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A single-institution retrospective analysis of the differences between 7th and 8th edition of the UICC TNM staging system in patients with advanced lung cancer

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Abstract. – OBJECTIVE: The TNM (Tumor, Node, Metastasis) classification of Union for International Cancer Control is a system describing the anatomical extent of the solid tumors that leads to staging and decision on the type of treatment. The latter TNM system (2017) as compared to the previous version (2010) has brought numerous changes. Our aim was to examine whether significant changes in the new TNM edition have altered the components of the TNM classification in patients and the stage of the disease to which they are ascribed.

PATIENTS AND METHODS: The study is retrospective and is based on radiological examination reports and case reports of 100 patients of the Department of Pneumonology, Allergology and Oncology of the Medical University in Lublin, Poland. One hundred randomly selected patients, who were hospitalized at the Clinic between 2013 and 2018 with primary lung cancer were enrolled in the study. The chi-square test, Mann-Whitney U test, Kruskal-Wallis test and an appropriate post-hoc test were used in statistical analysis.

RESULTS: It was calculated that the T descriptor evaluated as per TNM in revision 8th in comparison to revision 7th changed in 41% of patients, the M descriptor - in 29% of patients, which resulted in change in staging in 11 patients. In spite of this scale amendments, only three patients could be treated differently because of the change in the stage of the disease.

CONCLUSIONS: Changing the treatment method, including withdrawal from surgery, can help avoid unnecessary treatment, but on the other hand, may potentially reduce the patient's chances of survival by depriving them of the possibility of radical treatment.

Key Words:
Lung cancer, TNM, Staging system.

Introduction

Lung cancer is the most common malignancy in men and the main cause of cancer deaths both in men and women[1,2]. Smoking is the most important etiological factor followed by air pollution and ionizing radiation[3].

From a practical point of view, two types of lung cancer are distinguished: (1) small cell carcinoma, with an extremely unfavorable prognosis and (2) non-small cell carcinoma - a histologically heterogeneous, with the dominant glandular and squamous cell type, which is more often treated surgically and may have target points for modern biological and immunological treatment[4-6].

The anatomical classification based on the size and location of the primary tumor, lymph node involvement and the presence of metastases is used to assess the stage of the tumor. Most solid tumors can be assessed as per the TNM (Tumor, Node, Metastasis) classification, which covers the above three features and based on their patterns, the clinical stage of cancer can be determined[7,8]. Reproductive organ tumors are an exception, as they are assessed per FIGO criteria[9]. In the TNM system, the letter T refers to the primary tumor and describes its size and topography. Depending on the stage, it is assigned a number from 1 to 4 or marked with - Tis (*in situ*) in the case of pre-invasive cancer. The N component indicates the involvement of local lymph nodes on a scale of 0 to 3. The M concerns distant metastases reaching other organs or lymph nodes. Number 0 means no metastases and 1 stands for the presence of metastases.

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Based on the patterns of these three values, cancer can be assigned to one of four stages, which is decisive in selecting the patient's treatment method and is also related to the chances of recovery and survival[4,8,10]. For many years, this classification only applied to non-small cell carcinomas but it is currently recommended for all types of lung cancer[4].

The basis for TNM assessment is imaging, primarily computed tomography (CT) scanning with contrast dye. Positron emission tomography (PET) is useful in assessing lymph nodes, scintigraphy is used in bone examination and magnetic resonance imaging (MR) is used in diagnosing the conditions within the central nervous system[4,11]. TNM can also be assessed pathomorphologically (pTNM)[10] - particularly in determining lymph node involvement which is difficult to assess radiologically. Sampling material from the chest lymph nodes has become easier thanks to using a bronchofiberoscope with an ultrasound head (EBUS) in biopsy[12]. TNM is also evaluated after treatment (yTNM) and posthumously (aTNM)[10].

The main aim of using TNM is to determine the initial stage of cancer, which is conducive to determining the prognosis and treatment method. It also allows following the effects of oncological treatment. In addition, TNM can be used as a standardized indicator in clinical research[13]. The advantage of this classification is its simplicity, which guarantees universality and dissemination. However, there are significant drawbacks to the simplicity of the method. TNM does not account for many additional predictive factors, such as cancer biology, genetic mutations or patient-specific factors such as age or gender. The TNM system should, therefore, be only one of the elements of the overall assessment of the patient's condition and should not be the only criterion for treatment selection[13-15]. From the oncologist's point of view, TNM primarily determines cancer's operability - solid tumors have a much better prognosis if they can be completely resected. However, from the surgical point of view, TNM classification seems to be too vague. While referring to the penultimate TNM edition in lung cancer, Giron et al[12] suggested a more detailed content of the T category for surgical treatment. They recommended additional categories of T4 resectable (T4r) and unresectable (T4ur or T5), and even conditionally operative T4 infiltrating the oesophagus (T4rd), in which case the procedure would be associated with a high risk of postoperative fistula complicated by septic mediastinitis. Another limitation of the TNM system is its limited usefulness in assessing the response to treatment. In response to these criticisms, RECIST criteria were introduced in 2000 to allow for a more accurate assessment of anatomical changes in cancer in subsequent CT scans. PERCIST is a newer and probably better method, which instead uses PET imaging with fluorodeoxyglucose F-18[16].

The revisions introduced in the 8th TNM classification appear to be significant and may have clinical implications. If TNM grades were changed in a large number of patients in comparison to the previous classification, especially in terms of the T component, that change could lead to adjusting staging in some of them and possibly increasing it. This, on the other hand, could, in some cases presumably affect the method of treatment. The most pronounced change would be changing the qualification of a tumor from operable to inoperable.

The aim of this work is to examine whether significant changes in the new TNM edition have changed the components of the TNM classification in specific patients and the stage of the disease to which they are ascribed. The authors are particularly interested in the practical effects of such changes, i.e. in determining if there are significant changes in the selection of treatment in patients assessed by new categories and, in particular, what the impact is on the cancer operability.

Patients and Methods

The study is retrospective and is based on radiological and case reports of 100 randomly selected patients with primary lung cancer treated in the Pneumonology, Allergology and Oncology Department of the Medical University in Lublin between 2013 and 2018. The inclusion criterion was the first CT scan in which lung cancer was detected in a given patient retained at the Department along with medical records to determine the histopathological type of cancer. Patients with rare types of cancer and pleural mesothelioma were not included in the study.

Based on each patient's oldest CT scan of the tumor, TNM and staging were separately evaluated according to the criteria of the seventh edition (2010) and eight edition (2017). The basis for the assessment of the imaging examination was a report written by a radiologist. In questionable situations, the IASLC and the Polish Cancer

Table I. Gender distribution in the study group.

Variable		n	%	Result
Gender	Women	30	30.0	$\lambda^2(1)=15.36$; $p<0.001$
	Men	70	70.0	

Society guidelines were used. The TNM classification components and staging of both editions were then compared and the direction of possible change was determined. Finally, we verified if the change in staging would affect the selected way of treatment as per the newer classification and, in particular, whether it would change the qualification for surgical resection.

Statistical Analysis

To compare the equivalence of the examined groups, as well as to examine the relationship between nominal variables, the chi-square test was used. The Mann-Whitney U test allowed us to check if there were statistically significant differences between two independent groups of patients. In cases where there were more groups, the Kruskal-Wallis test was used. When there were statistically significant differences, an appropriate *post-hoc* test was used. Spearman's correlation analysis allowed to check whether there is a statistically significant relationship between the analyzed variables. In the statistical analysis of the results, a frequency analysis (n, %) was used. The level of $p<0.05$ was considered statistically significant. All analyses were carried out with the IBM SPSS statistical package (IBM Armonk, NY, USA), version 25 for IBM.

Results

One hundred randomly selected patients with primary lung cancer were enrolled to the study. Male patients were found to be the majority in the study group (M = 70.0%, F = 30.0%; Table I).

The dominant pathomorphological diagnosis was adenocarcinoma in both men and women. The second-largest group of diagnoses comprised squamous cell carcinoma, small cell cancer, NOS (not otherwise specified) and large cell carcinoma (Table II).

The T component evaluated as per TNM classification in revision 8 in comparison to revision 7 changed in 41 patients, the M component change was reported in 29 people. This resulted in adjusting the staging in 11 patients (Table III).

In one case, the T change meant assigning a new T(mi) category to the patient. In all other cases, the changes involved qualifying a case as a higher stage of progression. Only three subjects could be treated differently because of the change in the stage of the disease, of which only one originally had operable cancer which would be classified as inoperable ($p<0.001$, Table IV).

Discussion

The origins of the TNM classification date back to the 1940s, but the first such system describing lung cancer was established in 1968 thanks to the Union for International Cancer Control (UICC). In 1973, the next edition introduced a division into progression steps used to date, determined by a certain pattern of T, N and M components. There were initially three degrees but in 1978 grade IV was added for distant metastases. The classification issued this year is also applicable for the pathomorphological staging of tumors (pTNM). Subsequent editions were issued in 1992, 1997, 2002 and 2009. The latter ones were based on studies involving more than 50,000 patients with mainly non-small cell lung cancer[10,17]. In this edition, the cancerous pleural effusion was classified in the M1 category thus reflecting the trend to tighten the criteria[12]. Since 2017, the latest, eighth edition is in force. As compared to the previous version, it has brought numerous changes. The authors have clearly tightened the evaluation criteria so that more tumors

Table II. The results of the histopathological examination in the study group.

Variable		n	%	Result
Result of the histopathological examination	Adeno	43	43	$\lambda^2(5)=93.68$; $p<0.001$
	Micro	23	23	
	NOS	3	3	
	Squamous cell carcinoma	29	29	
	Large cell carcinoma	2	2	

Table III. Comparison of the T-descriptor and Stage distribution as assessed by TNM7 vs. TNM8 (n=100). *- new categories.

		T (TNM7) T1a	T1b	T2a	T2b	T3	T4	%
T (TNM8)	T1(mi)*		**2**				2	
	T1a							0
	T1b	**7**						7
	T1c*		**8**					8
	T2a			**2**				2
	T2b			**8**				8
	T3				**7**	**3**		10
	T4					**9**	**54**	63
%		7	10	10	7	12	54	

		stage (TNM7) IA	IB	IIA	IIB	IIIA	IIIB	IV	%
stage (TNM8)	IA1*	**1**							1
	IA2*	**1**							1
	IA3*	**1**							1
	IB								0
	IIA		**1**						1
	IIB			**2**	**1**				3
	IIIA				**1**	**15**			16
	IIIB					**1**	**20**		21
	IIIC*						**6**		6
	IVA*							**23**	23
	IVB*							**27**	27
%		3	1	2	2	16	26	50	

can be restaged as more advanced, which may affect the method of treatment and prognosis[18].

This study, which uses the new TNM classification, reported a change in the T component in 41% of patients. A change in the M component was reported in 29% of cases. In 11 patients, this resulted in restaging the tumor. The effect of restaging the tumor on the recommended treatment method was recorded in 3% of patients but this affected the operability in only 1 patient.

Comparison of 2010 and 2017 Editions

The most significant changes between the 7th and 8th editions are reflected in the criteria for the T component, specifying the size and position of the tumor (Table V). Within the T1 class, the authors introduced the T1 (mi) category for minimally invasive adenocarcinoma, defined as single adenocarcinoma ≤ 3 cm, mainly covering alveolar septum with infiltration ≤ 5 mm in one

Table IV. Changes in the T and M descriptors, the disease stage and its impact on the mode of treatment and operability in the study group.

Variable		n	%	Result
Shift of T descriptor	Yes	41	41	$\lambda^2(1)=3.24$; $p>0.05$
	No	59	59	
Shift of N descriptor	Yes	29	29	$\lambda^2(1)=17.64$; $p<0.001$
	No	71	71	
Change of stage	Yes	11	11	$\lambda^2(1)=60.84$; $p<0.001$
	No	89	89	
The impact of stage changing on the mode of treatment	Yes	3	3	$\lambda^2(1)=88.36$; $p<0.001$
	No	97	97	
The impact of stage changing on the operability	Yes	1	1	$\lambda^2(1)=96.04$; $p<0.001$
	No	99	99	

Table V. Changes in the scope of T descriptor according to TNM classification version 8 *vs.* version 7. New categories are marked*.

T descriptor	TNM classification version 8 *vs.* version 7
T1(mi)*	Minimally invasive adenocarcinoma (individual adenocarcinoma ≤ 3 cm, mainly covering the alveolar septa, with infiltration ≤ 5 mm in one of the foci)4
T1a	The maximum T1a tumor size decreased from 2 cm to 1 cm
T1b	The maximum T1b tumor size decreased from 3 cm to 2 cm
T1c*	T1c introduced for tumor size > 2 cm and ≤ 3 cm
T2	The maximum T2 tumor size decreased from 7 cm to 5 cm. In addition, this category includes whole-lung pneumonia (formerly T3 category) and a tumor involving the main bronchus not infiltrating the trachea, regardless of how close it is (previously tumors <2 cm from the bifurcation of the trachea were classified as T3)
T2a	The maximum T2a tumor size decreased from 5 cm to 4 cm
T2b	The maximum T2b tumor size decreased from 7 cm to 5 cm
T3	The T3 tumor size changed from > 7 cm to up to 7 cm
T4	Each tumor with the largest dimension >7 cm is included in the T4 category, regardless of its location and infiltrated structures. A diaphragm-infiltrating tumor is transferred to T4 from T3

of the foci (4). A T1c category has also been added for tumors previously corresponding to T1b. In the T2 class, the criterion was changed by as much as 20 mm, so that there are now tumors between 3 and 5 cm in diameter. Also, pneumonia affecting the whole lung and main bronchial tumor were included in this category (previously in the T3 class). A tumor whose largest dimension exceeds 7 cm is automatically classified as T4, even though it may previously have been in the T3 class. A similar change concerns diaphragm infiltration, which is within the T4 class according to the new guidelines (Figure 1).

As compared to the previous edition, no changes were introduced to the N feature which characterizes the thoracic lymph nodes considered as local ones. A more detailed division of the M component was introduced (Table VI), dividing M1 into three subcategories (Figure 2).

While the seventh edition of TNM classified every extracellular metastasis as M1b, at present this category only refers to a single lesion. Multiple metastases outside the chest should be determined as M1c.

Changes in TNM have resulted in the modification of staging criteria (Table VII). IA is divided into three subcategories - IA1 corresponding to T1 (mi) or T1a, IA2 for T1b and IA3 for T1c. Further modifications are introduced for stage II. IIA is limited only to the isolated T2a tumor, while the presence of T2b or N1 classifies the tumor in the higher group IIB (Figure 3).

T3 tumor has been transferred from stage IIIA to IIIB with N2 node involvement, which clearly defines it as inoperable. IIIC has been isolated from stage IIIB and it includes the T3N3M0 and T4N3M0 cancer. Stage IV has been divided into IVA for each tumor with M1a or M1b, and IVB

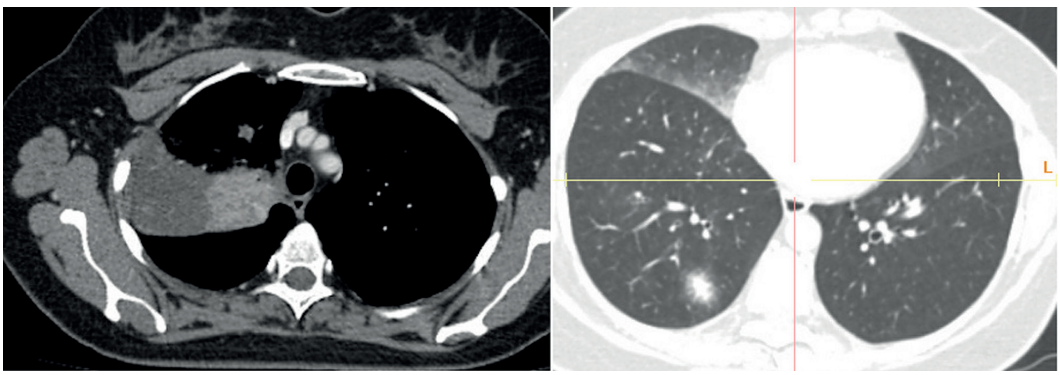

Figure 1. Separate tumor nodule in a different lobe of the same lung, representing T4 tumor.

Table VI. Changes in the scope of M descriptor as per TNM classification version 8 *vs.* version 7. *-new categories.

T descriptor	TNM classification version 8 *vs.* version 7
M1a	No changes
M1b	M1b narrowed as it previously included all distant metastases. Currently, M1b stands for a single distant metastasis (excluding chest). It also applies to a single, distant (non-regional) lymph node[4]
M1c*	• The M1c was separated from M1b and it covers multiple distant metastases outside the chest, which may affect one or many organs

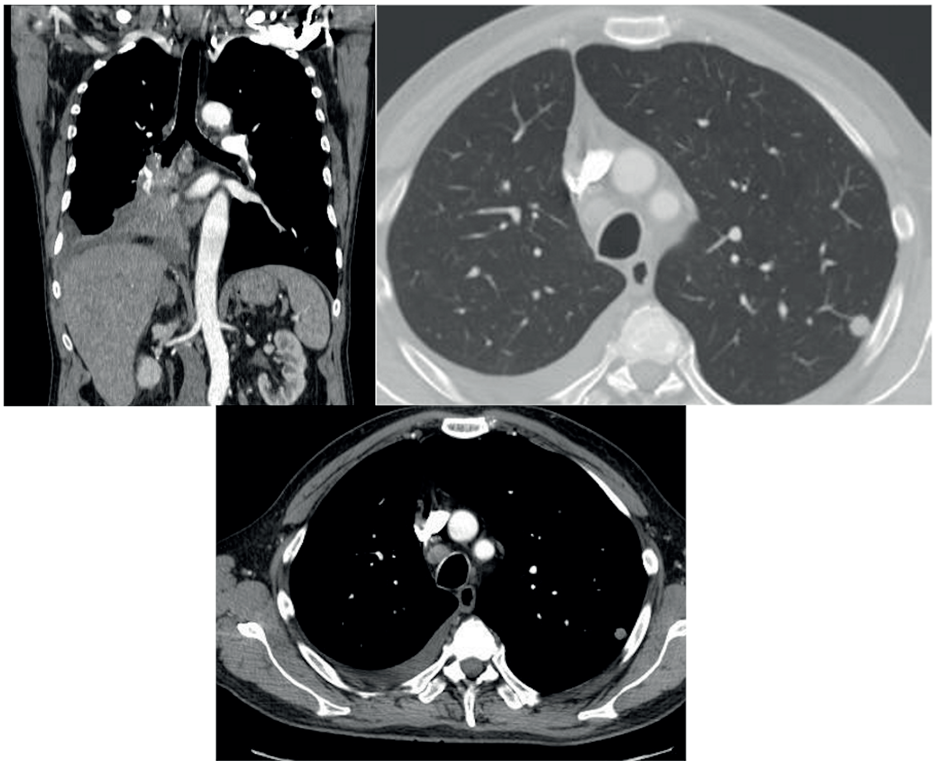

Figure 2. The atelectasis of the right lower pulmonary lobe due to the obstruction by the tumor, which indicates T2. Additionally, the small nodule in the left lung is visible - descriptor of M1a.

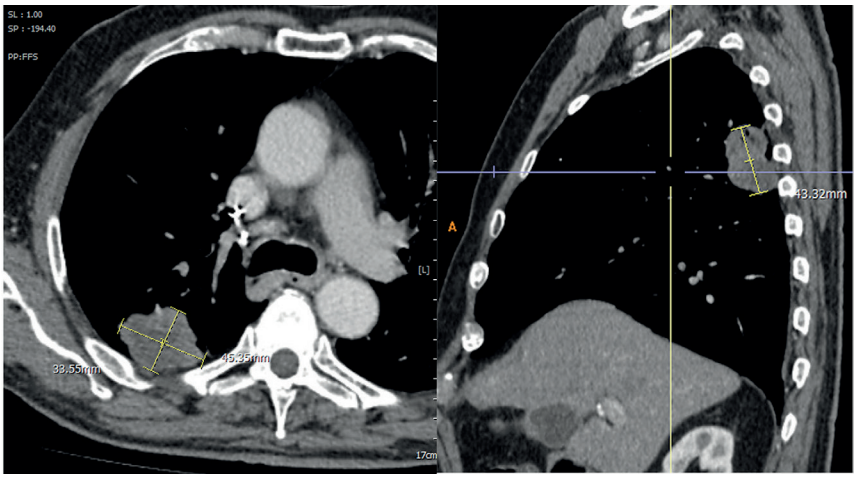

Figure 3. Pathological mass of the right lung with the diameter > 4 cm but ≤ 5 cm which indicates T2b.

Table VII. Changes in staging in version 8 *vs.* version 7.

T descriptor	TNM classification version 8 *vs.* version 7
M1a	No changes
M1b	M1b narrowed as it previously included all distant metastases. Currently, M1b stands for a single distant metastasis (excluding chest). It also applies to a single, distant (non-regional) lymph node[4]
M1c*	• The M1c was separated from M1b and it covers multiple distant metastases outside the chest, which may affect one or many organs

Table VIII. Changes in the proposed therapy depending on cancer staging version 8 *vs.* version 7.

Cancer stage
1. In IA and IB, the role of surgical treatment was emphasized, while abandoning chemotherapy
2. The priority of radiotherapy or radiochemotherapy was indicated at stage IIIA. Surgery as part of comprehensive therapy is recommended only in selected patients
3. Only radiotherapy and systemic treatment can be administered in patients with stage IIIB and IIIC
4. Biological treatment and immunotherapy[4,18-20] have been added to the treatment methods proposed for patients with stage IV cancer

for cancer with multiple distant metastases, i.e. M1c. In addition to the shifts between stages, several new categories were introduced, which made the new classification more precise.

The above changes also introduced some modifications in the treatment method (Table VIII). At grade IA and IB, the emphasis is placed on surgical treatment, while abandoning chemotherapy. At grade IIIA, priority is indicated for radiotherapy or radiochemotherapy, and considering surgery as part of therapy is only recommended in selected patients. Only radiotherapy and systemic treatment can be administered in patients with stage IIIB and IIIC. At stage IV, in addition to traditional chemotherapy and symptomatic treatment, newer therapeutic options, such as targeted treatment or immunotherapy are listed[18-20].

Conclusions

We can state that the T descriptor evaluated as per TNM in revision 8 in comparison to revision 7 changed in 41% of patients and the M descriptor changed in 29% of patients. This resulted in adjusting the staging in 11 patients. Only 3 patients could be treated differently because of the change in the stage of the disease. 1% patients who could be operable according to the TNM in 7th revision, but according to 8th revision was inoperable.

It is difficult to assess the impact of the described changes on the effects of treatment. The distinction of single metastases outside the chest as the feature of M1b (oligometastasis) may be of clinical significance. In the case of non-small cell carcinoma such changes can sometimes be successfully treated with local methods such as radiotherapy and surgical resection[21]. Changing the treatment method, including withdrawal from surgery, can help avoid unnecessary treatment, but on the other hand may potentially reduce the patient's chances of survival. The latest edition of TNM has been in force for about three years, so it is too early for a comprehensive and objective assessment of the health effects of these changes.

Conflict of Interests

All authors declare that there is no conflict of interest.

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