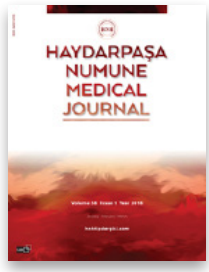
HAYDARPAŞA NUMUNE MEDICAL JOURNAL

DOI: 10.14744/hnhj.2022.45477
Haydarpasa Numune Med J 2023;63(3):305–311



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ORIGINAL ARTICLE

Analysis of Difference Between Survivals in Seventh and Eighth Editions of TNM Staging in Resectable Multiple Primary Lung Cancers (MPLC)

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Abstract

Introduction: Staging of multiple primary lung cancer (MPLC) cases and planning the treatment are of great importance in terms of the prognosis of the disease. Size of lung lesion (T) and lymph node status (N) are of the most reliable indicators of prognosis in patients with lung cancer. In this study, we evaluated whether there was a survival difference in T and N status in the survival analysis of the seventh and eighth edition of staging in MPLC who underwent curative radical surgery.

Methods: A total of 55 patients diagnosed with MPLC in our clinic between January 2000 and April 2016 were retrospectively screened. These patients were divided into 2 main groups: 20 synchronous and 35 metachronous lung cancers. Survivals for both groups were calculated according to both the seventh and eighth edition of TNM staging systems (TNM7 and TNM8), taking into account the tumor sizes at first operation, stages, lymph node presence, histopathological type, and tumor localization.

Results: In our study, a statistically significant difference was found in terms of survival between tumor sizes and stages in TNM7 staging system, according to the results of the pairwise comparison test applied in synchronous lung cancers ($p<0.05$). However, no statistically significant difference was found in terms of survival in TNM8 staging system ($p>0.05$). In metachronous lung cancers, no statistically significant difference was found in terms of tumor size and survival between stages in both TNM7 and TNM8 staging systems according to the results of the pairwise comparison test ($p>0.05$). A statistically significant difference was found between lymph node groups in terms of survival in TNM8 staging system in synchronous and metachronous lung cancers ($p<0.05$). Staging according to the TNM8 staging system in synchronous lung cancers changed in 11 of our patients and in 22 patients in metachronous lung cancers.

Discussion and Conclusion: TNM7 staging was found to be more sensitive in terms of survival difference according to tumor size and stages in synchronous tumors, while TNM8 staging was found to be more sensitive in terms of survival difference due to lymph node involvement in both synchronous and metachronous tumors. In cases with MPLC, the proposed eighth edition of staging system is superior to the seventh edition as descriptors of tumor sizes are elaborated.

Keywords: Curative surgery; multiple primary lung cancer; TNM staging system; survival.

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Submitted Date: 23.02.2022 **Revised Date:** 23.02.2022 **Accepted Date:** 13.04.2022

Lung cancer remains one of the most common causes of cancer deaths, despite the understanding of the root cause of the disease. The most important risk factors in the etiology of lung cancers are exposure to carcinogens, especially smoking, and the underlying individual genetic predisposition. Smoking increases the risk of lung cancer 5-10 times with a clear dose-response relationship. The risks for marijuana and hookah use, as well as for new e-cigarettes, have not yet been consistently defined and will be important areas for ongoing research as the use of these products increases. Host factors, including a family history of lung cancer, chronic obstructive pulmonary disease, and a history of infection have also been associated with lung cancer risk[1].

The presence of more than one tumor in the lung at the same time but in different lobes suggests either metastasis or multiple primary lung cancer (MPLC). Some clinical parameters have been determined in the evaluation of patients with this condition. One of these parameters is the Martini and Melamed criteria[2]. Synchronous tumors are used to refer to a different primary lung cancer at the time of diagnosis, while metachronous tumors are used to refer to a different primary lung cancer that occurs following curative treatment of the primary tumor. The synchronous tumor rate ranges from 0.2% to 8% and is increasing due to the widespread use of multislice spiral CT. It is estimated that 4% to 10% of patients diagnosed with lung cancer subsequently develop metachronous tumors[3].

Accurate identification, staging and treatment planning of cases with MPLC are of great importance for the prognosis of the disease. The size of the pulmonary lesion and lymph node status are considered to be one of the most reliable indicators of prognosis in patients with lung cancer. Therefore, it is very important to accurately assess the stage of the tumor and to decide on the stage-specific treatment strategy. The tumor, lymph node, metastasis (TNM) staging system of the American Joint Cancer Committee (AJCC) / International Union for Cancer Control (UICC) is the main tumor staging system used in the investigation of various solid tumors, including lung cancer. In order to learn more about lung cancer staging, the eighth edition of the TNM classification (TNM8) began to be used as a result of several changes in the seventh edition (TNM7), especially regarding T categories. According to the proposed eighth edition for TNM, T categories have been redefined to increase its prognostic validity[4-6].

In this study, we aimed to present the analysis of the survival difference between the seventh edition and the eighth edition in TNM classification in patients with MPLC who underwent surgery.

Materials and Methods

Patient Selection

A total of 55 patients who were diagnosed with multiple primary lung cancer among 4610 patients who underwent resection for non-small cell lung cancer in the Department of Thoracic Surgery of the Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital, Health Sciences University, between January 2000 and April 2016, were included in this retrospective study. These patients were divided into two main groups as 20 synchronous and 35 metachronous lung cancers. The pathology results of the patients in both groups after the first and second operation were individually staged according to both TNM7 and TNM8 staging systems. In the synchronous lung cancer group, both tumors were staged separately, the side with higher stage was operated first.

In our study, in the survival calculations of both groups, tumor sizes, stages, maximum standardized uptake (SUVmax) values, presence of lymph nodes, histopathological type and tumor localization at the first operation were calculated according to both TNM7 and TNM8 staging systems.

Patients who were diagnosed with MPLC but could not undergo any surgery for any reason, whose first or second operation was performed in an external center, for whom we could not obtain sufficient data about the surgery made from the patient files during the scan or the pathological stage of the patient, were not included in the study.

Technique

In our cases, chest computed tomography (CT), positron emission tomography-computerized tomography (PET-CT) and cranial magnetic resonance imaging (MRI) examinations were performed in the preoperative period. Lung perfusion scintigraphy, echocardiography, coronary angiography, and maximal oxygen uptake (VO2max) were applied to selected patients who had limited reserves in terms of pulmonary functions or were followed up due to cardiac ischemia and arrhythmia.

In patients who were predicted to have synchronous lung cancer, both tumors were diagnosed preoperatively, each tumor was clinically staged separately and surgery was planned to be peformed starting from the side with the higher stage. If both tumors were on the same side, their anatomic resections were performed simultaneously. If both tumors were on different sides, anatomic resections were performed with sequential video-assisted thoracoscopic surgery (VATS) or thoracotomy at 4-6 week intervals.

Endobronchial lesions were evaluated by performing flexible or rigid bronchoscopy in all patients in the preoperative period. Before VATS or thoracotomy, patients underwent mediastinoscopy. Surgical intrathoracic staging was completed by performing systematic mediastinal lymph node dissection along with resection. Both tumors were separately staged according to the TNM7 and TNM8 staging system, in the light of pathology results. Patients were evaluated for survival.

Chemotherapy (CT) and/or radiotherapy (RT) were applied to the cases in the postoperative period according to their stages. The patients were followed closely due to the possibility of recurrence, metastasis or metachronous tumor development. In our study, the mean follow-up period of synchronous lung cancer patients was 27.60±21.972 months (2 months-64 months), and the mean follow-up period of patients with metachronous lung cancer was 67.58±47.66 months.

Gender, age, localization of the first and second tumors, histopathology, lymph node involvement, presence of recurrence or metastasis in postoperative follow-ups, mortality, and follow-up periods of these cases were retrospectively analyzed.

Statistical Analysis of Data

The data were transferred to the IBM SPSS (Statistical Package for Social Sciences) Statistics 22 program. While evaluating the study data, the frequency and percentage distributions of the categorical variables are provided. Life table and Kaplan-Meier methods were used during survival analysis. The Logrank test was used to examine the differences between the active groups in terms of survival. Chi-square analysis was used to determine whether there was a relationship between two independent categorical variables. All data are given as mean±standard deviation. $p \leq 0.05$ was accepted for statistical significance.

Results

95% of the patients in the synchronous lung cancer group were male, and 55% were over 60 years of age. The localization of the lesion was bilateral in 90% of cases. In 60%, the pathology was squamous cell carcinoma. Metastasis (brain and bone metastasis) was detected in 10% of the patients during their follow-up. Recurrence was seen in 5% of the patients. In terms of follow-up period, 65% of the patients lived less than three years, 20% lived between three and five years, and 15% lived more than five years (Table 1).

Table 1. Demographic Distribution of Patients in the Synchronous Lung Cancer Group

	Number	%
Gender		
Female	1	5.0
Male	19	95.0
Age		
Age 60 and Under	9	45.0
Over Age 60	11	55.0
Mass Localization		
Left	2	10.0
Bilateral	18	90.0
Pathology		
First Operation		
Squamous cell carcinoma	12	60.0
Adenocarcinoma	7	35.0
Other types	1	5.0
Pathology		
Second Operation		
Squamous cell carcinoma	11	55.0
Adenocarcinoma	7	35.0
Other types	2	10.0
Metastasis		
No metastasis	18	90.0
Metastasis present	2	10.0
Relapse Status		
No relapse	19	95.0
Relapse present	1	5.0
Monitoring Time		
<3 years	13	65.0
3-5 years	4	20.0
>5 years	3	15.0

Of the patients in the metachronous lung cancer group, 97.1% were male and 51.4% were over 60 years of age. The lesion was bilateral in 42.9% of the patients. The pathology was squamous cell carcinoma in 62.9% of the patients. Metastases (bone, liver, supraclavicular lymph node, kidney and mediastinum-pericardium) were detected in 25.7% of the patients during their follow-up. Recurrence was observed in 14.3% of the patients. In terms of follow-up period, 20% of the patients lived less than three years, 22.9% lived between three and five years, and 57.1% lived more than five years (Table 2).

According to the results of the pairwise comparison test applied in synchronous lung cancers, a statistically significant difference was found in terms of survival between tumor sizes and stages according to the TNM7 staging

Table 2. Demographic Distribution of Patients in the Metachronous Lung Cancer Group

	Number	%
Gender		
Female	1	2.9
Male	34	97.1
Age		
Age 60 and Under	17	48.6
Over Age 60	18	51.4
Mass Localization		
Right	13	37.1
Left	7	20
Bilateral	15	42.9
Pathology		
First Operation		
Squamous cell carcinoma	22	62.9
Adenocarcinoma	10	28.6
Other types	3	8.6
Pathology		
Second Operation		
Squamous cell carcinoma	25	71.4
Adenocarcinoma	10	28.6
Metastasis		
No metastasis	26	74.3
Metastasis present	9	25.7
Relapse Status		
No relapse	30	85.7
Relapse present	5	14.3
Monitoring Time		
<3 years	7	20
3-5 years	8	22.9
>5 years	20	57.1

system ($p<0.05$). However, according to the TNM8 staging system, no statistically significant difference was found between tumor sizes and stages in terms of survival ($p>0.05$).

According to the results of the pairwise comparison test applied in metachronous lung cancers, no statistically significant difference was found in terms of tumor size and survival in both TNM7 staging system and TNM8 staging system ($p>0.05$).

In synchronous lung cancers, staging according to the TNM 8 staging system was changed in 11 of our patients, and in metachronous lung cancers, the stage of 22 patients was changed.

Of the 7 patients with synchronous lung cancer at stage 1A according to the TNM7 staging system, stages of the 4 patients were changed as stage 1A2 and of the 3 patients as stage 1A3 in the TNM8 staging system. In addition, the stage of a patient in stage 1B in the TNM7 staging system was changed to stage 2A in the TNM8 staging system (Tables 3, 4).

According to the TNM7 staging system, out of 10 patients with metachronous lung cancer stage 1A, 5 patients were changed to stage 1A2 and the other 5 patients to stage 1A3 in the TNM8 staging system. In addition, the stage of 4 patients in stage 1B in the TNM7 staging system was changed to stage 2A in the TNM8 staging system (Tables 5, 6).

Lymph node was positive in 25% of synchronous lung cancer patients; of these patients, while the rate of postoperative N1 positive patients was 80%, the rate of N2 positive patients was 20%. Lymph node was positive in 28.6% of metachronous lung cancer patients; of these patients, while the rate of postoperative N1 positive patients was 60%, the rate of N2 positive patients was 40%. According to the results of the Logrank test, there was no statistically significant difference in survival between lymph node groups in the TNM7 staging system in synchronous and metachronous lung cancers ($p>0.05$), but a statistically significant difference was found between lymph node groups in the TNM8 staging system ($p<0.05$).

When we look at the survival according to the histopathological type of the tumor in both groups, no statistically significant difference was found in both TNM7 and TNM8 staging systems according to the results of the pairwise comparison test ($p>0.05$).

Tumor was localized at the left side in 10% of synchronous lung cancer patients, and was bilateral in 90% of them. Tumor localization was on the right side in 37.1% of metachronous lung cancer patients, on the left side in 20%, and was bilateral in 42.9%. According to the results of the chi-Square analysis, a statistically significant relationship was found between tumor localization and synchronous

Table 3. Number of Patients whose Stages Changed in the TNM8 Staging System in the Synchronous Lung Cancer Group

TNM7	TNM8
1A (T1a,bN0M0)	1A2 (T1bN0M0)(4 Patients)
	1A3 (T1cN0M0) (3 Patients)
1B (T2aN0M0)	2A (T2bN0M0)
2A (T1aN1M0)	2B (T1bN1M0)
2A (T2aN1M0)	2B (T2aN1M0)
2B (T3N0M0)	2A (T2bN0M0)

Table 4. Stages and Number of Patients in the Synchronous Lung Cancer Group by TNM7 and TNM8 Staging System

TNM7		TNM8		Number of patients whose stage changed
Stage	**Number of Patients**	**Stage**	**Number of Patients**	
1A(T1a,bN0M0)	7	1A2(T1bN0M0)	4	7 patients
		1A3(T1cN0M0)	3	
1B(T2aN0M0)	6	1B(T2aN0M0)	5	1 patient progressed to stage 2A
2A(T2bN0M0)	2	2A(T2bN0M0)	2	2 patients progressed to stage 2B
2A(T2aN1M0)				
2B(T2bN1M0)	3	2B(T3N0M0)	4	1 patient progressed to stage 2A
2B(T3N0M0)		2B(T2aN1M0)		
		2B(T1bN1M0)		
		2B(T3N1M0)		
3A(T3N1M0)	2	3A(T3N1M0)	2	
3A(T2aN2M0)		3A(T2aN2M0)		

Table 5. Number of Patients whose Stages Changed in the TNM8 Staging System in the Metachronous Lung Cancer Group

TNM7	TNM8
1A (T1a,bN0M0)	1A2 (T1bN0M0)(5 Patients)
	1A3 (T1cN0M0) (5 Patients)
1B (T2aN0M0)	2A (T2bN0M0) (4 Patients)
2A (T1bN1M0)	2B (T1cN1M0)
2A (T2aN1M0)	2B (T2aN1M0) (3 Patients)
2A (T2aN1M0)	2B (T2bN1M0)
2A (T2bN0M0)	2B (T3N0M0)
2B (T3N0M0)	3A (T4N0M0) (2 Patients)

and metachronous lung cancer groups ($p<0.05$). Accordingly, it can be said that tumor localizations are more frequently bilateral in the synchronous lung cancer group, and are often unilateral in the metachronous lung cancer group.

In synchronous lung cancer, the 3-year survival rate was 61%, while the 5-year survival rate was calculated as 61%. The overall survival rate was 70%. In metachronous lung cancer, the 3-year survival rate was 80%, the 5-year survival rate was 62%, and the overall survival rate was 31.4%.

Table 6. Stages and Number of Patients According to the TNM7 and TNM8 Staging System in the Metachronous Lung Cancer Group

TNM7		TNM8		Number of patients whose stage changed
Stage	**Number of patients**	**Stage**	**Number of patients**	
1A	10	1A2	5	10 patients
		1A3	5	
1B(T2aN0M0)	10	1B(T2aN0M0)	6	4 patients progressed to stage 2A
2A(T1bN1M0)	6	2A(T2bN0M0)	4	6 patients progressed to stage 2B
2A (T2aN1M0)				
2A (T2bN0M0)				
2B(T3N0M0)	3	2B (T1cN1M0)	7	2 patients progressed to stage 3A
		2B (T2aN1M0)		
		2B (T2bN1M0)		
		2B (T3N0M0)		
3A(T1bN2M0)	4	3A(T1cN2M0)	6	
3A(T2aN2M0)		3A(T2aN2M0)		
3A(T4N0M0)		3A(T4N0M0)		
3A(T4N1M0)		3A(T4N1M0)		
3B(T4N2M0)	2	3B(T4N2M0)	2	

Discussion

Multiple primary lung cancer refers to the synchronous or metachronous detection of more than one primary lung cancer in a single patient. The survival rate of these patients is lower than those with primary lung cancer. Accurate identification, staging and treatment planning of cases with MPLC are of great importance for the prognosis of the disease. Therefore, it is of great importance to identify prognostic factors and select high-risk patients who need aggressive adjuvant therapy[3].

The 8th edition of the lung cancer TNM staging system was created to more accurately predict the prognosis in lung cancer and better guide lung cancer treatment options[4-6].

The main finding of our study is that T descriptors were defined as independent prognostic factors for survival in the seventh and eighth edition of TNM staging system. In synchronous tumors, statistically significant differences were found only in the seventh edition in the survival analyzes in terms of T descriptors and stages in the first operations ($p<0.05$), however, we could not detect a significant difference in survival analyzes in terms of T descriptors and stages in the eighth edition in synchronous tumors and in both the seventh and eighth editions in metachronous tumors ($p>0.05$). Studies show that the T descriptors in the TNM8 staging system are superior to the seventh edition in lung cancer as they are detailed, and it is a more accurate approach in terms of survival[4-6]. However, since the number of patients with synchronous and metachronous lung tumors is low, comparisons of MPLCs cannot be made in the literature.

Tumor size is an important prognostic factor for long-term survival in lung cancer. Wu Y et al.[7] studied a cohort of patients with previously resected non-small cell lung cancer who developed a second primary lung cancer; and found that the 5-year survival for patients with a tumor size of >1cm of the second primary lung cancer was worse than for patients with a tumor size of <1cm. In our study, in accordance with the literature, 5-year overall survival rates of patients with pathological tumor size ≤2cm were 66.7% in the synchronous lung cancer patient group and 80% in the metachronous lung cancer patient group, and 5-year overall survival rates of patients with a tumor size of >7cm were 50% in the synchronous lung cancer patient group and 75% in the metachronous lung cancer patient group, respectively; but no statistically significant difference was found ($p>0.05$).

Although there was no change in the TNM8 staging in the classification of the cases according to the N parameter, the N parameter caused a change in the case stage. Studies have shown that the frequency of lymph node involvement is higher in large tumors than in small tumors[8]. Liu et al.[9] reported that the incidence of lymph node metastasis as 9% in patients with tumor size <1 cm, as 18% in tumors between 1-1,5 cm, and as 25% in tumors >1.5 cm in size. In our study, a statistically significant difference was found between lymph node groups in terms of survival in TNM8 staging system in synchronous and metachronous lung cancers ($p<0.05$).

When the distribution of early stage cases in synchronous tumors was evaluated, 1 patient in Stage IB according to TNM7 was staged as stage 2A in the TNM8 staging system. In metachronous tumors, 4 patients in Stage IB according to TNM7 were staged as Stage 2A according to TNM8. In the comparison of the number of cases between the staging, it was observed that the number of cases in Stage IB decreased in the TNM8 staging system and these cases progressed to the advanced stage.

In addition, more synchronous tumors were progressed to advanced stages according to the seventh and eighth edition of TNM staging. However, the survival difference was found to be more significant in TNM7 staging in synchronous tumors. We think that the reason for this is that a large tumor is staged at a lower stage in TNM7 staging.

Patients with synchronous and metachronous tumors have a better prognosis than patients with metastases. The 5-year survival of patients with synchronous tumors is lower than that of metachronous tumors. Metachronous MPLCs should be considered as separate tumors and a separate prognosis for each disease should be described. In synchronous MPLCs, if the surgery of the second primary tumor is curative, 5-year survival is 30% and 10-year survival is 20%[2]. In our study, 3-year survival rate was 61%, while 5-year survival rate was 61% and overall survival rate was 70% in synchronous lung cancer, while in metachronous lung cancer, the 3-year survival rate was 80%, the 5-year survival rate was 62%, and the overall survival rate was 31.4%.

Conclusion

In this study based on data from a single center, we included only patients who had undergone surgery for multiple primary lung cancer. In our study, when T-stage, N-stage and general stages were evaluated in both the TNM7 staging and the TNM8 staging that we started to use recently, each in itself was seen to indicate a worse survival as the stage progressed. However, due to the insufficient number of our patients, we could not detect a significant difference

in survival analyzes in terms of T descriptors and stages in the eighth edition (p>0.05). In our study, we found a statistically significant difference in survival between lymph node groups in the TNM8 staging system only in patients who underwent surgery for multiple primary lung cancer (p<0.05).

Although the number of patients is small, lymph node staging in the TNM8 staging system is found to be more sensitive for survival in patients who have undergone surgery for multiple primary lung cancer.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: E.E.K., C.A.B.; Design: E.E.K., İ.Y.; Supervision: M.A., R.S.E., A.L.A.; Materials: E.E.K., C.A.B.; Data Collection or Processing: E.E.K., M.A.; Analysis or Interpretation: E.E.K., C.A.B., İ.Y; Literature Search: E.E.K., C.A.B.; Writing: E.E.K., C.A.B.; Critical Review: R.S.E., A.L.A., İ.Y.

Conflict of Interest: None declared.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Schwartz AG, Cote ML. Epidemiology of lung cancer. Adv Exp Med Biol 2016;893:21–41.
2. Martini N, Melamed MR. Multiple primary lung cancers. J Thorac Cardiovasc Surg 1975;70:606–12.
3. Shintani Y, Okami J, Ito H, Ohtsuka T, Toyooka S, Mori T, et al. Clinical features and outcomes of patients with stage I multiple primary lung cancers. Cancer Sci 2021;112:1924–35.
4. Rami-Porta R, Bolejack V, Crowley J, Ball D, Kim J, Lyons G, et al. The IASLC lung cancer staging project: Proposals for the revisions of the T descriptors in the forthcoming eighth edition of the TNM classification for lung cancer. J Thorac Oncol 2015;10:990–1003.
5. Asamura H, Chansky K, Crowley J, Goldstraw P, Rusch VW, Vansteenkiste JF, et al. The international association for the study of lung cancer lung cancer staging project: Proposals for the revision of the N descriptors in the forthcoming 8th edition of the TNM classification for lung cancer. J Thorac Oncol 2015;10:1675–84.
6. Eberhardt WE, Mitchell A, Crowley J, Kondo H, Kim YT, Turrisi A 3rd, et al. The IASLC lung cancer staging project: Proposals for the revision of the M descriptors in the forthcoming eighth edition of the TNM classification of lung cancer. J Thorac Oncol 2015;10:1515–22.
7. Wu Y, Han C, Chong Y, Liu J, Gong L, Wang Z, et al. Prognostic study for survival outcome following the treatment of second primary lung cancer in patients with previously resected non-small cell lung cancer. Thorac Cancer 2020;11:2840–51.
8. Jin Y, Chen M, Yu X. Comparison of the 7(th) and proposed 8(th) editions of the AJCC/UICC TNM staging system for non-small cell lung cancer undergoing radical surgery. Sci Rep 2016;6:33587
9. Liu T, Liu H, Li Y. Systematic lymph node dissection is necessary for T1a non-small cell lung cancer. Asia Pac J Clin Oncol 2015;11:49–53.