Evaluation of the eighth AJCC TNM stage for lung cancer (NSCLC): a meta-analysis of 8 validation studies

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Research

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Abstract

Introduction The AJCC eighth edition TNM classification for lung cancer was released in 2017 and included major newer modifications. External validation studies have evaluated the efficacy of the new system and obtained paradoxical results. **Methods** A meta-analysis was performed of these studies to evaluate the new classification. Eight eligible studies with 654,185 patients were included in the analysis. Hazard ratios (HRs) and associated 95% confidence intervals were extracted from identified studies. The primary outcomes were survival discrimination and prognostic value of the new staging system with respect to the 7th edition. **Results** The HRs for the eighth edition staging system were found to increase steadily showing linear progression with 1.52 in IB, 1.82 in IIA, 1.97 in IIB, 2.19 in IIIA, 5.03 in IIIB, and 7.15 in IIIC compared with IA. The prognostic values of both systems were almost the same. **Conclusion** This study indicated that the survival discrimination of the eighth edition of the TNM classification is valid but its prognostic ability needs further evaluation.

Introduction

Lung cancer is the leading cause of cancer related death with only second to prostate and breast cancer in terms of incidence. Lung cancer death rates have declined in the past decade but the 5 year survival still remains abysmal.^{1,2} Staging at the time of diagnosis is the most important predictor of survival and is a crucial part of lung cancer patient management. The 7th edition of TNM staging was published in 2009 based on datasets that were not meant for TNM staging and not all descriptors being validated.³ The 8th staging was released in 2017 with main changes related to tumor size, the extent of involvement, and sub-classification of extra-thoracic metastases.⁴ (Table 1) Investigators have tried to validate the new staging and obtained paradoxical results.⁵⁻¹⁶ This meta-analysis of studies is aimed to evaluate the efficacy of the new staging system with respect to the 7th edition.

Methods

Search strategy and selection criteria:

PubMed, Embase, Web of Science, and CBM databases were searched by using combinations of the following keywords: "lung cancer," "lung carcinoma," "carcinoma of lung," "lung neoplasms," "TNM classification," "TNM stage," "TNM system," "prognostic," and "prognosis" (last updated on October 31, 2018). The referenced literature in the identified reports was also retrieved for other potentially important researches. All researches were carefully estimated to identify repeated data. Criteria used to define duplicate data included study period, hospital, treatment information, and any additional inclusion criteria. No language restrictions were applied. To be included in the meta-analysis of all-cause mortality, eligibility criteria were as follows: overall survival curves generated from individual patient data, hazard ratios (HRs) could be calculated from the outcomes. Only NSCLC were included in the analysis.

Data extraction and quality assessment:

Data retrieved from the reports included publication details and study characteristics, such as sample size, median follow-up, and outcome measures.

Statistical analysis

The HRs and their variances were directly extracted from the articles or estimated indirectly from the number of events and the survival curves.¹⁷ Meta-analyses were performed using Comprehensive Meta-analysis (CMA) software version 3 (Biostat, NJ, USA) when there was more than one study. A fixed-effect model with the method of Mantel-Haenszel⁹ was used when there is no evidence of heterogeneity between studies, otherwise, a random-effects model with the method of DerSimonian and Laird was chosen. Heterogeneity between studies was evaluated using the Q statistic and I² test which describes the percentage of variability in the effect estimates that is because of heterogeneity beyond sampling error.^{18,19} To evaluate the presence of publication bias, we performed Begg's funnel plot¹² and Egger's regression test.²⁰⁻²² If the publication bias was found, the trim and fill method of Duval and Tweedie was performed by adding studies that appeared to be missing to enhance the symmetry.^{23,24} The adjusted pooled effect size and its 95% Confidence Interval (CI) were computed after the addition of potential missing studies.

Results

Characteristics of the studies

After a thorough search, twelve studies were included in the detailed evaluation. Of those, four studies did not provide sufficient information to calculate HRs, even after extracting data from the graphs.^{7,8,15,16} Of twelve studies, eight studies were eligible for analysis. Males represented 58.4% of all studies with a total of 654,185 patients. The average age was 63 years' old and the mean follow up duration was 90 months for all patients. The main characteristics of the patients and studies included were listed in Table 2.

Survival discrimination by TNM staging group

Overall survival results of TNM parameter are based on 337,198 patients for the 8th staging system and 3,861 for the 7th staging system with a median follow-up of 84 months. The pooled HRs of each 8th edition TNM classification showed linear progression with 1.52 in IB, 1.82 in IIA, 1.97 in IIB, 2.19 in IIIA, 5.03 in IIIB, and 7.15 in IIIC compared with IA. On the other hand, pooled HRs of each 7th edition TNM classification were 1.36 in IB, 1.88 in IIA, 1.89 in IIB, 1.50 in IIIA and 3.45 in IIIB compared with IA (Figure 1).

In the same context, heterogeneity was observed in almost all analyses mostly due to different populations and sample sizes included. Nevertheless, no publication bias was observed using Egger's regression test. The summary of the different parameters presented in Table 3.

Assessment of prognostic value using C-index

Four studies assessed the prognostic values of staging systems using C-index. The prognostic values of both systems were almost the same with a slight superiority for the 8th system. The mean values were 0.688 and 0.690 for the 7th and the 8th staging systems, respectively (Figure 2).

Discussion

Staging of cancer is designed to provide prognosis and treatment framework. It should be able to provide meaningful comparisons between different treatment modalities and the same treatment modality between different investigators. The AJCC has published the eighth edition of TNM classification of lung cancer which has adopted several newer modifications based on the database collected between 1999 and 2010 from 16 different countries and 35 sources.⁴

This edition has assimilated certain new descriptors including 23 non-anatomical elements viz. patient related elements such as smoking and demographics, tumor related factors such as standard uptake value (SUV) on PET for T and N, grade of tumor and environment related factors.²⁵ The new staging system has been analyzed in both eastern and western countries and drew inconclusive results. This meta-analysis was done to evaluate the new classification.

With respect to the survival discrimination, the eighth edition seemed to fare better than the seventh edition. In this study, the HR for each 7th edition TNM classification were 1.36 in IB, 1.88 in IIA, 1.89 in IIB, 1.50 in IIIA and 3.45 in IIIB compared with IA. HRs for the seventh edition was found to be showing an erratic pattern. On the other hand, HRs of each 8th edition TNM classification showed linear progression with 1.52 in IB, 1.82 in IIA, 1.97 in IIB, 2.19 in IIIA, 5.03 in IIIB, and 7.15 in IIIC compared with IA. It showed a steady and reasonable increase in HRs signifying a better ability to characterize disease according to its survival curve.

Sensitivity analysis indicated that heterogeneity owing to different sample size and population. It might also be attributed to widespread lung cancer screening program mostly in western population with an earlier presentation than the eastern studies.

Most of the validation studies included in the analysis have fared toward a clear prognostic advantage towards the eighth edition individually but the meta-analysis based on four studies showed almost similar prognostic value with only slight superiority to the new edition.^{5,12-14} (C-index 0.688 vs 0.690)

The new edition has finessed a number of issues which were lacking in the previous edition. It allowed the evaluation of several descriptors that is expected to help stratify patients and prognosis more accurately. It also promotes the importance of multidisciplinary meetings as a standard of practice. This is the first time when characterization of sub-solid nodules and multiple pulmonary nodules has been clarified with a distinct role of difference in clinical, radiological and pathological staging.²⁶

Even though this edition has incorporated some of the vital components as per the advent of scientific innovations, but still has several limitations. One of the major drawbacks is that a lot of data collected

was still not necessarily designed for TNM classification similar to its predecessor. This leads to a lack of necessary details and clarifications required for a specific descriptor. One of those descriptors is lymphangitis carcinomatosa which has still not found its place in the classification due to lack of representation in the dataset. Agencies like NCCN and American College of Chest Physicians have recommended PET scan for the initial characterization of clinically indeterminate pulmonary nodule > 8 mm with a probability of malignancy (5–65%) as well as for pretreatment evaluation of lung cancer but SUV uptake of individual tumors have not been included in the stage.^{27,28} Modern medicine has evolved from radical to a more personalized way of treating cancer. Some of the malignancies have incorporated methods of precision medicine into its staging system such as breast cancer in the recent update but lung cancer staging has still not incorporated factors like immunohistochemistry and mutation genetics e.g. EGFR which can impact on treatment response and outcome.²⁹

Like its predecessor, the eighth edition has been marred by the lack of representation of patients who were treated other than surgery. (12% to 4.7%) Owing to that generalizability of the new staging system for nonsurgical treatment modalities might affect the prognostic impact of the TNM descriptors.³⁰ This meta-analysis has taken that into consideration with the incorporation of validation studies which have used radiotherapy and chemotherapy as their treatment modalities and came to the conclusion that prognostic ability of the new stage is almost same as its predecessor. The validity of the prognostic ability of the staging system is under scrutiny and should be further investigated.

In conclusion, the application of the eighth edition of the TNM classification in survival discrimination is valid but the prediction of prognosis needs further evaluation. The future staging system should be based on the dataset which is designed for TNM classification with the incorporation of elements of precision medicine and more representation of non-surgically treated patients.

Clinical Practice Points

AJCC staging system for lung cancer was first devised in year 1977. Since then there has been eight editions which has refined various aspect so that there is minimal distinction between the data and the reality. Each new edition of staging system is designed with respect to the drawbacks of the previous editions. External validation studies have evaluated the efficacy of the new stage and have found paradoxical results. The meta-analysis of such 8 validation studies showed a better survival discriminatory ability of 8th edition but the prognostic ability is similar between the two staging system. This study validates the new stage but also has highlighted important aspects which should be taken into consideration for the upcoming editions such TNM classification based data set, more representation of non-surgically treated patients. The role of Lymphangitis carcinomatosa should be addressed. We have come a long way in terms of refining the staging system but there is still a long way to go.

Declarations

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Conflicts of interest: none

Informed consent: Relevant informed consent has been taken for the research.

Availability of Data and Materials: Author wishes to share the data and supplementary material associated with this research.

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Tables

Table 1: Key features distinguishing the eighth edition classification

Descriptors		7 th edition	8 th edition
Tumor Size	>1-≤2 cm	T1a	T1b
	>2-≤3 cm	T1b	T1c
	>4-≤5 cm	T2a	T2b
	>5-≤7 cm	T2b	T3
	>7cm	T3	T4
Tumor Descriptor	Within main bronchus <2 cm of carina	T3	T2
	Obstructive atelectasis (whole lung)	T3	T2
	Local invasion of Diaphragm	T3	T4
Metastases	M1b	Distant metastasis	Single extrathoracic metastasis or involvement of a single distant (non- regional) node
	M1c		Multiple extrathoracic metastases in one or several organs

Table 2: Study characteristics

Study by first author	Year	Country	No. of Patients	Males; N (%)	Age; Mean $\pm$ SD	Time frame
Koul ¹⁰	2018	Canada	295	150 (50.9)	71.8 $\pm$ 14.2	January 2011 to December 2014
Abdel-Rahman ⁵	2017	Egypt	127,096	66,353 (52.2)	-	2010 to 2013
Aokage ⁶	2017	Japan	1792	1,155 (64)	66 $\pm$ 9	January 2003 to December 2011
Chansky ⁹	2017	USA	982,647	577,305 (58.7)	-	1999-2010 and 2000-2012
Chen ¹²	2017	China	2,043	1,109 (54.3)	62 $\pm$ 11.9	January 2006 to September 2015
Jung ¹³	2017	Korea	1,316	816 (62.0)	63.1 $\pm$ 0.3	January 1999 to December 2012
Sui ¹¹	2017	China	3,929	2,279 (63.3)	58 $\pm$ 3.7	January 2005 to December 2012
Yang ¹⁴	2017	USA	858,909	-	-	2004 to 2013

Table 3: Hazard ratios and 95 % confidence intervals (95 %CI) for survival by stage (vs. IA)

Stage	System	No. of patients	HRs	95% LCI	95% UCI	P-value	I ² (%)	Egger's P-value
IB	7th	600	1.36	0.85	2.18	0.198	91.01	0.746
	8th	5,674	1.52	1.06	2.16	0.003	94.88	0.343
IIA	7th	1,786	1.88	0.88	4.03	0.106	95.19	0.741
	8th	13,908	1.82	1.16	2.86	0.006	96.01	0.268
IIB	7th	393	1.89	0.70	5.12	0.210	96.35	0.919
	8th	119,111	1.97	1.10	3.54	0.785	99.91	0.168
IIIA	7th	1,004	1.50	0.37	6.12	0.570	98.47	0.521
	8th	79,988	2.19	0.82	5.86	0.037	99.67	0.461
IIIB	7th	78	3.45	2.24	5.31	< 0.001	0.00	0.289
	8th	74,631	5.03	3.46	7.31	< 0.001	99.68	0.289
IIIC	7th	-						
	8th	19,196	7.15	3.33	14.38	0.001	99.80	0.401

Figures

Figure 1

Hazard ratios for survival by 8th and 7th AJCC TNM stage (vs. stage IA). Error bars represent 95 % confidence intervals.

Figure 2

Summary of C-index for 8th and 7th AJCC TNM stage.

Supplementary Files

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