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FULL PAPER

Pattern of lymph node metastases and its implication in radiotherapeutic clinical target volume in patients with non-small-cell lung cancer: a study of 2062 cases

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Objective: To study the pattern of lymph node metastasis (LNM) of non-small-cell lung cancer (NSCLC) and to clarify which node level should be included while undergoing radiotherapy (RT).

Methods: A total of 2062 patients with NSCLC patients who had undergone thoracotomy were retrospectively examined. The clinicopathological factors related to LNM were analysed.

Results: The LNM rates (the number of node-positive patients/the total number of patients) in patients with primary tumours in different lobes (left upper lobe, left lower lobe, right upper lobe, right middle lobe and right lower lobe) were 53.25%, 53.87%, 53.77%, 64.67% and 61.58%, respectively. We have found that in all of the clinicopathological factors, including sex, age, tumour location, histological type, maximum diameter, T stage, degree of differentiation and tumour growth pattern, only

maximum diameter ($p = 0.336$) and histological type ($p = 0.360$) did not have significant correlation with LNM rate. All of the above factors except tumour growth pattern ($p = 0.239$) and maximum diameter ($p = 0.613$) were significantly associated with lymph node ratio [LNR, ratio between metastatic and examined lymph nodes (LNs)] in linear regression.

Conclusion: For patients with NSCLC, LNM rate and LNR can be recommended as applicable parameters for LN involvement. Multiple clinicopathological factors should be considered comprehensively to design the clinical target volume for RT of NSCLC.

Advances in knowledge: This article can provide evidence to radio-oncologists how to choose range of lymph nodal clinical target volume when they are treating inoperable patients with NSCLC patients by analysing data of patients after surgery.

INTRODUCTION

Lung cancer is the most commonly diagnosed cancer as well as the leading cause of cancer death globally. >1.6 million (13%) new lung cancer cases are diagnosed each year, causing approximately 1.4 million (18%) deaths annually.¹ Approximately, 85% of patients with lung cancer will be non-small-cell lung cancer (NSCLC), of which about 60–76% required radiotherapy (RT) at least once during their course of diseases.² The pattern of lymph node metastases (LNMs) is one of the major factors influencing overall survival rate, which affect the therapeutic decision-making for NSCLC. In the present study, we wish to elucidate the pattern of LNM in patients with NSCLC who have undergone thoracotomy with systematic lymphadenectomy, to help the patients without surgery for their lymph nodal clinical target volume (CTVn) delineation. Thus, the predictors of

LNM on radiotherapeutic CTVn delineation in NSCLC were investigated.

METHODS AND MATERIALS

Patients

We retrospectively studied 2062 patients with NSCLC who had undergone thoracotomy with systematic lymphadenectomy at the Department of Thoracic Surgical Oncology in Shandong Cancer Hospital (Jinan, China) from January 2000 to December 2011. The pre-operative work-up included complete history, physical examination, basic blood tests and cardiopulmonary functional evaluation. CT of the chest, ultrasonography/CT of the abdomen, MRI/CT of the brain and bone scintigraphy had been performed to evaluate the respectability of the primary tumour and to exclude distant organ metastases. Other essential conditions such as no distant metastases, no pre-operative chemotherapy

Table 1. Clinicopathological features of 2062 patients with non-small-cell lung cancer

Characteristics	Number of cases (%)
Sex	
Male	1475 (71.5)
Female	587 (28.5)
Age (years)	
≤60	1171 (56.8)
>60	891 (43.2)
Tumour location	
Left upper lobe	477 (23.1)
Left lower lobe	401 (19.4)
Right upper lobe	529 (25.7)
Right middle lobe	150 (7.3)
Right lower lobe	505 (24.5)
Histological type	
Squamous cell carcinoma	796 (38.6)
Adenocarcinoma	912 (44.2)
Adenosquamous carcinoma	160 (7.8)
Large cell carcinoma	80 (3.9)
Other types	114 (5.5)
Tumour growth pattern	
Central lung cancer	770 (37.3)
Peripheral lung cancer	1292 (62.7)
Maximum diameter (cm)	
≤3.0	656 (31.8)
3.1–5.0	794 (38.5)
5.1–7.0	378 (18.4)
>7.0	234 (11.3)
T stage	
T1	202 (9.8)
T2	1082 (52.5)
T3	629 (30.5)
T4	149 (7.2)
Differentiation	
Well	267 (12.9)
Moderately	1034 (50.2)
Poorly	761 (36.9)
Type of surgery	
Lobectomy	1582 (76.7)
Bilobectomy	317 (15.4)
Pneumonectomy	163 (7.9)

(Continued)

Table 1. (Continued)

Characteristics	Number of cases (%)
Number of nodes dissected	
1–10	1032 (50.1)
>10	1030 (49.9)

and/or RT, and informed consents were obtained before treatment. Sex, age, tumour location, histological type, T stage, maximum diameter, degree of differentiation, tumour growth pattern, surgery type, number of lymph nodes (LNs) dissected and number of positive LNs were recorded.

Operative procedures

The type of surgery depended on the location and extent of the primary tumour. Patients who underwent lobectomy, bilobectomy or pneumonectomy with systematic lymphadenectomy were enrolled in this study. After surgery, *en bloc* dissected tissues were separated into each LN precisely. All resected specimens, including the primary tumour and hilar/mediastinal LNs, were examined to determine both the tumour histology and the extent of LNM.

Pathological analysis and lymph node classification

The resection specimens were evaluated pathologically using a standardized protocol in which the resection margins, the gross sample and regional LNs were extensively sampled. The histological types were determined using the new World Health Organization classification of lung tumours as squamous cell carcinoma (SCC), adenocarcinoma (Ac), adenosquamous carcinoma (ASc), large cell carcinoma (LCc) and other types.³ The locations of LNs and T stages were determined according to the seventh editions of the Union for International Cancer Control/American Journal of Critical Care staging manuals for NSCLC.⁴ In the present study, we grouped the dissected N2 nodes into four zones:⁵ *upper zone* included the highest mediastinal nodes (No. 1), upper paratracheal nodes (No. 2), pre-vascular and retrotracheal nodes (No. 3), and lower paratracheal nodes (No. 4); *aorto-pulmonary (AP) zone* included subaortic nodes (aorto-pulmonary window, No. 5) and para-aortic nodes (ascending aorta or phrenic, No. 6); *subcarinal zone* included subcarinal nodes (No. 7); and *lower zone* included paraoesophageal nodes (below carina, No. 8) and pulmonary ligament nodes (No. 9). Additionally, we grouped the dissected N1 nodes into two zones: *hilar zone* included hilar nodes (No. 10) and interlobar nodes (No. 11); *peripheral zone* included lobar nodes (No. 12) and segmental nodes (No. 13).

Statistics

The clinicopathological factors likely to influence LNM rate (the number of node-positive patients/the total number of patients) and LN ratio (LNR, ratio between metastatic and examined LNs) of NSCLC were all entered into statistical analysis. Univariate logistic analysis was used to determine the relationship between each clinicopathological factor and LNM rate/LN ratio. For multivariate analysis, the forward

Figure 1. Lymph node (LN) zoning and total LN metastasis rate/LN ratio (%) to 1–13 stations. AP, aorto-pulmonary. Adapted from Rusch et al⁶ with permission from Wolters Kluwer Health Inc.

step-wise procedure was performed using a binary logistic regression model containing all statistically significant variables in univariate analysis ($p < 0.05$). Linear regression analysis was used to assess the relationships between above-mentioned factors and LNR. A statistically significant difference was set as $p < 0.05$. Statistical analysis was performed using SPSS® v. 16.0 for Windows (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL), and all statistical tests were two sided.

RESULTS

Patients and clinicopathological features

A total of 1475 (71.5%) males and 587 (28.5%) females with a median age of 59 years (mean: 58.31 ± 9.951 years, range 11–83 years) were investigated. Primary tumours were located in the left upper lobe (LUL) in 477 (23.1%) patients, left lower lobe (LLL) in 401 (19.4%) patients, right upper lobe (RUL) in 529 (25.7%) patients, right middle lobe (RML) in 150 (7.3%) patients and right lower lobe (RLL) in 505 (24.5%) patients. The clinicopathological characteristics of 2062 patients are shown in Table 1.

Overall pattern of metastases

A total of 24304 LNs were resected with a median value of 10 (mean: 11.8; range 1–49) in all patients. The overall LNM rate was 56.4% (1162/2062), while LNR was 21.7% (5273/24304). In general, the LNM rates varied between 0.4% and 27.1% (Station 11) in 1–13 stations (Figure 1). According to LN zoning, the LNM rates varied between 2.8% and 51.3% (hilar zone). While LNR was varied between 9.0% and 25.2% (peripheral zone, Table 2). Pathological results after surgery showed that there were 574/2062 (27.8%) patients with a N2 LN staging, including 381/574 (66.3%) patients with a pre-operative staging for N2. Also, there were 73 (3.5%) patients who had a skip LN metastasis, including 52/73 (71.2%) patients who were ≤ 60 years old ($p < 0.05$) (Figure 1).

Tumour location and lymph node metastases

The LNM rates in patients with lesions in different lobes (LUL, LLL, RUL, RML and RLL) were 53.3% (254/477), 53.9% (216/401), 53.9% (284/529), 64.7% (97/150) and 61.6% (311/505), respectively. The LNR in different lobes were 19.2%, 22.6%, 19.6%, 28.5% and 24.4%, respectively.

From Table 2, we can find no matter which lobe the tumour located in, the most commonly involved LN zone was always hilar zone. In addition, our research showed that the involved LN zones roughly correlated with tumour location. We set 15% as the threshold value. To the LUL NSCLC, the higher rate of LNM appeared in hilar zone (50.7%) and AP zone (24.7%). To LLL tumours, higher rate exists in hilar zone (55.6%), and the rate of subcarinal zone (14.7%) was close to the standard. To RUL tumours, higher rate appeared in hilar zone (49.9%) and upper zone (35.5%). To both RML and RLL tumours, the higher rate of LNM appeared in hilar zone (48.7%, 50.5%), upper zone (26.7%, 16.8%) and subcarinal zone (20.7%, 27.3%) (Table 2).

From Figure 2, we can find that Station 10/11 was relatively high-incidence stations for all locations of tumours (LUL 31.7%/19.1%, LLL 22.9%/32.7%, RUL 26.8%/23.1%, RML 19.3%/29.3% and RLL 16.6%/33.9%, respectively), while Station 1, 8 and 13 were relatively less involved (Figure 2).

Factors associated with lymph node metastases

Univariate analysis showed that all of the 10 clinicopathological factors, including sex, age, tumour location, histological type, maximum diameter, T stage, degree of differentiation, tumour growth pattern, surgery type and number of LN dissected, showed obviously significant correlations with LNM rate as well as LNR of NSCLC (Table 3).

Table 2. Lymph node metastasis (LNM) rate (%) and lymph node ratio (LNR) (%) to different zones according to the location of primary tumour

Tumour location/LN zoning	Upper zone		AP zone		Subcarinal zone		Lower zone		Hilar zone		Peripheral zone	
	LNM rate	LNR	LNM rate	LNR	LNM rate	LNR	LNM rate	LNR	LNM rate	LNR	LNM rate	LNR
Left upper lobe	9.4 (45/477)	24.5 (80/326)	24.7 (118/477)	23.5 (265/1126)	5.0 (24/477)	10.3 (55/532)	1.7 (8/477)	3.7 (21/468)	50.7 (242/477)	20.6 (709/3443)	2.1 (10/477)	18.5 (28/151)
Left lower lobe	3.0 (12/401)	32.5 (25/77)	10.5 (42/401)	16.2 (84/518)	14.7 (59/401)	22.7 (142/627)	9.2 (37/401)	11.7 (54/462)	55.6 (223/401)	25.3 (643/2543)	2.0 (8/401)	31.7 (26/82)
Right upper lobe	35.5 (188/529)	24.2 (429/1770)	2.5 (13/529)	39.6 (40/101)	7.0 (37/529)	9.2 (97/1060)	1.9 (10/529)	6.4 (16/250)	49.9 (264/529)	20.6 (698/3386)	2.8 (15/529)	25.3 (25/99)
Right middle lobe	26.7 (40/150)	32.4 (115/355)	1.3 (2/150)	100.0 (10/10)	20.7 (31/150)	21.1 (68/322)	1.3 (2/150)	12.1 (4/33)	48.7 (73/150)	29.2 (197/675)	4.7 (7/150)	37.5 (15/40)
Right lower lobe	16.8 (85/505)	22.7 (193/849)	1.0 (5/505)	34.2 (13/38)	27.3 (138/505)	20.7 (338/1630)	6.1 (31/505)	13.4 (41/307)	50.5 (255/505)	28.0 (803/2868)	3.4 (17/505)	25.0 (39/156)
Total	17.9 (370/2062)	24.9 (842/3377)	8.7 (180/2062)	23.0 (412/1793)	14.0 (289/2062)	16.8 (700/4171)	4.3 (88/2062)	9.0 (136/1520)	51.3 (1057/2062)	23.6 (3050/12915)	2.8 (57/2062)	25.2 (133/528)

Bold values indicate values greater than the 15% threshold value set.

Since the aim of our study was to guide the delineation of CTVn for the patient who did not accept surgical treatment, we excluded two factors: surgical type and number of LN dissected. The rest of eight variables were enrolled in the multivariate logistic regression (for LNM rate) and linear regression analysis (for LNR). We have found that the only maximum diameter ($p = 0.336$) and histological type ($p = 0.360$) were excluded in multivariate logistic regression analysis (Table 4). In terms of linear regression analysis, all of the above factors but maximum diameter ($t = -0.506$, $p = 0.613$) and tumour growth pattern ($t = -1.178$, $p = 0.239$) were significantly associated with LNR (Table 5).

As shown in Table 4, the LNM rate was 1.32 [95% confidence interval (CI): 1.06–1.64] times greater for female patients than for male patients. Similarly, LNM rate decreased with elderly patients [Odds ratio (OR) 0.65, 95% CI: 0.54–0.78] and the reducing of differentiation degree (OR 1.43, 95% CI: 1.24–1.64) and increased with the elevating of T stage (OR 1.43, 95% CI: 1.27–1.63). We can also get the results that the LNM rate of histological type and tumour location sorted in descending order: LCc > Ac > ASc > SCc > other types; RML > RLL > RUL > LLL > LUL. In terms of linear regression analysis, the order was roughly similar to the results of logistic regression analysis.

DISCUSSION

Lung cancer is usually diagnosed at a regionally advanced or incurable metastatic stage. Local control is very essential in NSCLC treatment.⁷ The advanced technology, such as three-dimensional conformal radiotherapy (3D-CRT)/intensity modulated radiotherapy (IMRT), provides increased precision but requires accurate target volume. In this study, we analysed the pattern of LNM of patients with NSCLC who had undergone thoracotomy with systematic lymphadenectomy, to obtain useful information on how to define radiotherapeutic CTVn of patients with NSCLC.

At present, there are three perspectives on regional nodal irradiation: conventional elective nodal irradiation (ENI), selective nodal irradiation and involved-field RT (IFRT). The theoretical basis of ENI was the existence of occult mediastinal metastases, which cannot be detected with clinically existed methods.⁸ In recent years, however, many researchers suggested that compared with ENI, IFRT did not increase nodal failure rates in clinically uninvolved nodal areas.⁹ While some researchers believed that this was because of the existence of an incidental radiation “cloud” around the planning target volume (PTV) with 3D-CRT/IMRT in which the dose may have significant cancericidal effect in “intermediate/low-risk” target volumes.¹⁰ However, Rosenman et al¹¹ believed that “selective elective” nodal RT for NSCLC may remain important. The present study showed that the likelihood of regional LNM increased when the patient was female, younger, the lesion was central lung cancer (CLC) or located in RML/RLL, the T stage and degree of differentiation was poor. A limitation in evaluating the association between clinicopathological factors and the number of positive LNs is that this relationship is inherently confounded by the number of resected LNs. To solve this limitation, LNR has been added to assess the situation of the extent of the involvement of LNs in several diseases, which also include NSCLC.^{12–15} The LNR could be looked upon as a more accurate assessment of prognosis.

Figure 2. Lymph node metastasis rate/lymph node ratio (%) to 1–13 stations according to different locations of the primary tumours. Adapted from Rusch et al⁶ with permission from Wolters Kluwer Health Inc.

Patients with a high LNR seem at a risk of worse outcomes and should be considered for more aggressive post-operative treatments.¹⁶ The result of our study showed that many factors, including sex, age, histological type, T stage, degree of differentiation and tumour location had significant correlations with LNR. These results are partially consistent with previously published studies.^{16,17} Few articles had reported that there were correlations between age/sex and LN metastatic rate. We found that the LN metastatic rate in younger female patients is higher than in older male patients. In particular, skip LN metastasis was more often founded in younger patients. This may be related to the higher degree of malignancy in younger patients. In our research, female patients have higher LN metastatic rate and LNR, maybe because in developing countries like China, when females get sick, they may postponed to visit a doctor if their family economic conditions are not good, while males are often the main labour in a family, so they can usually get an early treatment. In addition, we can also explain the sex results as sampling error. From the data, we also found that there were 574/2062 (27.8%) patients with a N2 LN staging after surgery, including 381/574 (66.3%) patients with a pre-operative staging for N2.

As mentioned earlier, many clinicopathological factors were related to LNM, thus, for a radiation oncologist, it is important

to get the information before delineating the target volume. For NSCLC, usually there were at least one or several areas, which are more vulnerable to involve, depending on the locations of the tumour.¹⁸ The results of our study suggest that for tumours located in different sites, radiation oncologists should design different radiotherapeutic CTVn. Hilar zone should be included in the CTVn no matter where the tumour located in. In addition, AP zone should be included when the tumour was in LUL, LLL tumours may include subcarinal zone (14.7%), RUL tumours should include upper zone, RML and RLL tumours should include both upper zone and subcarinal zone. In terms of LN stations, the results of this study suggest that apart from involved LN and 10–11 stations, the CTVn may include 5 stations for LUL tumours, 4 stations for RUL tumours and 7 stations for both RML and RLL tumours. 7 stations may be also considered entering into CTVn of LLL tumours because the LNM rate (14.71%) was nearly 15%. Nohl-Oser¹⁹ confirmed the findings that the upper lobe essentially drains to the homolateral mediastinum and rarely to the subcarinal LNs. The preferential pathways of drainage for lower lobe tumours are the subcarinal LNs. Our results were generally the same with their results.

The target in RT is the key factor to decrease local failure of NSCLC. The gross target volume (GTV) includes the primary tumour and

Table 3. Univariate analysis of the clinicopathological factors related to lymph node metastasis rate and lymph node ratio

Groups	Node-positive/negative cases	<i>p</i> -value	Positive/negative nodes	<i>p</i> -value
Sex				
Male	805/670	0.010	3459/14183	<0.001
Female	357/230		1814/4848	
Age (years)				
≤60	719/452	<0.001	3455/10153	<0.001
>60	443/448		1818/8878	
Tumour location				
Left upper lobe	254/223	0.007	1158/4888	<0.001
Left lower lobe	216/185		974/3335	
Right upper lobe	284/245		1305/5361	
Right middle lobe	97/53		409/1026	
Right lower lobe	311/194		1427/4421	
Histological type				
Squamous cell carcinoma	427/369	0.002	1566/8621	<0.001
Adenocarcinoma	542/370		2743/7256	
Adenosquamous carcinoma	95/65		430/1403	
Large cell carcinoma	50/30		277/816	
Other types	48/66		257/935	
Tumour growth pattern				
Central lung cancer	486/284	<0.001	2166/7234	0.028
Peripheral lung cancer	676/616		3107/11797	
Maximum diameter (cm)				
≤3.0	313/343	<0.001	1221/6063	<0.001
3.1–5.0	471/323		2271/7234	
5.1–7.0	243/135		1100/3605	
>7.0	135/99		681/2129	
T stage				
T1	78/124	<0.001	332/2140	<0.001
T2	602/480		2727/10861	
T3	371/258		1628/4980	
T4	111/38		586/1050	
Differentiation				
Well	121/146	<0.001	465/2497	<0.001
Moderately	572/462		2469/9488	
Poorly	469/292		2339/7046	
Type of surgery				
Lobectomy	819/763	<0.001	3496/14327	<0.001
Bilobectomy	218/99		1101/3049	
Pneumonectomy	126/37		676/1655	

(Continued)

Table 3. (Continued)

Groups	Node-positive/negative cases	<i>p</i> -value	Positive/negative nodes	<i>p</i> -value
Number of nodes dissected				
1–10	534/498	<0.001	1601/4788	<0.001
>10	629/401		3672/14243	

positive LNs. However, it is difficult to define clinical target volume (CTV) of patients with NSCLC accurately, and there is no explicit provision in RT how to define CTV. CTV includes two parts: sub-clinical invasion and intramural metastases of primary tumour (CTVp) and subclinical LN (CTVn). Our present study mainly focussed on the CTVn of patients with NSCLC. The results suggested that if radiation oncologists only define the CTVp rather than CTVn of NSCLC, RT field is not adequate and the subclinical LNM may be missed. It is true that CTVp may include parts of CTVn, so we must consider more comprehensively when we create a CTV. How to minimize the damage of such sensitive normal cells within irradiated fields without sparing cancer cells is a major issue for radiation

oncologists, especially as concurrent chemoradiotherapy has become a standard treatment. One way to achieve this task is accurate delineation of the target volume. Another way is the application of IMRT/3D-CRT, particularly in lung cancer with irregular irradiation fields. For radiotherapists, more conformal-limited fields RT could be electively adapted to the presentation of the disease allowing for higher doses to the GTV and, consequently, achieving better local control with acceptable toxicities. For patients with advanced unresectable NSCLC, chemoradiation may be an appropriate treatment measure, which can possibly facilitate surgical resection in selected cases. Studies have shown that pre-operative concomitant chemoradiation followed by surgery and consolidation chemotherapy is effective and well tolerated in patients with unresectable locally advanced NSCLC.²⁰ In clinical practice of RT, the extent of the target

Table 4. Multivariate analysis of risk factors associated with lymph node metastasis of non-small-cell lung cancer

Elements	OR (95% CI)	<i>p</i> -value
Sex		
Male	Reference	
Female	1.320 (1.060–1.644)	0.013
Age (years)		
≤60	Reference	
>60	0.645 (0.536–0.775)	<0.001
Locations		
Left upper lobe	Reference	
Left lower lobe	1.044 (0.792–1.377)	0.759
Right upper lobe	1.050 (0.812–1.359)	0.709
Right middle lobe	1.535 (1.033–2.280)	0.034
Right lower lobe	1.515 (1.164–1.973)	<0.001
Histological type		
Squamous cell carcinoma	Reference	
Adenocarcinoma	1.556 (1.235–1.960)	<0.001
Adenosquamous carcinoma	1.364 (0.948–1.963)	0.095
Large cell carcinoma	1.701 (1.034–2.798)	0.037
Other	0.547 (0.359–0.835)	0.005
Tumour growth pattern		
Central lung cancer	Reference	
Peripheral lung cancer	0.547 (0.445–0.674)	<0.001
Maximum diameter	—	0.336
T stage	1.434 (1.265–1.625)	<0.001
Differentiation	1.428 (1.243–1.639)	<0.001

Table 5. Linear regression analysis of risk factors associated with lymph node ratio of non-small-cell lung cancer

Elements	<i>t</i>	<i>p</i> -value
Sex		
Male	Reference	
female	2.952	0.003
Age (years)		
≤60	Reference	
>60	−6.235	<0.001
Locations		
Left upper lobe	Reference	
Left lower lobe	0.764	0.445
Right upper lobe	0.405	0.686
Right middle lobe	3.798	<0.001
Right lower lobe	4.833	<0.001
Histological types		
Squamous cell carcinoma	Reference	
Adenocarcinoma	7.505	<0.001
Adenosquamous carcinoma	3.353	0.001
Large cell carcinoma	2.649	0.008
Other	0.530	0.596
Tumour growth pattern	−1.178	0.239
Maximum diameter	−0.506	0.613
Differentiation	3.594	<0.001
T stage	8.422	<0.001

volume is not static for all cases. We must not only master the biological principles of tumours but also combine the specific situation of the patients. Only in this way can we achieve the goal of individualized treatment.

In conclusion, we should perform selective nodal irradiation including correlated lymphatic drainage regions according to clinical and pathological factors such as sex, age, tumour

location, T stage, histological differentiation etc. For young, female, relatively late T stage, poorly differentiated lung Ac, ASc or LCc, the irradiation field should be enlarged appropriately.

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