7th lung cancer TNM classification and staging system: Review of the changes and implications. *World J Radiol*, 2012, 4: 128-134.
2. Rami-Porta R., Crowley J.J., Goldstraw P.: The revised TNM staging system for lung cancer. *Ann Thorac Cardiovac Surg*, 2009, 15: 4-9.
3. Mountain C.F., Carr D.T., Anderson W.A.: A system for the clinical staging of lung cancer. *AJR*, 1974, 120: 130-138.
4. Goldstraw P., Crowley J., Chansky K., et al.: The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. *J Thorac Oncol,* 2007, 2: 706-714.
5. Pfannschmidt J., Muley T., Bulzebruck H., Hoffmann H., Dienemann H.: Prognostic assessment after surgical resection for non-small cell lung cancer: experiences in 2083 patients. *Lung Cancer*, 2007, 55: 371-377.
6. Naruke T., Tsuchiya R., Kondo H., Asamura H.: Prognosis and survival after resection for bronchogenic carcinoma based on the 1997 TNM-staging classification: the Japanese experience. *Ann Thorac Surg*, 2001, 71: 1759-1764.
7. Goya T., Asamura H., Yoshimura H., et al.: Prognosis of 6644 resected non-small cell lung cancers in Japan: a Japanese lung cancer registry study. *Lung Cancer*, 2005, 50: 227-234.
8. Wynder E.L., Muscat J.E.: The changing epidemiology of smoking and lung cancer histology. *Environmental Health Perspectives*, 1995, 103 Suppl 8: 143-148.
9. Nair A., Klusmann M.J., Jogeesvaran K.H., Grubnic S., Green S.J., Vlahos I.: Revisions to the TNM staging of non-small cell lung cancer: rationale, clinicoradiologic implications, and persistent limitations. *Radiographics*, 2011, 31: 215-238.
10. Gomez M., Silvestri G.A.: Endobronchial ultrasound for the diagnosis and staging of lung cancer. *Proceedings of the American Thoracic Society*, 2009, 6: 180-186.
11. Feinstein A.R., Sosin D.M., Wells C.K.: The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *New Engl J Med*, 1985, 312: 1604-1608.
12. Flieder D.B., Port J.L., Korst R.J., et al.: Tumor size is a determinant of stage distribution in t1 non-small cell lung cancer. *Chest*, 2005, 128: 2304-2308.
13. Asamura H., Goya T., Koshiishi Y., Sohara Y., Tsuchiya R., Miyaoka E.: How should the TNM staging system for lung cancer be revised? A simulation based on the Japanese Lung Cancer Registry populations. *J Thorac Cardiovasc Surg*, 2006, 132: 316-319.
14. Takeda S., Fukai S., Komatsu H., Nemoto E., Nakamura K., Murakami M.: Impact of large tumor size on survival after resection of pathologically node negative (pN0) non-small cell lung cancer. *Ann Thorac Surg*, 2005, 79: 1142-1146.
15. Lopez-Encuentra A., Duque-Medina J.L., Rami-Porta R., de la Camara A.G., Ferrando P.: Staging in lung cancer: is 3 cm a prognostic threshold in pathologic stage I non-small cell lung cancer? A multicenter study of 1,020 patients. *Chest*, 2002, 121: 1515-1520.
16. Oliaro A., Filosso P.L., Cavallo A., et al.: The significance of intrapulmonary metastasis in non-small cell lung cancer: upstaging or downstaging? A re-appraisal for the next TNM staging system. *Eur J Cardio-Thorac Surg*, 2008, 34: 438-443.
17. Urschel J.D., Urschel D.M., Anderson T.M., Antkowiak J.G., Takita H.: Prognostic implications of pulmonary satellite nodules: are the 1997 staging revisions appropriate? *Lung Cancer*, 1998, 21: 83-87.
18. Vallieres E., Shepherd F.A., Crowley J., et al.: The IASLC Lung Cancer Staging Project: proposals regarding the relevance of TNM in the pathologic staging of small cell lung cancer in the forthcoming (seventh) edition of the TNM classification for lung cancer. *J Thorac Oncol*, 2009, 4: 1049-1059.
19. Shepherd F.A., Crowley J., Van Houtte P., et al.: The International Association for the Study of Lung Cancer lung cancer staging project: proposals regarding the clinical staging of small cell lung cancer in the forthcoming (seventh) edition of the tumor, node, metastasis classification for lung cancer. *J Thorac Oncol*, 2007, 2: 1067-1077.
20. 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.
21. Postmus P.E., Brambilla E., Chansky K., et al.: The IASLC Lung Cancer Staging Project: proposals for revision of the M descriptors in the forthcoming (seventh) edition of the TNM classification of lung cancer. *J Thorac Oncol*, 2007, 2: 686-693.
22. Rusch VW., Asamura H., Watanabe H., Giroux D.J., Rami-Porta R., Goldstraw P.: 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, 4: 568-577.