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ORIGINAL ARTICLE

Prognosis of stage pIIIA non small cell lung cancer after mediastinal lymph node dissection or sampling

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Summary

Purpose: *The aim of this study was to define the impact of systematic mediastinal lymph node dissection (MLD) and mediastinal lymph node sampling (MLS) on the long-term results of patients suffering from non-small cell lung cancer (NSCLC) with N2 disease (pIIIA/N2).*

Patients and methods: *From 1999 to 2002, patients with NSCLC in stage pIIIA/N2 were retrospectively classified according to MLD or MLS procedure. Several clinical and pathological factors such as overall survival, disease-free interval, and complications were recorded and analyzed.*

Results: *Ninety-seven (64%) patients were subjected to MLD and 54 (35%) to MLS. Comparison between the two studied groups disclosed more frequent detection of one station pN2 nodes in MLS specimens ($p < 0.001$), while skip metastasis was more often encountered after MLD ($p=0.05$). Duration of the operation, amount of postoperative bleeding and incidence of prolonged air leak were not significantly different between MLD and MLS groups. Cox regression analysis of all cases disclosed squamous histology as the only favorable factor of survival. The disease-free interval was significantly longer after MLD ($p < 0.001$).*

Conclusion: *Although radical lymphadenectomy did not offer significant prolongation of survival, the disease-free interval was significantly longer after MLD compared with MLS.*

Key words: lymph node metastasis, mediastinal nodal dissection, mediastinal lymph node sampling, non-small cell lung cancer

Introduction

The presence or absence of lymph node metastasis is the single most important factor for estimating the possibility of disease recurrence and prognosis after surgical treatment of NSCLC. Unsuspected N2 disease plays a central role for postoperative decision-making concerning the use of adjuvant therapy and for prognosis.

The extend of lymphadenectomy after lung resection for NSCLC remains controversial as in other types of solid tumors. Although radical systematic MLD is considered by many thoracic surgeons to be the procedure of choice [1-4], there are still several others that recommend only sampling (MLS) of N2 lymph nodes [5-7].

The authors conducted this retrospective analysis in order to study the effect of MLD and MLS on the prognosis of patients suffering from NSCLC with metastatic disease to the mediastinal lymph nodes.

Patients and methods

From January 1999 to December 2002, patients with NSCLC in stage pIIIA/N2 due to metastatic N2 disease were the target study group. All of them were preoperatively staged by different means of chest imaging (radiograph, computed tomography/CT, magnetic resonance imaging/MRI) and invasive procedures (mediastinoscopy, anterior mediastinotomy, etc). The indication for mediastinoscopy was the detection of enlarged mediastinal lymph nodes at preoperative

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chest CT scan. The pIIIA/N2 group consisted of 151 patients submitted to 49 (32.5%) pneumonectomies and 102 (67.5%) lobectomies. These were cases of unsuspected N2 disease, i.e. metastatic lymphadenopathy was preoperatively not detected and was documented at the postoperative pathology results. All cases with clinical (c) N2 disease were administered induction chemotherapy protocol and were excluded from the study. All the operations performed were radical (pR0). Postoperatively all patients were subjected to cisplatin-based adjuvant chemotherapy.

Patients in stage IIIA/N2 were grouped according to MLD (group A) or MLS (group B) procedure. Since no survival benefit has ever been proved for either MLD or MLS, there was no consensus in our team for a common policy. MLD was defined as the *en-bloc* removal of all ipsilateral lymph nodes along with the surrounding fat tissue, while MLS as the systematic sampling from all ipsilateral mediastinal lymph node stations. Specifically, number 2, 4 and 7 were sampled for right upper and middle lobectomy, number 7, 8 and 9 for either right or left lower lobectomy and 2, 4, 5, 6 and 7 in case of left upper lobectomy. No case of MLS was converted to MLD. The sites of the mediastinal lymph nodes were named according to lymph node map for NSCLC proposed by Naruke et al [8]. Specifically numbers 1-6 were designated as upper mediastinal lymph nodes (UMLN) whereas 7-9 as lower mediastinal lymph nodes (LMLN).

Age, gender, type of resection, right or left lesion, T status, primary tumor location, histology, N2 node level and number of stations involved, skip metastasis status and overall survival were recorded and analyzed. The N2 lymph nodes were classified according to their stage, level, number of stations involved and skip metastasis occurrence (Table 1).

Duration of operation and complications such as postoperative bleeding rate and prolonged air leak were recorded. The results were analyzed and compared between groups A and B.

Survival analysis referred to the 3-year survival rate of MLD and MLS groups, since the study has not matured for 5-year survival estimation. Survival was studied according to age, gender, type of resection, right or left lesion, T status, primary tumor location, and histology. Moreover, survival was analyzed according to N2 node level, number of stations involved and skip metastasis status.

Statistical methods

Statistical analysis was performed using Student's t-test (otherwise the Wilcoxon rank-sum test) and chi-square (Fisher's exact test when needed) test where appropriate. Survival was calculated by the Kaplan-Meier method including all cancer-related deaths and excluding all postoperative ones. The records of all patients entered into multivariate Cox regression analysis to test the relationship of survival to age, gender, type of resection, MLD, MLS, right or left lesion, T status, TNM stage, primary tumor location, histology, number of stations involved and skip metastasis status.

Table 1. Mediastinal lymph node (N) metastasis results

	MLD/N2 n=97 n (%)	*MLS/N2 n=54 n (%)*	*p-value*
N status			
One station	10 (10)	29 (54)	$p < 0.001$
≥ 2 stations	87 (90)	29 (54)	$p < 0.05$
N level			
Upper	57 (58)	35 (65)	NS
Lower	20 (21)	12 (22)	NS
Upper + Lower	20 (21)	7 (13)	NS
Skip metastasis	34 (35)	10 (18.5)	NS

MLD: mediastinal lymph node dissection, MLS: mediastinal lymph node sampling, NS: non significant

Results

Among 151 cases with positive mediastinal lymph nodes ($pN2^+$), 97 (64%) were subjected to MLD (MLD/N2) and 54 (35%) to MLS (MLS/N2). Patient characteristics of both groups are detailed in Table 2. Statistical comparison between group A and B disclosed that MLD was more commonly performed after lobectomy ($p < 0.05$) and MLS after pneumonectomy ($p < 0.05$). T2 status was more often encountered in the MLS group ($p < 0.05$) and T3 in the MLD group ($p < 0.05$).

The characteristics of the detected positive lymph nodes detected are summarized in Table 2. Comparison between the findings of the two studied groups disclosed more frequent detection of one station pN2 nodes in the MLS specimens ($p < 0.001$), while ≥2 stations N2 disease was more often encountered after MLD ($p < 0.001$).

The duration of the operation, the amount of postoperative bleeding and the incidence of prolonged air leak were not significantly different between MLD and MLS groups (Table 3).

Although not statistically significant, survival analysis showed better results after MLD than after MLS (29 vs. 26%, respectively). Three-year survival according to several clinicopathological parameters is fully described in Tables 4 and 5. No statistically

Table 2. Comparative characteristics of patients with N2 positive lymph nodes

	MLD/N2 n=97 n (%)	*MLS/N2 n=54 n (%)*	*p-value*
Gender			
Male	81 (83.5)	44 (71.5)	NS
Female	16 (16.5)	10 (18.5)	NS
Type of resection			
Pneumonectomy	59 (61)	43 (80)	<0.05
Lobectomy	38 (39)	11 (20)	<0.05
Side			
Right	58 (60)	34 (63)	NS
Left	49 (40)	20 (37)	NS
T status			
T1	1 (1)	3 (5.5)	NS
T2	51 (52.5)	39 (72)	<0.05
T3	45 (46.5)	12 (22.5)	<0.05
Primary tumor location (lobe)			
RU	26 (27)	14 (26)	NS
RL+RM	32 (33)	20 (37)	NS
LU	26 (27)	14 (26)	NS
LL	13 (13)	6 (1)	NS
Histology			
Adeno Ca	40 (41)	31 (57.5)	NS
Squamous Ca	52 (54)	20 (37)	NS
Other	5 (5)	3 (5.5)	NS

MLD: mediastinal lymph node dissection, MLS: mediastinal lymph node sampling, NS: non significant, RU: right upper, RL: right lower, RM: middle, LU: left upper, LL: left lower, Ca: carcinoma

significant difference between MLD and MLS groups was recorded. Survival according to N status revealed comparable results for MLD and MLS groups except the subclassification of one station pN2 nodes where MLD proved superior to MLS ($p < 0.05$).

Cox regression analysis (Table 6) of all cases disclosed squamous histology as the only favorable factor of survival (p=0.03, odds ratio 0.05, 95% CI 0.32-0.47).

Table 3. Technical characteristics and complications

	MLD/N2 n=97 n (%)	*MLS/N2 n=54 n (%)*	*p-value*
Mean duration of operation (min)	150	137	NS
Bleeding	9 (9.2)	3 (5.5)	NS
Prolonged air leak	12 (12.4)	4 (7.4)	NS

For abbreviations see footnote of Table 2

The rate of local recurrence and distant metastasis was not statistically different between the two groups (Table 7). However, the disease-free interval was significantly longer after MLD than after MLS ($p < 0.001$).

Table 4. 3-year survival analysis

	MLD/N2 n=97 n (%)	*MLS/N2 n= 54 n (%)*	*p-value*
	28 (29)	14 (26)	NS
Gender			
Male	25 (31)	9 (23)	NS
Female	3 (25)	5 (26.3)	NS
Type of resection			
Pneumonectomy	11 (29)	3 (27.2)	NS
Lobectomy	17 (29)	1 (25.6)	NS
Side			
Right	18 (31)	8 (23.5)	NS
Left	10 (25.6)	6 (30)	NS
T status			
T1	0 (0)	2 (50)	NS
T2	19 (37)	9 (21.4)	NS
T3	9 (20)	1 (12.5)	NS
Primary tumor location (lobe)			
RU	6 (23)	3 (21.4)	NS
RL+RM	9 (28)	6 (30)	NS
LU	8 (30.7)	3 (21.4)	NS
LL	5 (38.5)	2 (33.3)	NS
Histology			
Adeno Ca	12 (30)	7 (22.5)	NS
Squamous Ca	15 (29)	7 (35)	NS
Other	1 (20)	0 (0)	NS

For abbreviations see footnote of Table 2

Table 5. 3-year survival according to the number of stations and the location of positive mediastinal lymph nodes

	MLD/N2 n=97 n (%)	*MLS/N2 n=54 n (%)*	*p-value*
One station	7 (70)	8 (27.5)	<0.05
≥2 stations	23 (26.4)	6 (24)	NS
N level			
Upper	20 (35)	10 (28.5)	NS
Lower	5 (25)	3 (25)	NS
Upper + Lower	3 (15)	1 (14)	NS
Skip metastasis	13 (38)	3 (30)	NS

For abbreviations see footnote of Table 2

Table 6. Cox regression analysis of survival

Variable	*Odds ratio*	*95% CI*	*p-value*
Age	0.6610	0.4410-0.9908	0.0450
Gender	1.7035	1.1521-2.5188	0.5549
Type of resection	0.9934	0.6985-1.4128	0.9707
MLD	1.2987	0.9430-1.7887	0.1095
Right side	0.8986	0.6120-1.3194	0.5852
T1	1.1606	0.6811-1.9779	0.839
T2	1.6743	0.7359-3.8094	0.2191
T3	1.4159	0.8429-2.3785	0.1888
Squamous Ca	0.05	0.32-0.47	0.03
Adeno Ca	1.3139	0.8687-1.9873	0.1959
Other histology	1.1837	0.7993-1.7528	0.3999
Number of node stations	0.8890	0.5833-1.3549	0.5841
Skip metastasis	0.6427	0.3998-1.0330	0.679

MLD: mediastinal lymph node dissection, 95% CI: 95% confidence interval

Table 7. Oncologic outcome

	MLD n= 97 n (%)	*MLS n= 54 n (%)*	*p-value*
Median disease-free interval, months (range)	34 (7-46)	22 (2-35)	p <0.001
Local recurrence	40 (41)	26 (48)	NS
Distant metastasis	37 (38)	25 (46)	NS

For abbreviations see footnote of Table 2

Discussion

Mediastinal lymph node metastasis is one of the most serious prognostic factors in bronchogenic carcinoma. N2 group is an extremely heterogeneous one and IIIA (N2) stage is characterized by several subgroups with variable survival rates. For example number 5, 6 N2 nodes have better prognosis, cN2 worse than the respective unsuspected pN2, single vs. multiple N2 stations, the number of involved lymph nodes, the extracapsular spread, the presence of subcarinal node metastasis, skip metastasis, etc. Each of these subclassifications should be considered as a completely different subpopulation of positive mediastinal lymph nodes. This means that, in order to accurately determine the patient's N status, the largest possible number of the mediastinal lymph nodes should be available to the pathologist.

However, the intraoperative approach to the mediastinal lymph node is controversial in patients with apparently resectable NSCLC. The first radical mediastinal lymphadenectomy was reported in 1951 by Cahan and associates [9]. Clues in favor of radical MDL are improved survival rates and more precise staging [2, 4,9-11]. On the contrary, one major argument against MLD is higher morbidity [5,6].

Although MLD and MLS showed comparable survival rate for pN2 cases, MLD offered better 3-year survival for one station pN2. The difference in survival according to N status should be interpreted as more accurate staging with MLD. The worse survival of MLS patients with one N2 station compared to MLD patients means that MLS patients are incorrectly characterized as having one station and they probably have multistational N2. This fact has been missed due to inaccurate N status staging because of residual N2 disease left behind after MLS. On the contrary, in the MLD group one N2 station and skip metastasis findings represent the real N status. Furthermore, the superiority of MLD was also clearly documented even in cases with not advanced local disease (T1 and T2). Sampling was not sufficient for an accurate evaluation of N2 disease, since in the MLS group a positive lymph node might have been left behind. Patients subjected to MLS might be considered as under staged. Even small tumors might involve mediastinal lymph nodes with metastatic disease [12,13]. Skip metastasis, as well as micrometastasis [14], are two examples that MLD should be performed in order to estimate these two conditions. This might be interpreted as superiority of MLD for more accurate intraoperative staging. It is beyond any argument that macroscopic intraoperative evaluation of lymph node metastasis is an unreliable method [15]. Under these circumstances sampling might lead to miss a skip lesion and consequently to erroneous pathological interpretation (understaging) [16]. This has deleterious effects on decision-making based on estimated prognosis, life expectancy and on evaluating the possibility for adjuvant therapies.

The duration of the operation, the amount of postoperative bleeding and the incidence of prolonged air leak were not significantly different between MLD and MLS groups. This is in accordance to previous reports [16-18]. Potential complications of MLS and MLD that may arise are bronchopleural fistula due to interruption of the blood supply to the bronchial stump, injury to the recurrent laryngeal nerve (especially the left one) hemothorax and chylothorax.

The significance of lymphadenectomy on the long-term outcome is still controversial. In our study multivariate analysis did not disclosed MLD as an independent favorable factor for long-term survival. Recent randomized and nonrandomized trials showed that survival might be prolonged when complete lymphadenectomy is performed [16-21].

There are two major deficiencies in this study: firstly, the retrospective nature of the study and secondly the small number of patients that does not provide clear statistical evidence. However, there is a trend towards improved survival rates and longer disease-free interval for the patients with unsuspected N2 disease, who were subjected to MLD.

Although the rate of local recurrence and distant metastasis was not statistically different between the two groups, the disease-free interval was significantly longer after MLD than after MLS. Apart from stage migration, the failure of MLD to improve survival indicates that N2 disease signifies a systematic disease with a dismal outcome. Radical lymphadenectomy did not offer significant prolongation of survival. However, the removal of all affected mediastinal tissues contributed to the prolongation of disease-free survival of patients in stage IIIA. The latter is an important parameter in thoracic surgical oncology.

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