Classification of lung cancer: first experiences with the new TNM classification (4th edition)

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ABSTRACT: In January 1987, the 4th edition of the TNM classification for malignant lung tumors by the International Union Cancer (UICC) came into effect. Thus, for the first time, a uniform worldwide staging system for lung cancer became available.

In order to validate the new TNM definitions for lung cancer the data of 3,000 patients were analysed prospectively. Several items were examined: 1) the agreement between clinically (TNM) and pathologically (pTNM) confirmed classification; 2) the value or the various diagnostic techniques estimating the pathologically confirmed classification; 3) the influence of the TNM definitions on separating distinct prognostic groups.

With regard to the primary tumour (T), clinical and pathological classifications were identical in 64%; for lymph node involvement (N) the agreement was 48%; for distant metastases it was 90% and for the stages it was 85%.

As for the primary tumour (T) the accuracy of radiography (59%) was nearly identical to computed tomography (58%). Both techniques were less precise in determining the extent of lymph node involvement (computed tomography 50%, radiography 43%, correct assessments).

The statistically significant differences in prognosis for the various T-, N- and M-categories as well as for the stages could be confirmed.

By the new 1987 TNM definitions (4th edition) for lung cancer international conformity became feasible as well as practical, and the improvement in its prognostic relevance provided, therefore, a more reliable basis for establishing guidelines for individual oncological concepts of therapy.

The TNM system has attained international importance for the classification of malignant diseases. In 1987, a fourth edition of this system was presented [1] and is identical to the third edition of the Manual for Staging of Cancer published by the American Joint Committee on Cancer (AJCC) [2].

For carcinoma of the bronchus the new classification differs from the old one with a new category “T4” for extensive extrapulmonary extension of disease, and a new “N3” for cases with contralateral and/or supraventricular lymph node involvement. T1N1M0 was dropped from stage I to Stage II; stage III was subdivided into IIIA (T3 and/or N2 without distant metastases) and into IIIB (T4 and/or N3 without distant metastases) [3].

These modifications were mainly based on retrospective investigations or reclassifications [4–6]. Our objective, therefore, was to review the new classification prospectively in terms of concordance between clinically (TNM) and pathologically confirmed classifications (pTNM). Similarly, the accuracy of tumour and nodal detection by the various available techniques and the prognostic relevance of the new TNM definitions were discussed.

Material and methods

In May 1984, the Thoraxklinik Heidelberg-Rohrbach received a grant from the Federal Ministry for Research and Technology of West Germany to carry out a prospective study with selection-free recruitment of patients with histologically proven carcinoma of the bronchus (excluding pretreated patients) for the purpose of validating the 4th edition of the TNM definitions. This project was carried out under the auspices of the
German Speaking TNM Committee of the UICC (DSK) and in co-operation with the Institute of Radiology and Pathophysiology of the German Cancer Research Centre in Heidelberg.

The work was continued from January 1988, with a new grant for a project to establish “Oncological guidelines for the diagnostic, classification, therapy and postoperative care of carcinoma of the bronchus”.

For the documentation of both projects, computer systems were conceived and set up [7] which allowed a simultaneous classification both according to the definitions of the third edition (still in force until the end of 1986), and also to those of the fourth edition of the TNM classification which came into effect in 1987. A TNM checklist was conceived with the intention of combining the entire TNM-relevant diagnostic information as well as the details of the clinical overall TNM formula.

In order to obtain definite histological diagnosis and to assess the tumour extension as carefully as possible, extensive clinical examinations were carried out, starting with basic diagnostic procedures in all patients, and continued in selected patients by supplementary procedures. The basic procedures comprised case history, clinical and physical examination, laboratory tests, X-rays and bronchoscopy with bronchial lavage and biopsy. The radiography included chest X-rays and also supplementary hilar filter tomograms for the evaluation of the hilar lymph nodes (N1), as well as tomograms of the mediastinum for the assessment of N2 lymph nodes. Supplementary diagnostic procedures optionally performed to assess the primary tumour and mediastinal lymph nodes comprised computed tomography, mediastinoscopy, thoracoscopy, pulmonary angiography and diagnostic thoracotomy.

Computed tomography was performed as a routine on all central growths, and optionally on peripheral lesions. Contiguous cuts (8 mm) were made from the thoracic inlet to below the suprarenal glands. Lymph nodes measuring 15 mm or more in diameter were regarded as suspicious. A mediastinoscopy was carried out in all patients to be operated on with suspected N3-disease, advanced age or other risk factors with suspected N2-disease; or with small cell carcinoma. A thoracoscopy was performed if pleural involvement by tumour was suspected. Pulmonary angiography was carried out if tumour involvement of the main thoracic vessels was possible. A diagnostic thoracotomy was performed when the above tests proved inconclusive.

Regarding distant metastases, sonography of the upper abdomen and a bone scan were performed in all cases. All patients with small cell cancer had a bone marrow biopsy in addition. If brain metastases were suspected, or results of the upper abdomen were doubtful, computed tomograms of these regions were made [8].

Therapeutic management was discussed and agreed between the departments of thoracic surgery, oncology, pneumology and radiology. The detailed documentation of the surgical therapy and the pathological evaluation of operative specimens formed the basis for the analysis of lymph node involvement and its prognostic relevance. Regarding lymph node resection, routine sampling from each of the major lymph node sites and radical mediastinal lymphadenectomy was performed before each pulmonary resection [9]. The location of each resected lymph node was marked using the mapping system of Naruke [10]. The allocation of a pathological classification (pTNM) was made subject to the requirement that the resection had been sufficiently extensive according to the general rules of the TNM classification for a pathological classification.

The concordance measure “kappa” (κ) corrected for chance was calculated, in order to judge the value of the agreement between clinical and the respective pathological classification [11, 12].

The 3,000 patients under review entered the study between October 1, 1984 and March 31, 1989. The cut-off date for initial evaluation was March 31, 1990. Thus, the follow-up time comprised at least one year, the maximum being five and a half years. At the time of evaluation, 2,275 (76%) of the patients had already died, leaving 725 (24%) censored observations.

The calculation of survival probability was by the method developed by Kaplan and Meier [13]. The checking of the significance between the survival of the respective subgroups of patients was based on the Log-Rank-Test [14]. For the multivariate analysis of prognostic factors the Cox Model [15] was used in a multiphase evaluation strategy combining a step-down and a step-up method [16]. The testing for proportional hazard functions was by means of empirical log-(log)-plots as well as by the Acceleration Test of Breslow et al. [17]. The starting point for the calculation of the survival probability was the date of onset of therapy. In those patients who did not undergo any treatment this date refers to the period after clinical staging, when it was decided to offer supportive care only. The date of death, or of the last follow-up, was taken as the end point.

Results

Table 1 gives a survey of all clinical TNM staging placements for all of the 3,000 patients.

The large proportion of patients with clinically advanced disease reflects the fact that the clinic has a catchment area exceeding regional limits and is highly specialized. In the data of the 1,086 patients with resections sufficiently complete to allow a classification by pathological methods (pTNM), the high rate of patients with advanced disease, is confirmed (table 2).

In assessing the primary tumour, the observed agreement between T and pT was 64% (κ=0.404) (table 3). The clinical staging overstaged patients in 22% of cases, and understaged the disease in 14%. The greatest agreement was 78% of T2 and the least was 38% for T4.

In 78% of the cases, the clinically determined size of the tumour (up to 3 cm or more than 3 cm, respectively) was confirmed pathologically; however, in 11% it was overestimated and in 11% underestimated.
Table 1. – Results of clinical TNM-classification (all patients, n=3,000)

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An extremely high agreement of 94% with the pathological findings was obtained for the T criterion of the tumour position within the airway, i.e. not in the main bronchus; 2 cm or more from the carina; less than 2 cm distal to the carina; or directly involving the carina. As far as extrapulmonary dissemination of tumour is concerned, the clinical findings were validated in 82% of the cases. With 11%, an extrapulmonary extension was not confirmed pathologically, whereas in 7% of the cases an extrapulmonary extension of the primary tumour was discovered which had not been clinically detected in advance.

Table 2. – Results of pathological classification (pTNM) (n=1,086)

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p-Stage I: 336 31%  
II: 215 20%  
III: 277 26%  
IV: 134 12%  
IV: 124 11%

pM: 962 89%
Validation = understaged; exploratory thoracotomy only. In the remaining 41 curative resection could still be performed.

For extrapulmonary metastases it was 27 out of 41 tumours that had been incorrectly classified as M1, a pathological confirmation of the clinically suspected metastases was confirmed by pathology. The ratio of metastases identified by clinical suspicion decreased the higher the N category.

In 6% of cases, distant metastases were discovered at pathological examination (K=0.242) and is considerably lower than for the T categories (table 4). In 29% of the cases the classification assigned was too high, and in 23% it was too low. The extent of agreement progressively decreased the higher the N category.

A detailed analysis of the location of lymph node involvement shows (table 5) that the incidence of a correct classification varied between 60% for lobar lymph nodes and 94% for paraoesophageal lymph nodes.

The highest agreement (90%) between clinical and pathological classification was obtained for the categories M0 and M1 (K=0.465). In 6% of cases, distant metastases were discovered at pathological examination that had not been clinically suspected. In 4% of the cases, clinically suspected distant metastases proved to be benign.

In 58 (59%) of 99 patients, the clinical suspicion of metastases was confirmed by pathology. The ratio of pathological confirmation of the clinically suspected intrapulmonary metastases was 31 out of 58 (53%). For extrapulmonary metastases it was 27 out of 41 (66%). In these 58 patients, the surgical intervention was, therefore, restricted to palliative surgery or exploratory thoracotomy only. In the remaining 41 tumours that had been incorrectly classified as M1, a curative resection could still be performed.

The table 3 shows the agreement between T and pT categories. The agreement of clinical and pathological classifications varies between 60% for T1 and 59% for T2. In T4 cases, the agreement is 42%.

The agreement of clinical and pathological classifications varies between 60% for T1 and 59% for T2. In T4 cases, the agreement is 42%.

The general agreement of clinical and pathological classification is 59% for radiography and 58% for computed tomography. Comparison of the concordance measures corrected for chance (radiography K=0.283, computed tomography K=0.291) did not result in a statistically significant advantage for computed tomography (p>0.05). The probability of a clinical overestimation of the actual extension of the primary tumour is also somewhat smaller with the two diagnostic methods than the risk of understaging. The most frequent errors of these two methods occurred for T3 and T4 tumours (correct classification T3: radiography 54%, CT 28%; correct classification T4: radiography 43%, CT 42%).

Comparison between the N categories (table 7A and B) showed considerably less agreement between clinical and pathological classification (observed agreement for computed tomography 50%, observed agreement for radiography 43%). Comparison of the concordance measures corrected for chance (radiography K=0.163, computed tomography K=0.253) did result in a statistically significant advantage for computed tomography (p=0.012).

It is common for both methods that the probability of understaging lymph node involvement is slightly greater than overstaging and that the ratio of agreement decreases with increasing N categories.

A prognosis-relevant classification has to meet three basic requirements:
1. the survival curves attributed to the respective stages of the classification should not intersect;
2. the prognosis should become significantly more unfavourable the worse the classification stage is;
3. the survival curves should cover the entire range of prognosis.
Table 6. — Agreement between T and pT with A) radiographic T categories and B) computed tomographic T categories (n=589)

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Correctly staged: Overall: 59%; T1: 48%; T2: 72%; T3: 34%; T4: 34%.

Table 7. — Agreement between N and pN with A) radiographic N categories and B) computed tomographic N categories (n=589)

<table>
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Correctly staged: Overall: 43%; N0: 51%; N1: 41%; N2: 35%. N3 (no data due to low number of cases).

The categories of the primary tumour meet all of these requirements (figs 1 and 2).

The different criteria for staging the primary tumour were investigated with respect to their prognostic relevance.

The tumour size of smaller or greater than 3 cm in diameter had a significant influence on prognosis (p<0.001). For tumour position within the airway no significant difference was observed for survival with involvement of the main bronchus more than 2 cm from the carina, to those within 2 cm of the carina. The prognostic relevance of extrapulmonary extension is unequivocal (p<0.001).

As far as involvement of the pleura is concerned, there was no prognostic difference between the two groups with and without infiltration of the visceral pleura. The prognosis, however, worsened significantly once the parietal pleura was infiltrated (p<0.001). It was also possible to prove that a malignant pleural effusion had a very unfavourable influence (p<0.001).
Fig. 2. - Prognosis for the primary tumour (pT) categories, n=1,086. pT1 (n=149); pT2 (n=658); pT3 (n=141); pT4 (n=138). pT1 vs pT2: p=0.001; pT2 vs pT3: p<0.001; pT3 vs pT4: p=0.012.

Fig. 3. - Prognosis for the lymph node (N) categories, n=2,918 (82 NX). NO (n=690); N1 (n=668); N2 (n=1,199); N3 (n=361). NO vs N1: p<0.001; N1 vs N2: p<0.001; N2 vs N3: p<0.001.

Fig. 4. - Prognosis for the lymph nodes (pN) categories, n=1,086. pN0 (n=415); pN1 (n=347); pN2 (n=285); pN3 (n=39). pN0 vs pN1: p<0.001; pN1 vs pN2: p=0.009; pN2 vs pN3: p=0.013.
The definitions of the categories of lymph node involvement satisfy all the requirements of a prognosis-relevance classification (figs 3 and 4). Here, it also becomes obvious that the N3 category is justified.

The prognostic relevance of the pM categories was undisputed and also the separation of stage III into the substages IIIA and IIB has proved to be valuable (figs 5 and 6).

Within each individual tumour stage there were significant differences for the survival between pT1N0M0 and pT2N0M0 (p=0.006) both of which used to be classified as stage I. However, pT2N0M0 also differed significantly from pT1N1M0 (p=0.014) and pT2N1M0 (p<0.001) (i.e. stage II).

Discussion

In 1981, Liehr and Gabler [18] edited a synopsis of ten publications which reported on the discrepancies between clinical and pathological staging based on the TNM classification. These varied between 5% and 50% for the T categories, between 17% and 64% for the N categories and came to 34% for the tumour stages (only investigated in one publication). Brandt and Lodenkemper [19] reported, in 1981, a congruency of 60% with the T classification for 52 patients who had undergone surgery for squamous cell carcinoma. These results can only be compared to our data with reservations because they used the old TNM definitions (2nd or 3rd edition) and because of patient selection.

Referring to the accuracy of the present diagnostic techniques, a reliable way of determining the tumour position within the airway is bronchoscopy. The imaging techniques, however, are often liable to lead to either over- or understaging of the actual extension of a primary tumour, particularly with more advanced tumours (T3 and T4 tumours). Radiography and computed tomography are often unsatisfactory for...
detecting infiltration of the parietal pleura, the chest wall (including sulcus superior tumours) or the mediastinal structures [20]. Assessment of actual extension of tumour is rendered even more difficult by secondary complications such as atelectasis and, centrally, by difficulty in differentiating between the primary tumour and infiltrated lymph nodes.

Doubts concerning the actual extent of tumour can ultimately only be cleared at thoractomy. If the intraoperative findings confirm inoperability, resection should not be carried out. The ratio of exploratory thoractomies, thus represents an indirect measure for accuracy of preoperative staging, and ratios between 5 and 10% are presently considered to be acceptable (in our own analysis 63 out of 1,086=6%).

All non-invasive methods of determining N category are of questionable significance. In spite of using hilar filter tomography for assessing the hilar lymph nodes (N1), and tomograms of the mediastinum, the accuracy of radiographic detection of infiltrated N2 lymph nodes was 43%. This is similar to the findings of Line et al. [21].

The accuracy of mediastinal nodal staging can be improved by computed tomography [22-25]. As with our results, a recent analysis [26], indicated that almost half of the resected, considerably enlarged mediastinal lymph nodes showed inflammatory changes only. Computed tomography undoubtedly helps to determine the size of mediastinal nodes but the assessment of size may not be sufficient to provide reliable evidence of malignancy.

If the results of computed tomography leave doubts concerning operability, a mediastinoscopy should be performed. As a diagnostic procedure it is more precise, especially for nodes in the tracheobronchial angle and paraatraclal area.

In conformity with Mountain [27] and with reports from the Mayo Clinic and the Memorial Sloan-Kettering Cancer Centre (MSKCC) [28-30], the prognostic relevance of the separation of the structures of extrapulmonary extension of the primary tumour into two groups (T3 or T4) could be confirmed.

A Japanese working party [31] obtained similar results for patients without pleural effusion or with an effusion but negative cytology. Only in the case of cytological evidence of a malignant effusion, was the prognosis significantly worse. According to the data gathered by an American working group [27], the existence of a pleural effusion is generally associated with a poor prognosis. Our own results for patients with a pleural effusion, suggest three significantly different groups: 1) no pleural effusion; 2) pleural effusion diagnosed on the basis of imaging techniques, but not histologically or cytologically confirmed to be malignant or with negative cytological or histological results; 3) cytologically or histologically positive. Thus, group 2 should be classified in T3, and group 3 in T4.

In conformity with the Japanese [31] and American [27] results, our own data confirm that the new N categories did not only greatly simplify the classification of lymph node involvement, but they did allow a clear prognostic separation.

There is still controversy over the value of a resection in patients with mediastinal lymph node involvement [10, 32, 33]. By a multivariate analysis in N2 patients with no residual lesion after resection, the influence of the exact location of the mediastinal lymph node involvement on prognosis was analysed. Only the paratracheal and the paraoesophageal lymph nodes were of independent and significant relevance to prognosis. These results agree with Pearson [34] and would also explain the relatively good results of the Toronto group [35] in cases of just isolated involvement of sub-aortal lymph nodes.

After the introduction of the third edition of the TNM classification for lung cancer it was pointed out by several groups [36-39], that the assignment of pT1N0M0, pT2N0M0 and pT1N1M0 to stage I was not justified, as there is no uniform prognosis for these tumours. As the definitions for pT1 and pT2 or pN0 and pN1, respectively, were incorporated into the fourth edition almost unchanged, these considerations still apply to the new classification. A recent study by Naruke et al. [31] which is based on a reclassification according to the new definitions, showed a statistically significant difference in prognosis between pT1N0M0 and pT2N0M0, as well as between pT1N1M0 and pT2N1M0, but not between pT2N0M0 and pT1N1M0. pT2N1M0 already has a similar prognosis to pT3N0M0 and pT3N1M0.

In contrast, our data showed that even though the prognosis for pT1N0M0 is significantly better than pT2N0M0, the latter, in turn, differs significantly from pT1N1M0 and pT2N1M0, which form one prognostic group. The reassignment of pT1N1M0 from stage I to stage II, which had been made with the fourth edition, therefore, could be confirmed. The prognostic difference between pT1N0M0 and pT2N0M0 could possibly be made allowable for by the introduction of new substages IA and IB.

References


Classification of lung cancer: TNM system
En ce qui concerne la tumeur primitive (T), les classifications cliniques et anatomo-pathologiques sont identiques dans 64%; pour l'atteinte des ganglions lymphatiques (N), l'accord est de 48%; pour les métabases à distance, il est de 90%, et pour la stadification de 55%. Pour ce qui concerne la tumeur primitive (T), la précision de la radiographie (59%) est presque identique à celle de la tomographie computed (58%). Les deux techniques sont moins précises pour déterminer l'étendue de l'atteinte ganglionnaire (appréciation correcte dans 50% à la tomographie computed et dans 43% à la radiographie).

Les différences statistiquement significatives de pronostic pour les différentes catégories T, N et M, ainsi que pour la stadification, ont pu être confirmées.

Grâce aux nouvelles définitions TNM 1987 (4e édition) pour le cancer du poumon, une conformité internationale est à la fois possible et pratique, et l'amélioration de la signification pronostique est évidente. Dès lors, l'on disposera d'une nouvelle base plus fiable pour établir des directives pour les concepts thérapeutiques oncologiques individuels.