

New TNM staging in lung cancer (8th edition) and future perspectives

Matilla JM¹, Zabaleta M², Martínez-Téllez E³, Abal J⁴, Rodríguez-Fuster⁵ A, Hernández-Hernández J⁶

1 Thoracic Surgery Department, University Hospital of Valladolid, Valladolid (Spain)

2 Pneumology Department, Valdecilla University Hospital, Santander (Spain)

3 Thoracic Surgery Department, Santa Creu y Sant Pau Hospital, Barcelona (Spain)

4 Pneumology Department, University Hospital of Orense, Orense (Spain)

5 Thoracic Surgery Department, Hospital del Mar, Parc de Salut Mar. Mar Institute of Medical Research. Barcelona (Spain)

6 Pneumology Department, Complejo Asistencial de Ávila, Ávila (Spain)

*Corresponding autor

José-María Matilla

Department of Thoracic Surgery, University Clinic Hospital of Valladolid, Ramón y Cajal Avenue, 47005 Valladolid, Spain.

Email: jmatillag@saludcastillayleon.es

Article information:

Received: March 7, 2020

Revised: May 5, 2020

Accepted: May 6, 2020

Abstract

Background. Carrying out a correct anatomical classification of lung cancer is crucial to take clinical and therapeutic decisions in each patient.

Aim. TNM staging classification provides an accurate anatomical description about the extension of the disease, however, the anatomical burden of the disease is just one aspect that changes the prognosis.

Relevance for patients. TNM staging classification is a tool that predicts survival but we must to consider that TNM is just one of the factors that concerns the prognosis. The impact of a factor over the prognosis is complex due to: it depends on the specific environment, the treatment strategy among others; and our level of certainty makes difficult to include all the factors just in a group of stages. In some groups, there are difficulties to get large series, due to the low frequency of cases and the small number of events (metastasis, loco-regional recurrence). It doesn't allow to obtaine evidence in a short period of time.. On the other hand, in the next years, new markers will be incorporated in the coming years, wich are going to be included in the new TNM classification. It could help to improve the classification giving more information about prognosis and risk of recurrence. All these aspects are being used by the International Association for the Study of Lung Cancer (IASLC) to develop a new prognosis model. This continues evolution of TNM system allows us to overcome the difficulties and build a flexible framework enough to continue improving the individual prognosis of the patients.

Keywords: TNM classification, staging, lung cancer

1. Introduction

Carrying out a correct anatomical classification of lung cancer is crucial to take clinical and therapeutic decisions in each patient [1]. The classification consists of three components: T (tumor) N (nodes) and M (metastases) in four stages (I to IV). This classification allows us to standardize the extension of lung tumours. It compares the clinical information collected from different centers with the purpose to homogenize patients in groups (stages) with similar prognosis and therapeutic approaches. The information related to the extension of the disease could be necessary too to decide if an individual could be part of a trial or not [2]. Lung cancer is unique among the different types of cancer with respect to stage classification. Most cancers staging systems are based on empirical results and based on consensus. The classification of lung cancer is the result of a sophisticated system of statistical analysis of more than 100,000 patients [3].

In 2017, the *Union Internationale Contre le Cancer* (UICC) later called *Union for International Cancer Control* and the *American Joint Committee for Cancer Staging and End Results Reporting* (AJC), later known as *The American Joint Committee on Cancer* (AJCC), in collaboration with the *International Association for the Study of Lung Cancer* (IASLC) agreed to publish the 8th edition of lung cancer TNM [4]. Although the classification in stages remains stable over the years, the AJCC and the UICC, make regular reviews. The 8th edition is a result of a multidisciplinary and continuous improvement of the previous ones. Following this idea, new patient data have been collected, to develop the 9th edition which is expected to be completed in 2024 [5].

2. The beginnings

Although several international organizations worked on the staging classifications, the T, N and M descriptors were proposed and developed by the French surgeon Pierre Denoix between 1943 and 1952 [6-8]. The first edition of the general classification of TNM tumours was published in 1968 under the supervision of the UICC. They included cases classified between T0 (no visible tumor) and T4 (tumours with the extension beyond the lung), from Nx to N1 (intrathoracic lymph nodes) and category M1 was subdivided into M1a (malignant pleural effusion), M1b (cervical nodes palpable) and M1c (distant metastases) [8].

In 1959 the AJC was created independent from the UICC. It made that the staging classification of both organizations was not exactly the same [9]. The lung cancer working group (Drs. Mountain, Carr and Anderson) analyzed the characteristics and progress of 2,155 patients. These studies were the basis to develop T and N, sections, and to introduce the idea of TNM stages, groups or subsets for with similar prognosis. These proposals were included in the second TNM classification of the UICC (1975) being the first edition of the AJC cancer staging manual [9]. Fortunately, on the proposals of Dr. Mountain,

an agreement was reached between the AJCC and the UICC bring their opinions closer creating a common international classification in 1988 [8,9].

Until the first publication of the staging manuals based on the 6th edition in 2002, the TNM updates were conducted by the M.D. Anderson Cancer Center in the United States of America (USA) created by Dr. Mountain [6,7]. In 1997, IASLC takes part in the review process for future classifications [1]. In that year the 5th edition was published, which had been based on the biggest series (5,319 patients) so far of non-small cell lung cancers (NSCLC) [9]. The IASLC created, in the same year, a Staging Committee with international representation and supported by the non-profit medical-statistical organization *Cancer Research And Biostatistics* (CRAB) [9]. The first phase of the staging project collected a retrospective database of 81,495 evaluable records of patients with lung cancer (13,032 SCLC and 68,463 NSCLC), diagnosed between 1990 and the year 2000, including all therapeutic modalities. It was proposed to collect the cases contributed by 20 databases of patients with a follow up for at least 5 years, also carrying out an internal (in different geographical areas) and external (using the *National Cancer Institute Surveillance, Epidemiology, and End Results Program* (SEER) database of the *American National Cancer Institute*) validation. The distribution of cases was: 58% came from Europe, 21% from North America, 14% from Asia and 7% from Australia [9].

With this great project underway, and awaiting its results, the 6th edition of the TNM was published in 2002, without any change over the 5th. The IASLC study conclusions were presented to the international community in 2007 and accepted by UICC and AJCC. This agreement was the origin of the 7th edition of the TNM classification of lung cancer [10]. They described an accurate definition of visceral pleura involvement and they eliminate the differences between the two mediastinal lymph node maps used so far, Naruke map and Mountain / Dressler map [11].

Despite the great methodological and seriousness progress observed in the 7th edition, there were improvements that justified further research. The initial retrospective project presented several limitations due to the lack of a specific database, for example, the changes proposed for the T descriptors was limited to the size, the existence of additional nodules or the presence of pleural effusion, and the lack of information for analyzing other factors such as tumor extension [3,12,13]. With the purpose of improving the database, they proposed to increase the number of non-surgical stages patients to get closer to the daily clinic and it was considered convenient a greater representation of other countries [3].

The second phase created to overcome the limitations of a retrospective project was the creation of a prospective database designed specifically for the TNM classification in lung cancer. Between 1999 and 2010 data, 94,708 patients were collected from four continents (Table 1).

The information collected in this new database includes: general characteristics of the patient, diagnostic descriptors of the disease, various general laboratory parameters at the time of diagnosis, SUV (standardized uptake value) of Positron Emission Tomography (PET) and some results of the respiratory function. The evaluation of the clinical TNM was performed by collecting data related to radiological studies, CT and PET scan, bronchoscopy and the different invasive diagnostic procedures including surgical procedures with no tumor resection. In the treatment section, the TNM classification of each patient was collected according to the 7th edition in force until that time. In the case of non-surgical patients, clinical TNM was used, and the type of treatment performed (chemotherapy and/or radiotherapy). In the case of patients treated surgically, the clinical TNM and pathological TNM were included, collecting different variables in relation to the surgical procedure, induction or adjuvant treatment and the final pathological study. Information was also collected for special cases such as the presence of multiple nodules related to a unique tumor or the presence of synchronous tumours, being recorded separately in the latter case. Finally, follow-up data and treatment results were collected. In relation to obtaining more information for further studies, a few data were collected in order to identify potential resources for future projects (Table 2) [13].

The analysis of all this information has helped to provide the recommendations of the current 8th edition of the TNM finally implemented in 2018 after being accepted by the UICC and the AJCC in 2017 [2]. The AJCC decided to defer the application of the 8th edition in the USA to 1 January 2018, while the UICC (applicable to the rest of the world) started the implementation of the current edition on 1 January 2017. The decision of the AJCC was based on several debates with other relevant organizations: SEER, the Centers for Disease Control and Prevention (CDC), the College of American Pathologists, the National Comprehensive Cancer Network (NCCN), the National Cancer Data Base and the Commission on Cancer [2].

We present below the most significant changes introduced in the 8th edition of the TNM system/stages of lung cancer and their future perspectives (Table 3).

3. T, N, M descriptors

The analysis of the **T component** was complex due to different descriptors were taken into account: tumor size, endobronchial location, atelectasis/pneumonitis, and invasion of anatomical structures close to the lung. To evaluate the prognosis of T descriptor, tumours with or without lymph node involvement were evaluated considering complete or incomplete resection. All findings were consistent in the populations analyzed [14]. These analyses showed that every centimeter of the tumour is important. It demonstrated a significantly different prognosis with a new cut-off to separate T1 to T4. It was observed that tumours with a size higher than 5cm (now T3) have a worse prognosis compared with previous editions of the TNM classification, and those with more than 7 cm (now T4) have a similar prognosis.

Another important finding regarding the endobronchial tumours is that the most important prognosis factor is the invasion of the carina while the distance of the tumour in relation to the carina was not important. The same happened with atelectasis/total pneumonitis, atelectasis or pneumonitis that affects the entire lung had the same prognosis as atelectasis/partial pneumonitis. In contrast, invasion of the diaphragm (a descriptor of T3 in the seventh edition, T4 in the eighth edition) had a worse prognosis than other T3 descriptors and similar T4 tumours. Finally, it was found that the mediastinal pleural invasion was rarely used as a descriptor [15]. The recommendations for T descriptors in the eighth edition are shown in Table 4: new categories based on tumor size, endobronchial location < 2cm of carina and total atelectasis/pneumonitis were staged toward below (from T3 to T2), and the invasion of the diaphragm was modified (from T3 to T4), while the invasion of the mediastinal pleura was eliminated as a descriptor.

Specific analyses of the visceral pleural invasion descriptor showed that the two types of invasion (PL1, the tumor invades beyond the elastic layer; and PL2, the tumor invades the pleural surface) had different prognoses, associating PL2 with a worse prognosis [16]. Therefore, the invasion of the visceral pleura is not only a negative prognostic factor but also, the precise evaluation of the invasion depth must be actively performed, further stratifying the prognosis subgroups (PL1 and PL2).

All these new categories in T descriptor are relevant because they help to divide the patients into new groups associated with changes in treatment models. In the 8th edition persists the discussion about which is the most accurate method to measure the nodules [17]. Finally, the conclusion was to measure based on the pulmonary window on CT scan [18] but, in contrast, other studies such as NELSON, the methods are different and probably it makes difficult to apply in common clinical practice [18].

Another important change was how to measure partially solid or subsolid tumours. For subsolid nodules, suggestive of non-mucinous adenocarcinoma, it involves measuring only the solid part on the CT scan to determine the size of the tumour. It allows a radiological-pathological and clinical correlation since it corresponds to the invasive tumour part in the pathological study [19]. This data takes special relevance for the pathological entities of adenocarcinoma, *adenocarcinoma in situ* (AIS) and *minimally invasive adenocarcinoma* (MIA) that were defined by a common working group of the IASLC, American Thoracic Society (ATS) and the European Respiratory Society (ERS), subsequently joined the histological classification of lung, pleura, thymus and heart tumours of the World Health Organization (WHO) of 2015 [20]. In these partially solid lesions, it is also recommended to record the total tumor size for later analysis and comparison.

The TNM classification of lung cancer classifies the **N descriptor** according to the location of nodal involvement, unlike other cancers such as digestive tumours- which consider the number of affected

regional nodes. The N0-N3 categories have remained unchanged since the 4th edition of the UICC in 1987; the involvement of the supraclavicular and scalene nodes previously was considered M1. The pathologic nodal stage is the most important prognostic factor in resected NSCLC. This prognostic value depends on the thoroughness of surgical nodal dissection [21]. The 8th edition confirms the consistency of the N descriptor to establish groups with significant differences in overall survival between the four categories N0-N3, both in clinical and pathological staging [22]. The prognostic impact of nodal involvement is also determined by the intensity of tumour load expressed by the number of affected nodes (nN) [23,24]. In this sense, the IASLC carried out a prognosis analysis on the combination of pN categories with the number of node stations involved in those cases M0 of the database used for the revision of the 7th edition. The impact was subdivided according to whether it was single or multiple stations. Survival at 5y of the subgroups was: 58% in cases pN1 with a single affected station (pN1a); 50% when they had several positive stations pN1 (pN1b); 52% in cases with solitary pN2 without affection N1 (pN2a1); 41% in the group with solitary pN2 and simultaneous affection pN1 (pN2a2) and 36% in cases with multiple pN2 (pN2b) [22]. Despite their prognostic value, these subdivisions were not included in the 8th edition because they had only been contrasted with cases with pathological staging. The IASLC recommends recording both, the number of affected nodes and their location, for prospective information collection for the future [22].

For the upcoming 9th edition of TNM, the Staging Committee and Prognostic Factors of the IASLC (SPFC-IASLC) proposes the following study objectives for nodal involvement [6]:

- a) To revalidate **the prognostic impact of state N**.
- b) **To study the prognostic impact of nodal extension**. Carrying out the study of single or multiple nodal involvements in the N1/N2 locations and assess the impact of the number of nodes affected. Several studies have shown that the number of involved nodes is an independent prognostic factor in patients with a complete resection [23,24] and that classification according to the number of nodes affected (nN) is a better prognostic factor than location-based (pN) [25,26].
- c) **The ratio of nodes affected**. This ratio expresses the relationship between positive nodes over the total of resected nodes. A recent meta-analysis has found that a low ratio is associated with better overall survival [27]. However, it seems reasonable to think that its predictive value may be influenced by several factors, the location of the nodal station affects (N1 vs N2/N3); the total number of resected nodes - the prognostic potential is likely to be different in one case with one positive node of four resected nodes than in another case with five positive out of twenty, although the ratio is the same in both cases -; and the type of nodal dissection performed (systematic or sampling) [27].

- d) **To study the prognostic value of node size.** Patients with bulky pN2 nodes (diameter > 2cm) have a worse prognosis than those with smaller nodes, although paradoxically in the same study patients with micrometastases were associated with a worse prognosis [28].
- e) **Impact of extracapsular involvement.** Extracapsular involvement is associated with a worse prognosis, as well as tumors with a high degree of malignancy with vascular and lymphatic invasion [29].
- f) **To study the N3 prognostic value.** In the 7th edition, all N3 cases without distant disease were grouped as IIB. The 8th edition has separated this condition into two IIB substations (T1a-c / T2a-b N3M0) and IIC (T3, T4 N3M0). However, the IASLC database only included 2,488 cases with clinical or pathological N3 involvement without distance extension [22]. Validation analysis of the IIB / IIC classification based on SEER database between 1988 and 2013 confirms a significant difference in overall survival between both categories. The 5-year survival of the N3 global cohort was 8.4%, 9.2% in group IIB and 7.7% in group IIC [30].

In **M descriptor**, the 8th edition of the TNM classification introduced some changes compared with to the 7th (Table 3). In the M1a category, the overall survival (OS) in patients with intrathoracic metastases (pleural and malignant pericardial effusion, pleural and pericardial malignant nodules and contralateral separate tumour nodules) showed a similar prognosis, so it was no necessary to modify the M1a descriptor [15].

However, in the analyses of extrathoracic metastasis, there were clinically relevant findings: a) overall survival of all metastatic site locations was not significantly different; b) single extrathoracic metastases had a significant better prognosis than multiple extrathoracic metastases, although similar to intrathoracic metastases, and c) multiple extrathoracic metastases in one or different organs had a similar prognosis. Following these findings, category M1b was redefined to include a single extrathoracic metastasis, and the new category M1c was created to include multiple extrathoracic metastases in one or different sites/organs. The M1a and M1b categories have a very similar prognosis but represent different types of anatomical spread. It makes sense, then, to keep them in different M-categories, but they are grouped together in the new stage IVa because they have a better prognosis than the M1c category (stage IVb) [31,32].

There are some special situations that require attention. In the *diffuse pulmonary adenocarcinoma type pneumonia* like, if there is a multifocal disease, the classification of the tumor is based on the location of the areas involved: T3 if it is in the same lobe, T4 if it is in other ipsilateral lobes, and M1a if in the contralateral lung [33]. And in SCLC, the IASLC recommends that the subdivision of the M-descriptors into M1a, M1b and M1c has to be the same as in the NSCLC. The evaluation of patients with M1b disease showed no significant differences in survival between patients with metastatic disease in a single

organ or multiple organs. However, a significant difference in OS in the first year was observed between patients with single-organ metastases when involving the brain and those with single or multiple metastases in other organs (36% versus 23% and 20%, respectively) [34].

After the analyses made for the 8th edition, there are some aspects of the M-component that need further clarification. Thus, Dias et al. [35], validated in their study the classification proposed in the 8th edition, but they also found that patients with single metastases had a significantly better prognosis than those with multiple metastases in one or more organs. In addition, at different locations most had a similar prognosis, although adrenal metastases tended to have a worse prognosis. Similar findings observed by other authors [36], although with the limitation that they are all retrospective studies. However, there was sufficient data to create the new M1c category for tumours with multiple extrathoracic metastases in one or several organs.

Also, the II Cooperative Group of Bronchogenic Carcinoma of SEPAR [37] in the 7th edition, assessed prospectively the different prognostic between the categories M1a and M1b. In the M1a subgroup, patients with pleural spread had a worse OS than those with contralateral nodule(s) (32 versus 50 weeks), while single versus multiple nodule did not differ. Regarding to the M1b subgroup, patients with isolated metastases had significantly better OS than those with multiple sites/organs of metastases; and in cases with isolated metastases, those with single lesions were better off than with multiple lesions. However, only 7.9% of cases with contralateral pulmonary nodules were confirmed cythistologically. The results support the division of category M1 into two subgroups, M1a and M1b. M1b could be divided in three categories: M1b1 (isolated metastases and only one lesion), M1b2 (multiple metastases in one organ) and M1b3 (multiple metastases at different sites). The OS was different between the subgroups (better in M1b1) [37].

In recent years, the staging in lung cancer has improved according to the developed in imaging and invasive techniques. This improvement together with the advances in molecular medicine [38], are going to be basic for the upcoming TNM classification. They are going to play an important role to analyze the ways to metastasize the tumour, treatment response and survival [39].

For the 9th edition of the TNM classification, the IASLC is collecting data of M1a category: pleural and pericardial effusion, pleural and pericardial nodules, location and number of contralateral metastatic lesions. In category M1b the site or organ affected, and in M1c, the number of lesions in an individual organ or multiple sites/organs. Single metastases and their size should be confirmed in the final pathological diagnosis for future results. All this data will help to better define oligometastatic and polymetastatic disease, which together with the analysis of biomarkers, it will improve our prognostic capacity and maybe for therapy [5].

4. Other factors

There are other factors apart from the anatomical description of the extension of the disease that affect the prognosis. This group of factors includes: related to the patient (e.g. age and comorbidities), related to the tumor (e.g. histotype and molecular characteristics), related to the environment (e.g. access to care and geographical region), and related to the treatment (e.g. treatment received, quality of care and response to treatment) [2]. In cases of more aggressive tumours, the prognosis is basically determined by the anatomical extension of the tumour [2]. In contrast, in less aggressive or less advanced tumours, prognosis will be determined by other factors such as health, age, the effectiveness of the treatment performed, health system, socioeconomic level, adherence to treatment, cultural aspects

One of the characteristics of tumours is the presence of mutations in advanced disease that makes them a candidate to target therapies. Taking into account the data collected in the database, the Molecular Subcommittee - SPFC is trying to incorporate certain genetic mutations such as ROS1, ALK, EGFR, KRAS, HER2, among others, which are quite characteristic. There is also a group of different EGFR mutations that could correspond to disease stages and could be included in the future. Other markers: the presence of a histologic pattern such as micropapillary, tumor interactions with the PDL1 host, differentiation considered as general biological aggressiveness, PET activity or Ki-67 staining may be useful in establishing a structure showing a clear prognostic significance. All these molecular characteristics should be considered for inclusion in the staging classification by the SPFC-IASLC.

On the other hand, incomplete resection, currently defined as a residual disease in the resection margin [40], is associated with a high risk of recurrence, progression and mortality, compared to complete resection (R0) [41,42]. To address this problem, the IASLC proposed a broader definition of incomplete resection (R reclassification), including the creation of a new category of uncertain resections with negative margins but a high risk of residual disease [43]. Therefore, these proposals need to be validated in the next edition of the TNM classification, by the new Residual Disease (R) Subcommittee. Uncertain resection due to suboptimal nodal evaluation is significantly the most common, increasing the risk of recurrence after resection with curative intent. This point is particularly important as it can change the comparison between lung cancer survival data according to the environment [22,44]. There are other variables that define this potential incomplete resection: margin involvement, extracapsular extension, and less frequent positive cytology of the pleural or pericardial fluid [45]. Some authors already propose to consider the subcategorization of uncertainty R marking particularly adverse patient groups, for their involvement in lung cancer survival comparisons [45].

Moreover, in the next years, the progressive introduction of screening programs allows diagnosing the presence of small lung nodules. The consensus of the IASLC Strategic Screening Advisory Committee recommends anatomical sublobar resections for pure ground-glass opacity lesions (GGO) or with a solid part less than 2 cm located in the external third of the lung, after histological confirmation of T1aN0M0 status (46). It also recommends a cytological analysis of the margins of resection. There are two clinical trials studying the role of sublobar resection in small tumors, CALGB 140503 (USA) y JCOG 0802 (Japan), which will provide more reliable data when the results are available [47]. Their results may modify the definition of complete resection.

As regards the Neuroendocrine Tumours Subcommittee, carcinoid tumours remained excluded from the AJCC staging manual, although many experts applied the TNM classification and its descriptors to these patients, being proposed their incorporation from the 7th edition [48]. However, this inclusion is limited due to their odd structure, morphology, immunohistochemistry and molecular characteristics [49]. In future editions, the survival curves keep overlapping between the different substations due to their better prognosis [49,50]. We have recently attended the publication of several articles that try to validate the TNM classification for bronchial carcinoids [49,51] talking about the possibility of modification of the TNM system [49,52]. Some studies show that despite the improvements introduced in the 8th edition, this is still an imperfect system for lung carcinoid tumors, especially related to the tumour recurrence in stages II and III [50,51]. The inclusion of carcinoid tumours in the TNM staging system has been the objective of several studies to highlight the importance of nodal involvement in the prognosis of these tumours [53,54], in opposition to tumor size which is not a significant variable in this type of tumours [49,55]. Other studies has been focused on the histological grade, analysing the mitotic index as a predictor prognosis [55]. There are differences in DSS (Disease specific survival) according to the M subcategory. The DSS M1a patients is close to M0 patients with a non-significant Hazard Ratio (HR), and being better than M1b [50]. Cattoni and cols. [49] propose to combine the pathological T-descriptor of the TNM classification and the histological type, trying to create a specific prognostic model. There are other factors that may provide information about recurrence possibilities, such as Ki-67 [56,57]. The most important limitation to create a TNM for carcinoid tumours is the low number of cases introduced in the database [56], although this cannot imply the creation of a staging system specific to each tumor histotype.

The data collected to create the 8th edition represents patients with lung cancer diagnosis between 1999 and 2010 being possible to draw a 5-year survival. There are differences in outcomes depending on the region and the specific treatment approaches, showing an improvement (30-50%)[58]. It could be necessary to validate the data collected by an outside database. However, an outside database does not allow to match all the data collected. Although there are data collected in recent years, such as in the SEER database, it is impossible to identify and reclassify all cases such as those with diaphragmatic

invasion classified as T3 in the 7th edition [32]. On the other hand, the decision of the AJCC to delay the implementation of the 8th edition creates differences between the data collected in 2017 in the USA comparing with the rest of the world [2].

There are studies that have tried to validate the classification, although they do not find differences between group IIA and IIB in the 8th edition. These findings are in line with other validation attempts of the 7th edition [59,60] and 8th edition [61,62]. It demonstrates that the difference between the IIA and IIB stages is not as big as other groups [62]. Although these analyses are retrospective with a small number of patients from one center [60-62]. Therefore, it is necessary to restrict the databases and create national registries that can reduce the variability between areas being a strong help to improve the treatment of patients. In any case, stratification according to the 8th edition is valid from the prognosis in patients with complete resection. Most studies conclude that the 8th edition shows an improvement to differentiate between subgroups being an independent predictor for prognosis [62-64]. Therefore, the 8th edition is superior in terms of survival and recurrence-free interval [62].

5. Conclusion

The 8th and the previous editions of the TNM classification of lung cancer provide new categories, especially in T and M descriptors [1] (Table 5). Staging is a tool that defines survival, but it must be considered in conjunction with other factors that influence prognosis. The impact of a factor is complex as it depends on the specific environment, treatment strategy and other aspects; and the level of certainty of our knowledge makes it difficult to find the ability to fit it into a real prognosis simply grouping by stages (Table 5) [65]. It is difficult to obtain a large serie in a short period of time, especially in some groups, due to the low incidence and number of events (metastases, local recurrence). Moreover, new descriptors will be included in future editions and it will improve the classification in relation to its prognosis and risk of recurrence. All these data collected could be the key to create a prognostic model by the IASLC. This model could provide a better analysis of the individual prognosis [66].

Acknowledgments

To Dr. Juan Carlos Trujillo (Oncology Area of the Spanish Society of Pneumology and Thoracic Surgery-SEPAR) for his contributions to the review.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Table 1. General characteristics of the databases used for the 7th and 8th edition of the TNM Classification of lung cancer.

	7th edition database	8th edition database
Diagnostic period	1990 - 2000	1999 - 2010
Total of patients	100,869	94,708
Geographical origin		
Europe	58,701 (58%)	46,560 (49%)
North America	21,130 (21%)	4,660 (5%)
Asia	11,622 (11,5%)	41,705 (44%)
Australia	9,416 (9,3%)	1,593 (1,7%)
South America	0	190 (0,3%)
Excluded patients	19,374 (19%)	17,552 (18%)
Treatment modalities		
Surgery +/- adjuvant treatment	50%	80,3%
Chemotherapy	23%	9,3%
Radiotherapy	11%	1,5%
Chemo + Radiotherapy	12%	4,7%
Trimodal treatment	3%	4,4%

Table 2. Variables collected for the 8th edition and for the 9th edition.

	Variables database 8th edition	News 9th Edition
General features	Age, race, sex, smoking, weight loss in the previous 6 months, performance status, specific weight, height and comorbidities (Colinet score: smoking, kidney failure, cardiovascular, respiratory, neoplastic comorbidities, alcoholism).	
Diagnostic descriptors	Inclusion date, detection method, diagnostic confirmation (histological or cytological), location of the primary tumor, degree of tumor differentiation, histological type.	

		Small cell tumors: paraneoplastic syndromes and type.	
Laboratory variables		LDH, Hb, Ca, Na, ALP, ALB, white blood cell, neutrophils and platelets count	
Lung function		FVC; FEV1	
PET		SUV values: primary tumor and for lymph nodes.	
TNM descriptors.	pre-treatment	Clinical characteristics of the tumor, size and extension. Carcinomatous lymphangitis. Nodal involvement evaluation confirmed by biopsy or cytology	
Treatment	Non surgical treatment	Clinical TNM. Chemotherapy, Radiotherapy and radiation area.	Immunotherapy
	Surgical treatment	Type, extent and degree of resection (Complete, incomplete or uncertain). Adjuvant treatment with chemotherapy and/or radiotherapy. Clinical and pathologic TNM. <ul style="list-style-type: none"> • T-component: pleural extension, vascular invasion, fissure situation, lymphatic and perineural invasion and cytology of pleural lavage. • N-component: Number of nodes explored, number of positive nodes, extracapsular involvement. All by regions N3, N2 and N1. • M-component: Findings that imply changes in the indication of radical surgical treatment. 	STAS
Multiple nodes secondary to primary tumor		Size, histology and distance of the nodules in relation to the primary tumor.	
Synchronous multiple tumors		Staging data for each lesion will be collected separately and independently for each lesion..	
Follow-up		Follow-up date, situation in relation to the tumor, relapse and date, date of exitus.	
Molecular parameters			Genetic biomarkers, type of mutation and detection technique. Type of sample. Protein alterations: type, detection technique, sample type, antibody used.

* Clinical history and examinations - radiology, PET, bronchoscopy, necessary invasive or surgical examinations that do not include therapeutic resection of the tumor.

** The lymph node evaluation will be carried out following the node map published by the IASLC in 2009

Abbreviations: PET: Positron emission tomography; LDH: Lactate Dehydrogenasa; Hb Hemoglobin; Ca: calcium; NA: sodium; ALP: alkaline phosphatase; FVC: Forced Vital Capacity; FEV1: Forced Expiratory Volume in the 1st second; SUV: Standardized Uptake Value; STAS: presence of free cells in the alveolar space

Tabla 3. Most relevant changes in 8th edition TNM

Major changes in 8th edition TNM	
T descriptor	Subdivisions T1–T2 with 1 cm increments till 5 cm T3–T4 new size criteria: 5–7 and >7 cm Subsolid lesion: invasive—solid part is measured for T factor Specific stage classification adapted to new T categories
N descriptor	No changes
M descriptor	Subdivision extrathoracic metastases M1b Only one extrathoracic metastases Mic Multiple metastases

Tabla 4. Changes in T-descriptor in 8th edition of TNM compared with 7th edition

T COMPONENT	7th EDITION	8th EDITION
0 cm (pure lepidic adenocarcinoma 3 cm total size)	T1a if ≤ 2 cm; T1b if $>2-3$ cm	Tis (AIS)
≤ 0.5 cm, invasive size (lepidic predominant adenocarcinoma ≥ 3 cm total size)	T1a if ≤ 2 cm; T1b if $>2-3$ cm	T1mi
≤ 1 cm	T1a	T1a
$>1-2$ cm	T1a	T1b
$>2-3$ cm	T1b	T1c
$>3-4$ cm	T2a	T2a
$>4-5$ cm	T2a	T2b
$>5-6$ cm	T2b	T3
$>6-7$ cm	T3	T4
Bronchus < 2 cm from carina	T3	T2
Total atelectasis/pneumonitis	T3	T2
Invasion of diaphragm	T3	T4
Invasion of mediastinal pleura	T3	-

Table 5. Lung cancer staging groups. Adapted from Detterbeck F [2].

Descriptor	Subcategory	N0	N1	N2	N3
T1 M0	T1a	IA1	IIB	IIIA	IIIB
	T1b	IA2	IIB	IIIA	IIIB
	T1c	IA3	IIB	IIIA	IIIB
T2 M0	T2a	IB	IIB	IIIA	IIIB
	T2b	IIA	IIB	IIIA	IIIB
T3 M0	T3	IIB	IIIA	IIIB	IIIC
T4 M0	T4	IIIA	IIIA	IIIB	IIIC

Any T M1	M1a	IVA	IVA	IVA	IVA
	M1b	IVA	IVA	IVA	IVA
	M1c	IVB	IVB	IVB	IVB

Epub ahead of print

References

- [1] Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT. The Eighth Edition Lung Cancer Stage Classification. *Chest*. 2017;151:193-203.
- [2] Detterbeck FC. The eighth edition TNM stage classification for lung cancer: What does it mean on main street? *J Thorac Cardiovasc Surg* 2018; 155:356-9
- [3] Rami-Porta R, Bolejack V, Giroux DJ, Chansky K, Crowley J, Asamura H, et al; International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee, Advisory Board Members and Participating Institutions. The IASLC Lung Cancer Staging Project: the new database to inform the eighth edition of the TNM classification of lung cancer. *J Thorac Oncol*. 2014; 9: 1618-24.
- [4] Goldstraw P. New TNM classification: achievements and hurdles. *Transl Lung Cancer Res*. 2013;2:264-72
- [5] Van Schil PE, Rami-Porta R, Asamura H. The 8th TNM edition for lung cancer: a critical analysis. *Ann Transl Med*. 2018; 6(5): 87.
- [6] Giroux D, Van Schil P, Asamura H, Rami-Porta R, Chansky K, Crowley J et al. The IASLC Lung Cancer Staging Project: a renewed call to participation. *J Thorac Oncol*. 2018; 13: 801-809
- [7] Rami-Porta R, ed. IASLC Staging Manual in Thoracic Oncology. Editorial Rx Press, North Ford Myers, FL, USA; 2016.
- [8] The Union for International Cancer Control. TNM History, Evolution and Milestones. Available from URL: https://docs.google.com/viewer?url=https%3A%2F%2Fwww.uicc.org%2Fsites%2Fmain%2Ffiles%2Fatoms%2Ffiles%2FTNM_History_updated_June2017.pdf&pdf=true (accessed 23/13/2019)
- [9] International Association for the Study of Lung Cancer. Staging Manual in Thoracic Oncology. Goldstraw, P. ed. <https://epdf.pub/queue/iaslc-staging-manual-in-thoracic-oncology.html>.
- [10] Goldstraw P, Crowley JJ, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, et al. The IASLC Lung Cancer Staging Project: Proposals for revision of the stage groupings in the forthcoming (seventh) edition of the TNM classification for lung cancer. *J Thorac Oncol* 2007; 2:706-714.
- [11] Rusch VW, Asamura H, Watanabe H, Giroux DJ, Rami-Porta R, Goldstraw P 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; 4: 568-577.
- [12] Cogen A, Dockx Y, Cheung KJ, Meulemans E, Lauwers P, Nia PS, et al. TNM-classification for lung cancer: from the 7th to the 8th edition. *Acta Chir Belg*. 2011; 111(6): 389-92
- [13] Giroux DJ, Rami-Porta R, Chansky K, Crowley JJ, Groome PA, Postmus PE, et al; International Association for the Study of Lung Cancer International Staging Committee. The IASLC Lung Cancer Staging Project: Data elements for the prospective project. *J Thorac Oncol*. 2009; 4: 679-83. doi: 10.1097/JTO.0b013e3181a52370. Review.
- [14] Rami-Porta R, Bolejack V, Crowley J, Ball D, Kim J, Lyons G, et al. The IASLC Lung Cancer Staging Project: Proposals for the Revisions of the T Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. *J Thorac Oncol* 2015;10:990-1003.

- [15] Rami-Porta R, Asamura H, Travis WD, Rusch VW. Lung cancer - major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin.* 2017; 67:138-155. doi: 10.3322/caac.21390.
- [16] Travis WD, Brambilla E, Rami-Porta R, Vallières E, Tsuboi M, Rusch V, et al. Visceral pleural invasion: pathologic criteria and use of elastic stains. Proposal for the 7th edition of the TNM classification for lung cancer. *J Thorac Oncol.* 2008; 3: 1384-1390
- [17] Travis WD, Asamura H, Bankier AA, Beasley MB, Detterbeck F, Flieder DB et al. The IASLC Lung Cancer Staging Project: Proposals for Coding T Categories for Subsolid Nodules and Assessment of Tumor Size in Part-Solid Tumors in the Forthcoming Eighth Edition of the TNM Classification of Lung Cancer. *J Thorac Oncol* 2016; 11:1204-23.
- [18] MacMahon H, Naidich DP, Goo JM, Lee KS, Leung ANC, Mayo JR et al. Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017. *Radiology* 2017; 284:228-43.
- [19] Asamura H, Hishida T, Suzuki K, Koike T, Nakamura K, Kusumoto M et al. Radiographically determined noninvasive adenocarcinoma of the lung: survival outcomes of Japan Clinical Oncology Group 0201. *J Thorac Cardiovasc Surg* 2013; 146:24-30.
- [20] Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG. Introduction to The 2015 World Health Organization Classification of Tumors of the Lung, Pleura, Thymus, and Heart. *J Thorac Oncol* 2015; 10:1240-2.
- [21] Smeltzer M, Faris N, Ray M, Osarogiagbon RU. Association of pathologic nodal staging quality with survival among patients with non-small cell lung cancer after resection with curative intent. *JAMA Oncol* 2018 1;4:80-87.
- [22] Asamura H, Chansky K, Crowley J, Goldstraw P, Rusch VW, Vansteenkiste JF 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; 10: 1675 -1684.
- [23] Wei S, Asamura H, Kawachi R, Sakurai H, Watanabe S. Which is the better prognostic factor for resected non-small cell lung Cancer: the number of metastatic lymph nodes or the currently used nodal stage classification? *J Thorac Oncol.* 2011; 6:310–8
- [24] Saji H, Tsuboi M, Yoshida K, Kato Y, Nomura M, Matsubayashi J et al. Prognostic impact of number of resected and involved lymph nodes at complete resection on survival in non-small cell lung cancer. *J Thorac Oncol.* 2011; 6:1865–71
- [25] Ichinose Y, Kato H, Koike T, Tsuchiya R, Fujisawa T, Shimuzu N, et al. Overall survival and local recurrence of 406 completely resected stage IIIa-N2 non-small cell lung cancer patients: Questionnaire survey of the Japan Clinical Oncology Group to plan for clinical trials. *Lung Cancer* 2001; 34:29–36
- [26] Ueda K, Kaneda Y, Sakano H, Tanaka T, Hayashi M, Li TS et al. Independent predictive value of the overall number of metastatic N1 and N2 stations in lung cancer. *Jpn J Thorac Cardiovasc Surg* 2003; 51:297–30
- [27] Zhou J, Lin Z, Lyu M, Chen N, Liao H, Wang Z et al. Prognostic value of lymph node ratio in non-small-cell lung cancer: a meta-analysis. *Japanese Journal of Clinical Oncology.* 2019 doi: 10.1093/jjco/hyz120.
- [28] Riquet M, Bagan P, Le Pimpec F, Banu E, Scotte F, Foucault C et al. Completely resected non-small cell lung cancer: reconsidering prognostic value and significance of N2 metastases. *Ann Thorac Surg* 2007; 8 4:1818 –24
- [29] Tabatabaei S, Nitche C, Michel M, Rasche K, Hekmat K. Prognostic impact of extracapsular lymph node invasion on survival in Non-small-Cell Lung Cancer: a systematic review and meta-analysis. *Adv Exp Med Biol - Clinical and Experimental Biomedicine* https://doi.org/10.1007/5584_2018_238

- [30] Shin J, Yoon J, Marwaha G. External validation of the new international association for the study of lung cancer tumor, node, and metastasis 8th edition staging system and updated descriptors in determining prognosis for patients with nonsmall cell lung cancer patients with N3 disease. *Clinical lung cancer*. 2017; 18: e481-9
- [31] Detterbeck FC, Bolejack V, Arenberg DA, Crowley J, Donington JS, Franklin WA et al. The IASLC Lung Cancer Staging Project: background data and proposals for the classification of lung cancer with separate tumor nodules in the forthcoming eighth edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2016; 11(5): 681 - 92
- [32] Goldstraw P, Chansky K, Crowley J, Rami Porta R, Asamura H, Eberhardt WE et al. 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. *J Thorac Oncol* 2016; 11:39-51
- [33] Detterbeck FC, Marom EM, Arenberg DA, FranklinWA, Hicholson AG, Travis WD 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; 11(5): 666 – 80.
- [34] Nicholson AG, Chansky K, Crowley J, Beyruti R, Kubota K, Turrisi A et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: proposals for the revision of the clinical and pathologic staging of small cell lung cancer in the forthcoming eighth edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2016; 11(3): 300 – 11.
- [35] Dias M, Antunes A, Campainha S, Conde S, Barroso A. Prognostic impact of M descriptors of the 8th edition of TNM classification of lung cancer. *J Thorac Dis*. 2017; 9: 685 - 91.
- [36] Park H, Dahlberg SE, Lydon CA, Araki T, Hatabu H, Rabin MS et al. M1b disease in the 8th edition of TNM staging of lung cancer: pattern of single extrathoracic metastases and clinical outcome. *Oncologist*. 2019; 24(8): e749 – e754.
- [37] Sánchez de Cos J, Abal J, Melchor R, Miravet L, Núñez A, Hernández-Hernández J et al. Tumor, node and metastasis classification of lung cancer – M1a versus M1b- Analysis of M descriptors and other prognostic factors. *Lung Cancer*. 2015; 84: 182 – 9.
- [38] Doval DC, Deshpande R, Dhabhar B, Baku KG, Prabhashet, Chopra R et al. Liquid biopsy: A potential and promising diagnostic tool for advanced stage non-small cell lung cancer patients. *Indian J Cancer*. 2017; 54 (Suppl 1): 25 – 30.
- [39] Shin J, Keam B, Kim M, Park YS, Kim TM, Kim DV et al. Prognostic impact of newly proposed M descriptors in TNM classification of non-small cell lung cancer. *J Thorac Oncol*. 2017; 12 (3): 520 – 8.
- [40] Purposes and principles of cancer staging. In: *Cancer Staging Handbook from the AJCC Cancer Staging Manual, 7th Edition*. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A (eds). Springer, NY, NY.
- [41] Wind J, Smit EJ, Senan S, Erenberg JP. Residual disease at the bronchial stump after curative resection for lung cancer. *Eur J Cardiothorac Surg* 2007;32[1]:29-34
- [42] Osarogiagbon RU, Lin CC, Smeltzer MP, Jemal A. Prevalence, Prognostic Implications, and Survival Modulators of Incompletely Resected Non-Small Cell Lung Cancer in the U.S. National Cancer Data Base. *J Thorac Oncol*. 2016 Jan;11[1]:e5-16
- [43] Rami-Porta R, Wittekind C, Goldstraw P. Complete resection in lung cancer: proposed definition. *Lung Cancer* 2005;49[1]:25-33.
- [44] Osarogiagbon RU, Smeltzer MP, Faris N, Rami-Porta R, Goldstraw P, Asamura H. Comment on the Proposals for the Revision of the N Descriptors in the Forthcoming Eighth

Edition of the TNM Classification for Lung Cancer. *J Thorac Oncol.* 2016 Oct;11(10):1612-4.

[45] Osarogiagbon RU, Faris NR, Stevens W, Fehnel C, Houston-Harris C, Ojeabulu P, et al. Beyond Margin Status: Population-Based Validation of the Proposed IASLC Residual Tumor Classification Re-categorization, *Journal of Thoracic Oncology* (2019), doi: <https://doi.org/10.1016/j.jtho.2019.11.009>.

[46] Field JK, Smith RA, Aberle DR, Oudkerk M, Baldwin DR, Yankelevitz D et al. International cancer for the study of lung cancer computed tomography screening workshop 2011 report. *J Thorac Oncol* 2012;7:10-9.

[47] Nakamura K, Saji H, Nakajima R, Okada M, Mizusawa M, Nakajima R et al. A phase III randomized trial of lobectomy versus limited resection for small-sized peripheral non-small cell lung cancer (JCOG0802/WJOG4607L). *Jpn J Clin Oncol* 2010;40:271-4.

[48] Travis WD, Giroux DJ, Chansky K, Crowley J, Asamura H, Brambilla E, et al. The IASLC Lung Cancer Staging Project: proposals for the inclusion of broncho-pulmonary carcinoid tumors in the forthcoming (seventh) edition of the TNM Classification for Lung Cancer. *J Thorac Oncol.* 2008; 3: 1213-23.

[49] Cattoni M, Vallières E, Brown LM, Sarkeshik AA, Margaritora S, Siciliani A et al. Improvement in TNM staging of pulmonary neuroendocrine tumors requires histology and regrouping of tumor size. *J Thorac Cardiovasc Surg* 155: 405-13.

[50] Yoon JY, Sigel K, Martin J, Jordan R, Beasley MB, Smith C et al. Evaluation of the prognostic significance of TNM staging guidelines in lung carcinoid tumors. *Journal of Thoracic Oncology* 2019; 14 [2]: 184-192.

[51] Dermawan JTK, Farver CFF. The prognostic significance of the 8th Edition TNM staging of pulmonary carcinoid tumors. *Am J Surg Pathol* 2019; 43: 1291-1296.

[52] Jackson AS, Rosenthal A, Cattoni M, Bograd AJ, Farvar AS, Aye RW et al. A staging system for neuroendocrine tumors of the lung needs to incorporate histological grade. *Ann Thorac Surg* 2019. DOI: 10.1016/j.athoracsur.2019.09.053

[53] Kneuert PJ, Kamel MK, Stiles BM, Lee BE, Rahouma M, Harrison SW et al. Incidence and prognostic significance of carcinoid lymph node metastases. *Ann Thorac Surg.* 2018; 106: 981–988.

[54] Cardillo G, Sera F, Di Martino M, Graziano P, Giunti R, Carbone L et al. Bronchial carcinoid tumors: nodal status and long-term survival after resection. *Ann Thorac Surg.* 2004;77:1781–1785.

[55] García-Yuste M, Matilla JM, Cueto A, Paniagua JM, Ramos G, Cañizares MA et al. Typical and atypical carcinoid tumours: analysis of the experience of the Spanish Multi-centric Study of Neuroendocrine Tumours of the Lung. *Eur J Cardiothorac Surg.* 2007; 31:192–197.

[56] Dermawan JTK, Farver CFF. The role of histologic grading and ki-67 index in predicting outcomes in pulmonary carcinoid tumors. *Am J Surg pathol* 2019, 00:000-000.

[57] Zahel T, Krysa S, Herpel E, Stezinger A, Goepfert B, Schirmacher P, et al. Phenotyping of pulmonary carcinoids and a Ki-67-based grading approach. *Virchows Arch.* 2012; 460: 299–308.

[58] Detterbeck F, Chansky K, Groome P, Bolejack V, Crowley J, Shemanski L, et al; IASLC Staging and Prognostic Factors Committee, Advisory Boards, and Participating Institutions. The IASLC Lung Cancer Staging Project: methodology and validation used in the development of proposals for revision of the stage classification of NSCLC in the forthcoming (eighth) edition of the TNM classification of lung cancer. *J Thorac Oncol.* 2016;11:1433-46.

[59] Rena O, Massera F, Robustellini M, Papalia E, Delfanti R, Lisi E et al. Use of the proposals of the international association for the study of lung cancer in the forthcoming

edition of lung cancer staging system to predict long-term prognosis of operated patients. *Cancer J* 2010; 16:176-81.

[60] Kameyama K, Takahashi M, Ohata K, Igai H, Yamashina A, Matsuoka T et al. Evaluation of the new TNM staging system proposed by the International Association for the Study of Lung Cancer at a single institution. *J Thorac Cardiovasc Surg* 2009; 137: 1180-4.

[61] Chen K, Chen H, Yang F, Sui X, Li X, Wang J. Validation of the Eighth Edition of the TNM Staging System for Lung Cancer in 2043 Surgically Treated Patients With Non-small-cell Lung Cancer *Clin Lung Cancer* 2017; 18:e457-66

[62] Yun JK, Lee GD, Kim HR, Kim YH, Kim DK, Choi SS. Validation of the 8th edition of the TNM staging system in 3,950 patients with surgically resected non-small cell lung cancer. *J Thorac Dis* 2019; 11(7): 2955-2964 | <http://dx.doi.org/10.21037/jtd.2019.07.43>

[63] Yang L, Wang S, Zhou Y, Lai S, Xiao G, Gazdar A, Xie Y. Evaluation of the 7th and 8th editions of the AJCC/UICC TNM staging systems for lung cancer in a large North American cohort *Oncotarget*. 2017, 24;8(40):66784-66795.

[64] Jung HS, Lee JG, Lee CY, Kim DJ, Chung KY. Validation of the T descriptor in the new 8th TNM classification for non-small cell lung cancer. *J Thorac Dis*. 2018; 10[1]:162-167.

[65] Gospodarowicz MK, O'Sullivan B, Koh ES. Factores pronósticos: principios y aplicaciones. En: Rami-Porta R, ed. *Manual de estadificación en oncología torácica*. North Fort Meyers (FL): Editorial Respira/Fundación Respira. SEPAR. 2019: 261 - 79.

[66] Detterbeck F. Desarrollo de un modelo de estimación pronóstica para el cáncer de pulmón. En: Rami-Porta R, ed. *Manual de estadificación en oncología torácica*. North Fort Meyers (FL): Editorial Respira/Fundación Respira. SEPAR. 2019: 281 – 307.