The 7th Edition of the TNM Classification for Lung Cancer: Proposals from the IASLC Staging Project

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Abstract

The purpose of this presentation is three-fold: (a) to inform the lung cancer community of the proposals submitted by the International Association for the Study of Lung Cancer (IASLC) to the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) for the Lung Cancer section of the forthcoming (7th) Edition of the TNM Classification of Malignant Tumours, (b) to stimulate discussion within the lung cancer community ahead of these revisions being enacted, and (c) to describe to the wider oncological community the IASLC Lung Cancer Staging Project in the hope that it might provide a useful template by which revisions to the TNM Classification for other tumours could be better informed. This last issue will entail a description of the development of TNM staging in lung cancer, which, inevitably will be somewhat critical of the pre-existing process for revision. The UICC has sought to improve this and the previous speaker will address their process for change initiative. However, the relevant specialist associations and National groups can help to inform such revisions by stimulating collaborative, international efforts for data collection.

The history of lung cancer staging

The TNM system for the classification of malignant tumours was developed by Pierre Denoix, a surgeon at the Institute Gustave Roussy in Paris, and published in a series of articles between 1943 and 1952 [1]. The following year, 1953, this staging system was endorsed by the recently-formed UICC Committee on Tumour Nomenclature and Statistics. The UICC process at this time developed proposals by consensus between experts in the field. These proposals were disseminated in a series of 23 brochures published between 1960 and 1967, covering the TNM classification of cancers in 23 sites, lung being included in the brochure published in 1966. Subsequently, the recommendations were brought together in the 1st edition of the UICC 'TNM Classification of Malignant Tumours' published in 1968 in a compact 'Livre de Poche' format [2]. The proposals were suggested for 'trial' from 1967–1971. Lung cancer was included under the section on 'other sites'. The T descriptors included T0 for cases in which there was no evidence of the primary tumour, T1 for tumours confined to a segment or segmental bronchus, T2 where there was lobar involvement, T3 if there was involvement of more than one lobe and T4 for tumours extending beyond the lung. The N descriptors were NX, N0 or N1 if 'intrathoracic' nodes were involved. Intrathoracic nodes were described as 'hilar' or 'peripheral' with no mention of nodes in the mediastinum. The M1 descriptor was sub-divided into M1a, in which there was a pleural effusion with malignant cells present, M1b cases with palpable cervical nodes or M1c for cases in which other distant sites were involved. Stage groupings were not proposed at this point.

The AJCC, formed in 1959 as the American Joint Committee for Cancer Staging and End Results Reporting (AJC), developed a separate and distinctive process in which 'Task Forces' were set up to gather data which was used to inform its proposals. There was clearly a possibility that these two organisations would make different, and possibly conflicting, recommendations to the cancer community. Therefore, at a series of meetings between the UICC and the AJC a rapprochement was reached which ensured that these two organisations would not produce further recommendations without consultation between themselves and 'other National TNM Committees and International non-governmental professional organisations'.

In 1973 the Task Force on Lung Cancer of the AAJC accepted proposals from Drs. Mountain, Carr and Anderson for 'A Clinical Staging System for Lung Cancer' [3]. This was based upon data from 2155 cases of lung cancer, of which 1712 were cases of non-small cell lung cancer (NSCLC), diagnosed at least 4 years before analysis. Practically all of the T, N and M

descriptors in use today were introduced at that time, including the impact on T category of such features as; the 3 cm cut-off between T1 and T2 tumours, invasion of visceral or parietal pleura, the bronchoscopic extent of disease, the extent of atelectasis/consolidation of the lung parenchyma and the invasion of chest wall, diaphragm or mediastinum. The T categories 0–3 were retained but T4 was dropped, N categories 0–1 were retained but N2 was added to address the issue of mediastinal node involvement and M categories 0–1 were retained. Pleural effusions were removed from the M1 category and became a T descriptor. The resultant TNM categories were grouped into stages I to III. Four of the possible TNM categories had too few cases for analysis and seven others contained less than 100 cases. Survival curves showed distinct differences between prognosis in overall T, N and M categories and the 3 stage groupings to 5 years and beyond. A table showed the differing survival at 12 and 18 months for those TNM sets for which data was available. No assessment of statistical significance was presented and there was no validation of the individual descriptors. These proposals were incorporated in the 2nd edition of the UICC TNM Classification of Malignant Tumours published in 1975 [4]. The 3rd edition of the UICC manual, published in 1978 [5] and revised in 1982, further divided stage I into Ia and Ib (N.B. at that time stage sub-groups were lower case) and established stage IV for cases with M1 disease. By 1986 Dr. Mountain had assembled a new database containing 3753 cases of lung cancer with a minimum follow-up of 2 years. The proposals from this source were accepted by the AJCC, and subsequently by the UICC and cancer committees in Germany and Japan, creating 'A new International Staging System for Lung Cancer' [6]. The recommendations were published in the 4th edition of the UICC TNM Classification of Malignant Tumours in 1987 [7]. Changes proposed in this edition included: the designation of superficial tumours limited to the bronchial wall as T1 irrespective of location, the recommendation that the occasional pleural effusion that was cytologically negative could be ignored in defining the T category, the re-emergence of the T4 category and the creation of an N3 category. The existing T3 descriptors were split between T3 and the new T4 on the basis that the former would retain those descriptors that indicated that such tumours were 'candidates for complete resection' whilst the latter would be 'inoperable'. The previous descriptor of mediastinal invasion was split into its component parts, with invasion of the mediastinal pleura or pericardium remaining within T3 whilst invasion of the great vessels, heart, trachea, oesophagus, carina and vertebral bodies became T4 descriptors, along with the presence of a pleural effusion. The situation was confused by the additional definitions of T3 and T4 given in the text. Those tumours with 'limited, circumscribed extrapulmonary extension' were to be retained within the T3 category whilst those with 'extensive extrapulmonary extension' became T4. These conflicting definitions resulted in a lack of clarity as to whether tumours invading such structures as the pericardium remained T3 if there was extensive invasion and were considered inoperable or became T4, or if invasion limited to a circumscribed area of the oesophagus and resected completely at surgery should be considered to be T3 or T4. Metastases to the ipsilateral mediastinal nodes and subcarinal nodes remained within the N2 category, and a new N3 category was added to accommodate metastases to the contralateral mediastinal nodes, contralateral hilum or ipsilateral and contralateral supraclavicular or scalene lymph nodes. Additional changes in that edition were: the moving of $T_1N_1M_0$ cases from stage I to stage II and the division of stage III into IIIA (containing T3 and N2 cases) and IIIB (containing T4 and N3 cases). Once again a table showed the differing survival prospects for TNM subsets, and a graph showed statistically significant survival differences between stage groupings. No validation was presented for the individual descriptors. At the time of the next revision in 1997 the database of Dr. Mountain has increased to include 5319 cases, all but 66 being NSCLC, 4351 cases treated at the MD Anderson Cancer Centre between 1975 and 1988 and 968 cases referred there from the National Cancer Institute cooperative Lung Cancer Study Group for confirmation of stage and histology [8]. Tables showed statistically significant differences in survival as far as 5 years between clinical/evaluative cTNM categories and pathological/post-surgical pTNM categories $T_1N_0M_0$ and $T_2N_0M_o$ and these were divided into a new stage IA and stage IB respectively. Similarly $T_1N_1M_0$ cases were placed in a new stage IIA and $T_2N_1M_0$ and $T_3N_0M_0$ cases became stage IIB. The remaining TNM categories in stages IIIA, IIIB and IV remained unchanged although statistically significant differences were found between some TNM categories. An additional paragraph determined that 'the presence of *satellite* tumors within the primary-tumor lobe of the lung should be classified as T4. Intrapulmonary ispilateral *metastasis* in a distant, that is, nonprimary lobe(s) of the lung, should be classified M1'. No data was presented to support these suggestions and the wording used to describe such additional pulmonary nodules was loaded to

underline the apparent logic of considering some to be 'satellite' lesions and therefore a T descriptor whilst those in other lobes were a 'metastasis' and therefore an M descriptor.

These recommendations were accepted by the AJCC and the UICC-TNM Prognostic Factors Project Committee and published by the AJCC and in the UICC 5th edition of the TNM Classification of Malignant Tumours in 1997 [9]. There were no changes in the lung cancer classification in the 6th edition of the TNM Classification of Malignant Tumours published in 2002 [10,11].

The IASLC Lung Cancer Staging Project

At an IASLC sponsored workshop in London in 1996 [12] Dr. Mountain presented his proposals for the forthcoming 5th edition of TNM. The Mountain database by this time had enlarged to include 5319 cases, still relatively small, but this had been accumulated over 20 years, during which many advances had been made in clinical staging, most importantly the routine application of CT scanning. This database was mostly populated with surgical cases leaving many oncologists unsure as to whether TNM had any relevance in non-surgical cases. The database reflected practice in one part of the world but informed a process of global importance. The lack of validation in previous editions of the TNM classification led to many of the descriptors being increasingly challenged by data from other sources. The delegates at that workshop felt that there was a need to develop a new database for future revisions. It was further felt that the IASLC, as the only global organisation dedicated to the study of lung cancer, representing all clinical and research aspects of lung cancer care, had a responsibility to become involved in the revision process. A proposal was made to the board at the 8th World Conference on Lung Cancer, in Dublin in 1997. In December 1998 the board agreed to this proposal and granted pump-priming funds for the project. Meetings were held in London in 1999 and 2000 during which the composition of the committee was developed to ensure speciality and geographical representation and the involvement of stakeholders such as the UICC, the AJCC and the joint Japanese societies involved in the study of lung cancer. At the next World Conference in 2000 we were introduced to colleagues from Cancer Research And Biostatistics (CRAB), a not-for-profit medical statistics and data management organisation based in Seattle with extensive experience with multi-centre data collection and analysis. At that meeting sufficient funds were guaranteed from the pharmaceutical industry to allow a major meeting in London in 2001 to which database proprietors were invited to present an outline of the data they held. Over the 2 day workshop data on 80,000 cases were presented from 20 databases across the globe. In was decided to estimate the budget based upon the assumption that 30,000 suitable cases could be recruited and that the length of the project would be the 5 year cycle used by the UICC and AJCC at that time. Cases would be solicited from databases world wide, treated by all modalities of care, between 1990 and 2000, a period during which there had been relative stability in staging methods. This would ensure a 5-year follow-up by the time of analysis. In collaboration with CRAB the data fields and data dictionary were finalised. Later that year full funding was obtained by the IASLC via a partnership agreement with the pharmaceutical industry.

Meetings continued to be held on an annual basis utilising the World Conferences, now held biennially, wherever possible. In May 2003 the UICC and AJCC extended its revision cycle to 7 years resulting in a proposal that the 7th edition of the TNM would be published in January 2009. The internal review processes within these two organisations would require that the IASLC proposals be submitted to the UICC in January 2007 and the AJCC in June 2008.

Data collection was discontinued in April 2005 by which time over 100,000 cases had been submitted to the data centre at CRAB. After an initial sift which excluded cases with insufficient data on stage, treatment or follow-up, cases outside the designated study period and cases in which the cell type was unsuited or unknown 81,495 were available for analysis, 68,463 cases of NSCLC and 13,032 cases of small-cell lung cancer (SCLC). The geographical distribution of the data sources is illustrated in Fig. 1 and the spread of treatment modalities is shown in Fig. 2.

At the 11th World Conference in Barcelona in June 2005 sub-committees were established to develop the proposals for key aspects of the project. Additional sub-groups were later added. The final list of sub-committees, their areas of responsibility and the chair persons are given in Table 1.

A full list of the members of the IASLC lung cancer staging committee is shown in Appendix 1.

Intensive validation was crucially important in this project and the lack of it in earlier editions had been a major motive for the development of the project. The validation and methodology sub-committee was

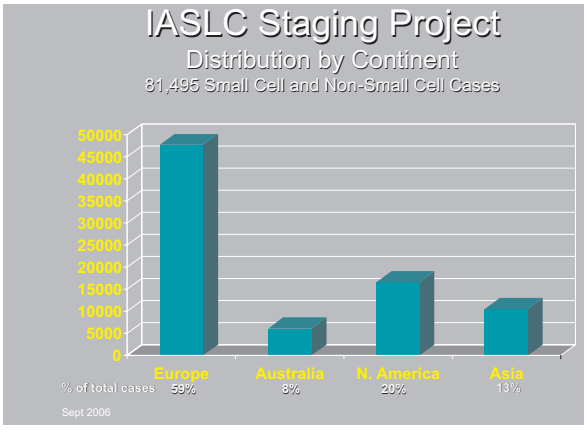

Fig. 1. A histogram illustrating the geographical spread of data submitted to the IASLC lung cancer staging project.

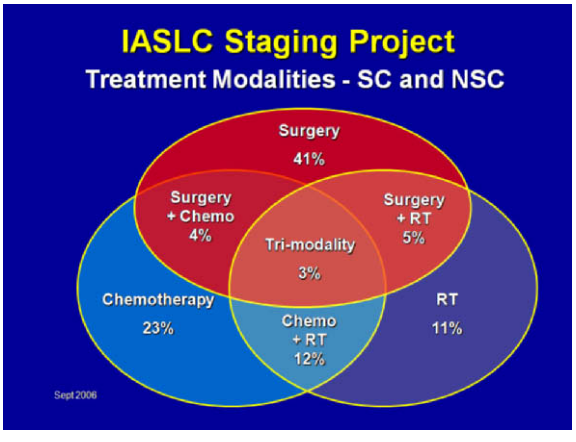

Fig. 2. Venn diagram showing the spread of treatment modalities employed in the cases submitted to the IASLC lung cancer staging project.

therefore intimately involved in the analyses conducted by CRAB and the development of the proposals from each sub-committee. Dr. P. Groome and her team collaborated with CRAB and the other sub-committee members to ensure that all proposals had internal and external validity. Internal validity ensured that all proposals were consistent across different types of databases and all geographical areas. External validity consisted of testing new proposals against the SEER data base and showing consistency with the international literature watch conducted by the UICC specialist lung cancer group. Such close collaboration with the UICC through their representatives on the IASLC committee, Dr. Leslie Sobin, the chair of the UICC TNM Prognostic Factors Core Group, and Dr. Patti Groome, who is a member of the UICC Process Task Force, has been enormously helpful, guiding our project from the outset. The proposals from the

Table 1
Sub-committee chairs

T Descriptors	Ramon Rami-Porta
N Descriptors	Valerie Rusch
M Descriptors	Pieter Postmus
Validation & Methodology	Patti Groome
Nodal Chart	Ryosuke Tsuchiya
SCLC	Frances Shepherd
Carcinoid Tumours	William Travis
Prognostic Factors	Jean-Paul Sculier

project were submitted to the board of the IASLC in September 2006 and approved unanimously. The recommendations regarding T, N and M descriptors and the TNM stage groupings, along with the details of the validation process were submitted to the UICC in December 2006 and to the AJCC in June 2007. In May 2007 the UICC TNM Prognostic Factors Core Group discussed the IASLC submission and minuted that they 'found the IASLC proposals to be scientifically robust, evidence based and consistent with TNM conventions, and therefore propose that they should be accepted for the revision of the lung cancer section of TNM 7th edition.' All of these proposals have been disseminated to the lung cancer community in a series of articles published in the Journal of Thoracic Oncology (JTO), the official journal of the IASLC [13–18]. Additional proposals regarding the role of TNM classification in SCLC and carcinoid tumours, the value of additional prognostic factors and proposals for a simpler international nodal chart were added to the AJCC submission and will be published in the JTO at a later date.

Proposals for lung cancer staging in the 7th edition

The recommendations of the T descriptors sub-committee were:

- Subclassify:
  - T1 as
    T1a ($\leqslant$2 cm) or
    T1b (>2 cm to $\leqslant$3 cm); and
  - T2 as
    T2a (>3 to $\leqslant$5 cm or T2 by other factor and $\leqslant$5 cm) or
    T2b (>5 to $\leqslant$7 cm).
- Reclassify T2 tumours >7 cm as T3.
- Reclassify T4 tumours by additional nodule/s in the lung (primary lobe) as T3.
- Reclassify M1 by additional nodule/s in the ipsilateral lung (different lobe) as T4.

- Reclassify pleural dissemination (malignant pleural or pericardial effusions, pleural nodules) as M1.

The recommendations of the N descriptors sub-committee were that the existing N descriptors used in the 6th edition of the TNM classification of lung cancer did not require changes or clarification. The recommendations of the M descriptors sub-committee were:

- Reclassify pleural dissemination (malignant pleural effusions, pleural nodules) from T4 to M1a.
- Subclassify M1 by additional nodules in the contralateral lung as M1a.
- Subclassify M1 by distant metastases (outside the lung/pleura) as M1b.

These descriptors were assimilated into the TNM subsets and the resultant stage groupings proposed are shown in table 2 with changes to the existing stage groupings in bold.

Occult Carcinoma	TX N0 M0
Stage 0	Tis N0 M0
Stage IA	T1a,b N0 M0
Stage IB	T2a N0 M0
Stage IIA	T1a,b N1 M0 **T2a N1 M0** **T2b N0 M0**
Stage IIB	T2b N1 M0 T3 N0 M0
Stage IIIA	T1, T2 N2 M0 T3 N1, N2 M0 **T4 N0, N1 M0**
Stage IIIB	T4 N2 M0 Any T N3 M0
Stage IV	Any T Any N M1a,b

Strengths and limitations of the project

The project has accumulated a database that is 15–20 times the size of that used to inform lung cancer staging in previous editions of the TNM Classification of Malignant Tumours. This has been achieved through amazing international collaboration with data submitted from 46 sources in over 19 countries. A full list of the contributing institutions is given in Appendix 1. We are enormously grateful to these colleagues for their selfless donation of such a valuable asset. The data covers patients treated by all modalities of care, including surgery, chemotherapy, radiotherapy, best supportive care as well as bi-modality and tri-modality regimens. The short period of accrual has ensured that the clinical staging used was consistent within centres and across the geographical regions. The intensive internal and external validation should ensure that the proposals, if ratified by the UICC and the AJCC, will be respected and implemented world wide.

However, there are limitations to such a retrospective data base. There are glaring gaps in the geographical spread of data. Whole continents such as Africa and South America were not represented and large countries such Russia, India and China were un-represented or under-represented. There was still a predominance of surgically treated cases, 53% of all cases had surgery and in 41% this was the only modality used. This is in stark contrast to the 20–25% of cases treated by surgery in most institutions. The period of data collection preceded the routine use of PET scanning which has had a profound influence on the accuracy of clinical staging and has changed investigative and treatment algorithms. The data was collected for a wide variety of reasons, and understandably the data fields were restricted to those necessary to fulfil the purposes of the investigators.

In many cases T, N and M categories were assigned without giving the details as to which descriptor placed a case into a particular category, and only in a small minority did the data state if a descriptor was the only one which led to a particular category being assigned. We were restricted in the audit of data quality when dealing with some many sources and many languages. Obvious contradictions could be clarified but we were unable to go back to check raw data. The size of the database allowed us to identify new descriptors, confirming some suggestions in the literature, and to re-assign some descriptors.

Many of the present descriptors were infrequently recorded and we could not prove or disprove their validity. Where the analyses showed new descriptors to have a prognosis that differed from the other descriptors in any T or M category, two alternative strategies were considered: (i) Retain that descriptor in the existing category, identified by alphabetical subscripts. For example, additional pulmonary nodules in the lobe of the primary, considered to be T4 in the 6th edition, would become T4a, whilst additional pulmonary nodules in other ipsilateral lobes, designated as M1 in the 6th edition, would become M1a. (ii) Allow descriptors to move between categories, to a category containing other descriptors with a similar prognosis, e.g. additional pulmonary nodules in the lobe of the primary would move from T4 to T3, and additional pulmonary nodules in other ipsilateral lobes would move from M1 to T4. The first strategy had the advantage of allowing, to a large extent, retrograde compatibility with existing

databases. Unfortunately this generated a large number of descriptors (approximately 20) and an impractically large number of TNM subsets (over 180). For this reason backwards compatibility was compromised and strategy (ii) was preferred for its clinical utility. In previous revisions new descriptors or stage groupings could be assigned to fit existing treatment algorithms. The size of this database, its international nature and the intensive validation process did not allow such a convenient allocation of new descriptors or stage groupings in this project. This has led us to arrive at decisions which we recognise will create problems for our colleagues in this field. The necessity to sacrifice backward compatibility with existing databases in the search for a staging system which is manageable in clinical practice has already been mentioned. We further recognise that moving some descriptors within stage categories and the proposed changes to the stage groupings will cut across established treatment algorithms. The moving of the larger, node negative T2 tumours (T2b cases more than 5 cm in greatest dimension) and tumours more than 7 cm in greatest dimension (which would become T3) from stage IB into stage IIA and stage IIB respectively will clearly raise the question as to whether such cases should have adjuvant chemotherapy after complete resection.

Whilst there is still doubt as to the value of adjuvant chemotherapy after complete resection for node negative cases in stage IB [19,20] at least two large trials have shown a benefit for node positive cases in stages II and IIIA [21,22]. The question as to whether these larger, node negative tumours benefit from adjuvant therapy will only be resolved by large, prospective randomised trials. The reassignment of cases with additional nodules in an ipsilateral, non-primary bearing lobe into a T4 descriptor rather than an M1 descriptor and the relocation of T4 N0 M0 and T4 N1 M0 cases into stage IIIA will also lead to questions as to the appropriate treatment algorithm. The limitations of our database do not allow us to be certain whether this reassignment is appropriate for cases with multiple additional tumour nodules or for all T4 cases. Multi-modality treatment models, some including surgery, will no doubt evolve, informed by appropriate trials. In other situations the changes suggested for inclusion in the 7th edition of the TNM classification might better reflect current practice as with the move of cases with malignant pleural effusions into an M category from a T category. Within our database there was a clear difference in prognosis between patients with metastases to the ipsilateral pleura or contralateral lung and those with metastases at distant sites outside the thorax. In general the latter have the worst prognosis and have been historically considered as stage IV, and candidates for primarily systemic treatment. Within the cases proposed in an expanded stage IV there is still a prognostic difference between those with spread within the thorax and those with metastases to distant sites and therefore differentiating between M1a and M1b seems to be of relevance.

The future

The deficiencies identified in this project can only be addressed by the establishment of a prospective database. Such an effort will be expensive and long-term. It will have to ensure that the geographical shortcomings are addressed by developing collaboration in un-represented geographical regions where often data collection is in its infancy. The selection of cases will have to better reflect the spectrum of treatments used in lung cancer whilst these same treatments are being re-evaluated as a result of the changes recommended for the 7th edition. This process is unlikely to be sufficiently mature for the 8th edition, due to be published in 2016 if the present cycle is retained. In the interim we will concentrate on refreshing and expanding the retrospective database, requesting longer follow-up on the cases already within the database, expanding the period of accrual from existing partners and establishing new partnerships to address the deficiencies of the present database.

The success of this project should ensure a place for the IASLC in all future revisions empowering the lung cancer community through their own global organisation. The IASLC remains committed to develop the project for future editions of the TNM Classification of Malignant Tumours for Lung Cancer. We hope that similar collaborative efforts will be developed in other malignancies, involving national organisations and international specialist associations.

Conflict of interest statement

None declared.

Appendix 1

IASLC International Staging Committee

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Peter MacCallum Cancer Institute, Australia; M. Tsao, Princess Margaret Hospital, Toronto, Ontario, Canada; S. Darwish, Policlinic of Perugia, Italy; H.I. Pass and T. Stevens, Karmanos Cancer Institute, Wayne State University, USA; G. Wright, St Vincent's Hospital, Victoria, Australia; and C. Legrand and J.P. van Meerbeeck, European Organisation for Research and Treatment of Cancer (EORTC), Brussels, Belgium.

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