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Comparison of 7th and 8th editions of the UICC/AJCC TNM staging for non-small cell lung cancer in a non-metastatic North American cohort undergoing primary radiation treatment

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ABSTRACT

Background: We compared the performance of 7th and 8th edition of the Union for International Cancer Control (UICC) / American Joint Committee on Cancer (AJCC) TNM staging for non-small cell lung cancer (NSCLC) in non-metastatic (stage I-III) North American cohort undergoing primary radiation treatment.

Methods: Newly diagnosed NSCLC between (Jan 2011 – Dec 2014) were screened through a Canadian Provincial Cancer Registry. Clinico-radiologically and pathologically confirmed non-metastatic NSCLC undergoing primary radiation treatment were included. Kaplan-Meier methods, Cox proportional hazard regression and Akaike information criterion (AIC) were applied to evaluate discriminatory ability and prognostic performance of 7th and 8th edition of staging systems.

Results: In this cohort of 295 patients, 8th edition stages IA3, IB, IIA, IIB, IIIA, IIIB, and IIIC showed progressive increase in the hazard ratio compared to best stage IA2 (8th edition IA3 vs IA2: HR 1.72; IB vs IA2: HR 2.04; IIA vs IA2: HR 2.66; IIB vs IA2: HR 2.91; IIIA vs IA2: HR 3.38; IIIB vs IA2: HR 3.62 and IIIC vs IA2: HR 8.22). In a multivariate model, 8th edition stage grouping had smaller AIC of 2342.08 compared to 7th edition 2349.55, confirming better performance. International Association for the Study of Lung Cancer (IASLC) map based nodal categorization N1, N2 and N3, showed good survival and hazard discrimination over stage N0 (1.39, 1.48 and 2.16 respectively).

Conclusion: In an independent cohort of non-metastatic NSCLC undergoing primary radiation treatment, improved performance of 8th edition UICC/AJCC staging system over 7th edition was observed.

1. Background

The prediction of prognosis is essential to the practice of medicine. The Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) TNM staging is used worldwide as a common language to describe disease extent in Oncology and is vital for evaluating prognosis, treatment decisions, and outcome assessments.

Lung cancer is a leading cause of cancer mortality for several decades [1]. For Non-small cell lung cancer (NSCLC) 7th edition of UICC/AJCC TNM staging is currently being used and significant revisions were proposed for the 8th edition [2]. International Association for the Study of Lung Cancer (IASLC) staging and Prognostic Factors Committee collected an enormous database of 94,708We compared performance of 7th and 8th cases treated from 1999 to 2010 [3]. This database was contributed from 35 sources in 16 countries around the globe, and Cancer Research and Biostatistics (CRAB) performed an extensive analysis [3,4]. Despite its strengths, database size, vigorous statistical testing, and validation cohort the proposed staging system has some drawbacks and could be improved further. Asia contributed almost 80% of clinically staged and pathologically staged tumors to the IASLC database, as compared to 53% in the database used for the 7th edition of AJCC/UICC [2,3,5]. The database is primarily derived from patients undergoing surgical treatment and only 563 patients were treated non-surgically [3].

Similarly, most of the data for N descriptor (59.1%- clinical and 74.7%- pathological) was derived from Japan. Only 3.6% (cN) and 8.7% (pN) data was representative of North/South American patient cohort. Importantly, during this period of 1999 to 2010, in this region N stage was derived from Japan representing nodal categorization based upon Japanese-Naruke map [5]. AJCC acknowledged further validation

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using nodal categorization according to Mountain-Dressler modification of the American Thoracic Society map (MDATS) might be helpful.

Thus in view of limitations in global representation; differences in nomenclature and treatment, Validation of UICC/AJCC TNM 8th edition for NSCLC, in an underrepresented cohort of North American population, undergoing primary radiation treatment may be helpful. We compared the performance of 7th and 8th edition of AJCC in lung cancers in the underrepresented cohort of non-surgically treated patients through a Provincial Cancer Registry in Canadian settings.

2. Materials and methods

The local research ethics board approved this retrospective study. Newly diagnosed NSCLC between Jan 2011 to Dec 2014 were screened through Provincial Cancer Registry. Clinico-radiologically and pathologically confirmed non-metastatic (stage group I-III) NSCLC undergoing primary radiation treatment were included in this study. For staging of the disease, all patients had Positron emission tomography (PET) and/or computed tomography (CT) chest – abdomen and cranial imaging (CT or MRI). In the province of Manitoba, during the period of this study (Jan 2011–Dec 2014), PET was the preferred imaging investigation for the staging of non-metastatic NSCLC. Lymph nodes were considered involved if pathologically positive on mediastinal assessment and/or if the radiologically smallest diameter was larger than 1 cm on CT and/or hypermetabolic on PETCT [6]. Patients undergoing primary surgical treatment, past history of malignancy apart from skin excluding melanoma and stage IV disease were excluded from this study. All patients underwent primary radiation treatment and were treated according to institutional guidelines consistent with NCCN guidelines [7]. Demographic parameters, tumor characteristics, and survival data were collected. Patients were followed up clinico-radiologically at regular intervals according to guidelines consistent with NCCN policy [7].

Patients were reclassified as per proposed 8th edition of UICC/AJCC TNM for T descriptor and stage grouping changes, after individual review of imaging details [3,8]. Descriptive statistics were generated. Overall survival was calculated from the date of diagnosis (pathological diagnosis of NSCLC) till death. The survival rate was calculated using the Kaplan Meier method, and. the log-rank test assessed the differences between curves. Cox proportional hazards regression was used to calculate hazard ratios (HRs) with 95% confidence intervals (95% CIs) to determine an association between clinical variables of interest and survival. The likelihood ratio x2 test related to the Cox regression model was used to measure homogeneity of the direct comparison of the two different edition stage systems, The Akaike information criterion (AIC) score is a quantitative measurement that considers model fit and model complexity [9]. AIC was applied to the Cox proportional hazard regression model to correct for the potential bias in comparing prognostic systems with different numbers of stages, in a multivariate model adjusted for age and gender. AIC was defined as follows: AIC = −log maximum likelihood + 2* (the number of parameters in the model). A smaller AIC value indicated a better goodness of fit. The Statistical Package for the Social Sciences (SPSS) versions 20 and Microsoft Excel 2007 were used for data processing and analyses.

3. Results

A total of 295 patients undergoing radiation treatment were included in the analysis. Of these 150 were male and 145 were female with the median age of the population was 71 years (range 48–97 years). Demographic and tumor-related details are elaborated in the Table (S-1).

3.1. T, N descriptor and stage grouping redistribution

Table 1 shows the number of patients in seventh and eighth edition T descriptor distribution by numbers. Expectedly, redistribution was primarily noted in T1a, T2a, T3 and T4 descriptor of 7th edition. Twenty-four patients classified as T1a -7th edition, were the redistributed as T1a (n = 2) and T1b (n = 22) as per 8th edition changes. All the patients with previous descriptor T1b (n = 56) and T2b (n = 29) as per 7th edition were upstaged as T1c (n = 56) and T3 (n = 29) respectively with the new 8th edition. Sixty-seven stage T2a patients as per 7th edition were redistributed as T2a (n = 45) and T2b (n = 22). Similarly, 45 patients with T3 descriptor were redistributed as T2a (n = 3), T2b (n = 5), T3 (n = 28) and T4 (n = 18). No changes were noted in the T4 category. In the study cohort frequency of N0, N1, N2, and N3 was 70 (30.8%), 19(8.4), 99(43.6) and 39(17.2%) respectively. No nodal changes were proposed in 7th and 8th edition of the staging system.

Table 1
N descriptor distribution by 7th and 8th edition of AJCC.

T stage		7th edition TNM						Total
		T1a	T1b	T2a	T2b	T3	T4	
8th edition TNM	T1a	2	0	0	0	0	0	2
	T1b	22	0	0	0	0	0	22
	T1c	0	56	0	0	0	0	56
	T2a	0	0	45	0	3	0	48
	T2b	0	0	22	0	5	0	27
	T3	0	0	0	29	28	2	59
	T4	0	0	0	0	18	63	81
Total		24	56	67	29	54	65	295

Table 2
Stage group distribution by 7th and 8th edition of AJCC.

Stage grouping		7th edition TNM						Total
		IA	IB	IIA	IIB	IIIA	IIIB	
8th edition TNM	IA2	16	0	0	0	0	0	16
	IA3	28	0	0	0	0	0	28
	IB	0	11	0	0	0	0	11
	IIA	0	7	0	2	0	0	9
	IIB	0	0	15	5	0	0	20
	IIIA	0	0	1	7	85	0	93
	IIIB	0	0	0	0	43	55	98
	IIIC	0	0	0	0	0	20	20
Total		44	18	16	14	128	75	295

Table 3
N descriptor - 8th edition of AJCC.

N stage	N	Events	Median survival (months)	HR	p value
N0	95	67	22.51		
N1	24	21	18.83	1.39 (0.85-2.27)	0.19
N2	133	112	14.69	1.48 (1.09-2)	0.01
N3	43	39	8.77	2.16 (1.45-3.21)	< 0.001

Table 2 shows stage group distribution of cohort by 7th and 8th AJCC edition. Stage IA had 44 patients, subgrouped as IA2 (n = 16) and IA3 (n = 28) respectively. Our cohort did not have any IA1. Major redistribution were also noted in stage IIIA and IIIB – 7th edition of AJCC/UICC. A total of 128 patients from the 7th edition of AJCC were redistributed as IIIA (n = 85) and IIIB (n = 43) as per 8th edition changes. Similarly, 75 patients of stage IIIB from 7th edition were redistributed as IIIB (n = 55) and IIIC (n = 20).

3.2. Performance of N descriptor – IASLC map

Survival analysis of N descriptor categories (Fig. S-1) showed good separation ($p < 0.05$) and MST for N0, N1, N2, and N3 was 22, 19, 15 and 9 months respectively (Table 5). All N descriptors N1, N2, and N3