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Evaluating lung cancer care in the Netherlands: staging, treatment and surgical quality assurance

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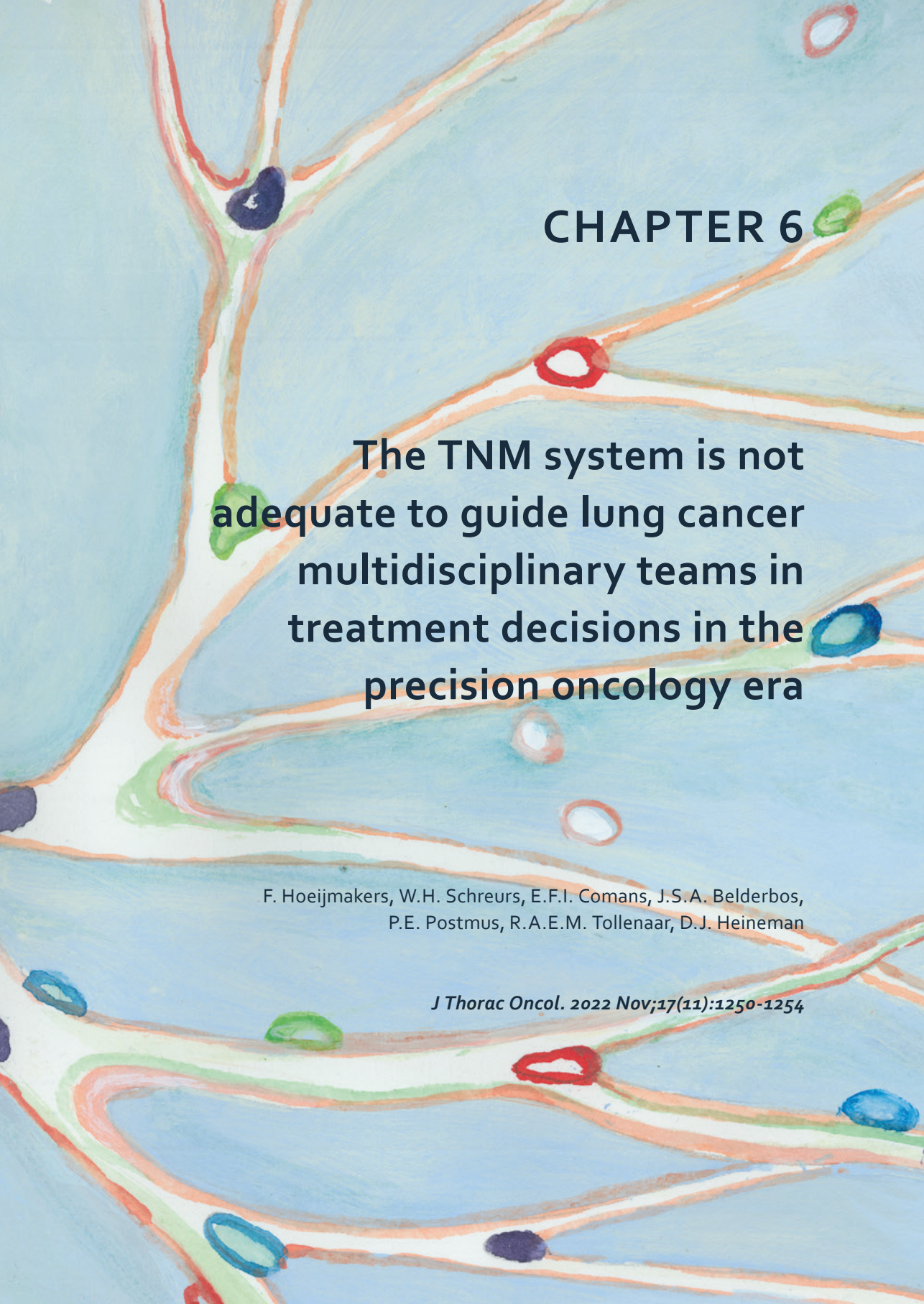
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CHAPTER 6

**The TNM system is not
adequate to guide lung cancer
multidisciplinary teams in
treatment decisions in the
precision oncology era**

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What is the clinical problem? Accuracy of clinical staging

The TNM staging system is currently guiding our multidisciplinary team (MDT) meetings and the process of clinical decision making for patients with NSCLC. The combination of tumor (T), nodes (N), and metastases (M) is used to define the stage of disease. Owing to the extensive work of the International Association for the Study of Lung Cancer, a prognosis might be precisely predicted in relation to stage, taking into account that prognosis will be determined by the treatment options available at the time the databases were filled with cases.¹

Figure 1 illustrates the current staging algorithm according to the guidelines of the European Society of Thoracic Surgeons and the European Society for Medical Oncology and the respective sensitivity and negative predictive value of the different staging procedures. Recent advances in imaging techniques (i.e., qualitative improvements in computed tomography [CT] and positron emission tomography [PET]) and invasive and noninvasive staging procedures contribute to a more accurate T, N, and M staging, and today's large real-world data sets may give us the opportunity to predict prognosis even more accurately.

Currently, in the eighth version of the TNM system, there are 11 options for the T stage, five options for the N stage, and four options for the M stage.² The more detailed options in every new version of the TNM system to define the T, N, and M stages make it possible to predict prognosis even more accurately for a patient. Nevertheless, the more detailed subdivision of the T, N, and M comes at a risk of high rates of inaccurate clinical staging. During the time that the seventh version of the TNM system was used, agreement between clinical TNM stage and pathologic TNM stage was only 53% in The Netherlands in daily clinical practice in a cohort of 5449 patients.^{3,4} In other countries, similar numbers were found.^{4,5} A more detailed classification (such as the eighth version of the TNM system) might reduce agreement even further. One may argue whether a small inaccuracy in tumor size is relevant for the treatment plan, but an inaccuracy in the N stage certainly may have large consequences for a patient with respect to the treatment plan. It is not known whether understaging or overstaging influences overall long-term survival, but it certainly influences treatment decisions. In addition, high levels of interobserver variation were found when locally advanced NSCLC was clinically staged by different MDTs.⁶ Tumor size is still measured manually, N stage on the basis of imaging has considerable false positives and negatives, and dedicated (nuclear) imaging experts are not always involved. It is hoped that, new techniques, for example, total body PET-CT and artificial intelligence, can reduce inaccuracy and interobserver variation in the future. Nevertheless, for our current era, a staging system on the basis of the prognosis of patients with lung cancer, with a low accuracy and a high level of interobserver variation

and outcomes affected by therapeutic possibilities of the past, is not very suitable for making treatment decisions.

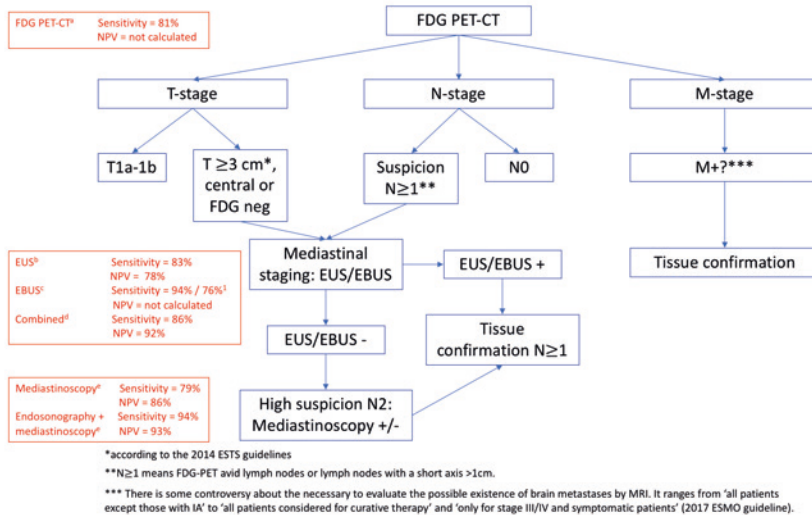


FIGURE 1. Staging algorithm for NSCLC including sensitivity and negative predictive value of staging modalities.

1 = Patients selected on the basis of CT or PET positive results/patients enrolled without the results of CT or PET.

CT, computed tomography; EBUS, endobronchial ultrasound; ESMO, European Society for Medical Oncology; ESTS, European Society of Thoracic Surgeons; EUS, endoscopic ultrasound; FDG, fluorodeoxyglucose; neg, negative; NPV, negative predictive value; MRI, magnetic resonance imaging; PET, positron emission tomography.

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What is the biggest challenge? Heterogeneous patient groups and multiple treatment regimens for each clinical stage

Figure 2 illustrates the TNM system and how the different stages are composed of the T, N, and M. The color coding in the figure indicates whether it is obvious which treatment options are available for a stage or whether (a combination of) multiple treatment options

are available for a certain stage and differentiating information is not supplied by the TNM system. For stages I and II, the MDT will usually propose radical local therapy as initial treatment (e.g., surgery or radiotherapy). Nevertheless, with new options for local therapy, for example, stereotactic irradiation or introduction of minimally invasive sublobar resections,⁷ treatment options are increasing. The MDT will make a decision on the basis of patient characteristics outside the TNM system, for example, performance status, pulmonary function, and patient preferences. Unfortunately, multiple attempts to acquire level I evidence for the optimal treatment for operable stage I NSCLC have failed in the past owing to problems with trial accrual, and this remains a topic of debate.

Especially stage III illustrates why the TNM system does not support the MDT in making treatment decisions, although patients share a similar prognosis. Stage III, but also the subgroups stage IIIA and IIIB, comprises a very heterogeneous group of patients, and the amount of treatment strategies is numerous, occasionally even for patients in the same subgroup.⁸ Furthermore, there is a lack of clear evidence for treatment of stage IIIA-N2 disease, expressed by different recommendations in national guidelines worldwide.⁹ Trials addressing new multimodality treatment regimens usually include all patients with resectable or irresectable stage III (or all IIIA or IIIB) and not just a specific subgroup (e.g., only IIIA-N2 disease), which will add to the lack of clarity. It is likely that the extremes within IIIA (T1aN2 versus T4N0) may have a different biological behavior and have different optimal treatment regimens. In the past, the prognosis of these tumors was similar with the available treatment options, but modern therapy may have a considerable impact on treatment decisions and outcome.

Left upper lobe NSCLC with (biopsy-proven) involvement of lymph node stations N5 or N6 also represents a specific group of patients. They are staged as having N2 disease; however, they behave as having N1 disease (and upfront surgery seems a good treatment option).¹⁰

	N0	N1	N2	N3
T1	IA	IIB	IIIA	IIIB
T2a	IB	IIB	IIIA	IIIB
T2b	IIA	IIB	IIIA	IIIB
T3	IIB	IIIA	IIIB	IIIC
T4	IIIA	IIIA	IIIB	IIIC
M1a	IVA	IVA	IVA	IVA
M1b	IVA	IVA	IVA	IVA
M1c	IVB	IVB	IVB	IVB

Stage I:	Local therapy (surgery or stereotactic body radiation therapy, depending on operability or preference of the patient)
Stage IIA:	Local therapy: preference for surgery (consider adjuvant chemotherapy in tumors >4cm)
Stage IIB N1:	Local therapy: preference for surgery (consider adjuvant chemotherapy in case of N1)
Stage IIB T3:	Local therapy: preference for surgery, when doubts about resectability neoadjuvant therapy can be considered (e.g. concurrent chemoradiation in sulcus superior tumors)
Stage IIIA N0/1:	Chemoradiotherapy +/- resection, depending on resectability. If irresectable, immunotherapy is advised after chemoradiotherapy.
Stage III N2:	Dependent on the amount of N2 disease (micro/single/multi/bulky): Concurrent chemoradiotherapy followed by immunotherapy; neoadjuvant therapy and resection; resection followed by adjuvant therapy.
Stage III N3:	Concurrent chemoradiotherapy and immunotherapy. In selected patients additional resection can be considered.
Stage IV:	Systemic treatment (chemotherapy/immunotherapy/targeted therapy) +/- radiotherapy

FIGURE 2. The extent to which the TNM stage is guiding in treatment, from green (= conclusive) to orange (= not useful in the decision for definitive treatment).

SBRT, stereotactic body radiation therapy.

TNM system versus tumor characteristics

In addition to morphologic tumor characteristics as expressed in the TNM system, an increasing number of evidence on the basis of prognostic biological factors may play an important role in clinical care and treatment decisions. The extended tumor profile, including histopathologic, molecular, and genetic features, provides us with possible targets for innovative treatments.¹¹ Recently, knowledge of some of these features has become available. An example is the publication of the light-microscopic subclassification of adenocarcinoma resulting in a refinement of that large subgroup within the combined description of NSCLC.¹² Shortly after this, the role of retinoblastoma gene in the neuroendocrine subgroup was highlighted.¹³ In 2020, the first targeted therapy, osimertinib, was approved for adjuvant use in patients with resected stages IB to IIIA NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R substitution mutations.¹⁴ The value of osimertinib and other targeted therapies in the neoadjuvant setting is currently investigated. The recently published CheckMate 816 trial included patients with resectable stages IB to IIIA and randomized between a regimen with

neoadjuvant nivolumab with platinum-doublet chemotherapy or chemotherapy alone before resection.¹⁵ Patients receiving nivolumab had a significantly longer event-free interval and higher rate of pathologic complete response. Long-term follow-up for patients treated with neoadjuvant immunotherapy and resection is not yet available, but it is expected that prognosis of patients with NSCLC will be improved significantly, as was proven in patients with irresectable stage III disease.¹⁶ When these results are available, it will be important to update the TNM system with these features not only to give patients a better prediction of their prognosis but also to guide MDTs in making treatment decisions. With the introduction of novel neoadjuvant regimens on the basis of tumor biology, histologic analysis of tumor cells and prediction of tumor response to targeted therapy by new PET ligands will become increasingly important before start of treatment. MDTs will increasingly analyze tumor biology in the coming years before starting treatment, to choose a patient-tailored strategy that suits best for every specific situation. In patients in whom this is impossible owing to small size or location of the tumor, there might be a preference for initial surgical treatment (preferably minimally invasive and parenchymal sparing) to obtain a full pathologic diagnosis. In case of future disease recurrence, new biopsies are usually preferred because of the possibility of tumor heterogeneity.

What do patients want?

As was stated before, correct clinical staging is complex and preferably comprises multiple staging procedures, such as a (PET-)CT scan, histologic biopsy, brain magnetic resonance imaging, endobronchial ultrasound or esophageal ultrasound with ultrasound bronchoscope, and (video)mediastinoscopy. In a study on patient preferences regarding mediastinal nodal staging, the most important attribute regarding patients was the duration of the staging period, followed by the risk of a futile surgical lung resection (defined as having unforeseen N2 after surgery). Nevertheless, there was a strong dichotomy among patients always or never willing to undergo confirmatory mediastinoscopy.¹⁷ This strengthens the idea that a correct TNM, something that is hard to achieve because of all the aforementioned arguments, is not necessarily the focus for most patients. If obtaining the correct clinical stage consists of invasive procedures with the risk of a complication, and delays the start of treatment, this will not correspond with the priorities of some patients. Therefore, it is important to use shared decision making before using these procedures by explaining risks and benefits of all possible scenarios to the patient.

What do doctors need?

The TNM system is a very valuable system to categorize patients, predict their prognosis, and facilitate communication between medical physicians. Nevertheless, recent developments in treatment of patients with lung cancer and improved understanding of tumor biology have made this system less useful in daily practice to guide treatment decisions. In the newest era, MDTs make treatment decisions combining morphologic and biological features, patient factors, and shared decision making, to optimize patient-tailored treatments. Ideally, a new system should be developed that takes all these factors into account.

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