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A CLINICOPATHOLOGICAL STUDY OF MEDIASTINAL LYMPH NODE METASTASIS OF LUNG CANCER

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ABSTRACT

Objective: To investigate pathologically the characteristics of lung cancer metastasis by mediastinal lymph node ways (N_2). Methods: Of 398 lung cancer patients who underwent radical pulmonectomy and extensive lymph node dissection, 160 patients were diagnosed as with N2 metastasis, their 352 groups of mediastinal lymph nodes invaded were subject to the pathological study. Results: Evidences showed that the N_2 metastasis of lung cancer was very active. It appears as single group or multi-group or jumping-form metastasis, rating 41.2%, 58.8% and 29.3% respectively. In addition, the extension of N_2 metastasis was large, the most concentrated site was the 7th group lymph node (48.8%), then the 4th, 3rd and 5th group, rating 45.6%, 31.3% and 25.6% respectively. The occurrence of N_2 metastasis was highly correlated with the site, size, histopathological type and the grade of differentiation of the cancer. An another feature of N_2 metastasis was the invasion of metastasized lymph node into the bronchial wall, especially in adenocarcinoma. Conclusion: In order to achieve the radical removal of tumor, it is necessary to dissect the lymph nodes of the hilar and upper and lower mediastinum at the homolateral thoracic cavity actively and completely; beside, attention may be paid to the bronchial wall invasion caused by the lymph nodes metastasized.

Key words: Lung neoplasms, Mediastinal lymph nodes, Metastasis, Radical lymphadenectomy

From Oct 1992 to Jun 1998, 398 patients with lung carcinoma underwent radical pulmonectomy in our hospital, pathological study was carried out on the removed lymph nodes in purpose to explore the characteristics of mediastinal lymph node metastasis (N_2) of lung cancer and to provide the theoretic basis for reasonable lymphadenectomy.

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MATERIALS AND METHODS

Clinical Data

Of the 398 patients in our group, 227 cases were with central lung cancer, 171 with peripheral lung cancer. 97 patients underwent total pulmonectomy, 301 lobectomy (including bilobectomy and bronchoplasty). Pathologically, 191 cases were with squamous cell carcinoma, 172 adenocarcinoma, 24 small cell carcinoma (9 of them had pre-operative chemotherapy), 11 large cell carcinoma.

Methods

The radical pulmonectomy and extensive lymphadenectomy were carried out in all the cases of our group. The location, size, extension and the degree of cancer metastasis were observed by the naked eyes and recorded successively. Specimens were made and labeled. Lymph nodes removed were classified according to Naruke[1] method of lymph node mapping for lung cancer and labeled respectively and made as specimens. The nodes were fixed in 10% formalin solution for 24-4 8 hours and then paraffine-embedded, and sectioned for microscopic examination.

Statistical processing was done with X^2 test.

RESULTS

The Correlation between the Pathological Type of Cancer and Lymph Node Metastasis

A total of 2826 groups of lymph nodes were

removed for the 398 patients, averaging 7.1 group for each patient. The overall N_2 metastasis rate was 40.2%, those for squamous cell carcinoma, adenocarcinoma, small cell carcinoma and large cell carcinoma were 30.9%, 48.3%, *54.2%* and *45.6%* respectively (Table 1).

Table 1. Correlation between the pathological types of cancer and lymph node metastasis

Pathological types	Cases	Lymph node metastasis			
		N0	N1	N1+N2	N2
Squamous cell	191	109	23	35	24
Adenocarcinoma	172	72	17	64	19
Small cell	24	7	4	11	2
Large cell	11	5	1	3	2
Total	398	193	45	113	47

The Correlation between the Primary Site of Cancer and Mediastinal Lymph Node Metastasis

In 160 N_2 lung cancer of our group, there were 352 groups of mediastinal lymph node metastasized, of them the single group N_2 metastasis taken a part of 41.2%, $\geqslant$2 groups N_2 metastasis, 58.8%. The most concentrated sites for N_2 metastasis were the 7, 4, 3, 5th group of lymph nodes (Table 2). Jumping-form metastasis occured in 47 cases, 15 cases in right upper lobe, 11 in left upper lobe (more concentrated at the 3rd, 4th and 5th, 7th group respectively), 13 cases in right lower lobe, 8 in left lower lobe (more concentrated at 7th and 4th group).

Table 2. Site of cancer and mediastinal lymph node metastasis

Cancer site	Cases	Group of mediastinal lymph nodes									Total
		1	2	3	4	5	6	7	8	9	
Right upper	45	7	13	24	30	--	--	17	4	2	97
Right lower & middle	40	4	10	17	20	--	--	22	10	8	91
Left upper	39	1	2	7	13	28	17	19	1	0	86
Left lower	36	0	1	2	10	13	9	20	10	13	78
Total	160	12	26	50	73	41	26	78	25	23	352

Differentiation Grade and N_2 Metastasis

The correlation between the differentiation grade and N_2 metastasis in 191 cases with squamous cell carcinoma and 172 cases with adenocarcinoma was indicated in table 3. The N_2 metastasis rate of lower grade differentiated adenocarcinoma was significantly higher than the high grade differentiated ($P<0.0$ 1). In the lower differentiated cases, the nodes metastasized may be distant from the invaded main bronchus wall. There were 6 such cases in our group, including 3 adenocarcinomas, 2 squamous cell carcinomas and 1 small cell carcinoma.

Table 3. Differentiation grade and N_2 metastasis

Differentiation grade	Squamous cell carcinoma		Adenocarcinoma	
	Cases	N2	Cases	N2
High	42	12	76	27
Middle	123	38	65	33
Lower	26	9	31	23*
Total	191	59	172	83

Notes: *$P<0.01$ as compared with the high-differentiated grade

The Correlation between the Size of Tumor and N_2 Metastasis

In our group, no N_2 metastasis occurred in cases with long axis less than 1 cm for squamous cell carcinoma or adenocarcinoma. The N_2 metastasis rate increased in proportion with the long axis increases (Table 4). When the tumor long axis exceeds 3 cm, the N_2

metastasis rate of adenocarcinoma was higher than squamous cell carcinoma significantly.

Table 4. The size of tumor and N_2 metastasis

Long axis (mm)	Squamous cell carcinoma		Adenocarcinoma	
	Cases	N_2	Cases	N_2
0~10	4	0 (0)	5	0 (0)
11~20	10	1 (10.0)	17	4 (23.5)
21~30	22	4 (18.2)	31	11 (35.5)
31~50	79	24 (30.3)	73	39 (53.4)*
>50	76	30 (39.5)	46	29 (63.0)**

Notes: the number in ( ) means %; * *means* $P<0.01$; ** means $P<0.05$ as compared with squamous cell carcinoma

DISCUSSION

In recent years, with the expansion of operation indication and the improvement of surgical technique for lung cancer, the number of extensive lymphadenectomy for patients with N_2 metastasis increases day by day. Therefore to explore pathologically the characteristics of mediastinal metastasis of lung cancer, such as the rules, extension and related agents affecting the distribution of metastasized nodes, is of great significance for rational practice of extended lymphadenectomy.

The Characteristics of Mediastinal Nodal Metastasis in Lung Cancer

Lymphatic channels is the main pathway for lung cancer metastasis. The incidence of node metastasis was 75.6% in autopsy cases and 46.3% in resected cases. [2] The hilar and mediastinal nodal metastasis in our group was 51.5%, the N_2 metastasis was 40.2%. The results of our study show that: (1) The N_2 metastasis was very active. Regardless the primary lesion occurred at what lobe, the N_2 metastasis could exceed the segmental mediastinum and invade the non-segmental mediastinum. In our group, among patients with upper lobe tumor, occurred 43 lower mediastinal metastasis (23.5%), among patients with lower lobe tumor, occurred 86 upper mediastinal metastasis, even more active than the segmental metastasis; (2) The extension of invaded mediastinal nodes was very large. Regardless the types of, or the lobes where located the tumor, N_2 metastasis may spread to all group of nodes. The most concentrated site was the 7th group (48.8%), then the 4th, 3rd and 5th group, rating 45.6%, 31.3% and 25.6% respectively; (3) The mode of N_2 metastasis was multiform. They may be single group metastasis, but more frequently is multi-group metastasis, even jumping-form metastasis. The latter was metastasis directly from the sub-pleural visceral nodes to mediastinal lymph nodes.[3] 47 jumping-form metastasis was occurred in our group (29.3%). The jumping-form metastasis was more frequently in upper lung cancer than in lower lung cancer. In the former, the metastasis often occurred at the 3rd and 4th group for right side, and at the 5th and 7th group for the left side. In the latter, the metastasis occurred mostly at the 7th and 4th group; (4) The factors affecting the distribution of N_2 metastasis are various. It is dependent to the site, size, histopathologic type and the grade of differentiation of the tumor. The metastasis of small cell carcinoma was the highest (54.2%), then adenocarcinoma (48.2%), large cell carcinoma (45.5%) and squamous cell carcinoma (30.9%). For cases with squamous cell carcinoma or adenocarcinoma without pre-operative chemotherapy or radiotherapy, no any N_2 metastasis occurred for the cancer with long axis less than 1 cm; for long axis more than 1 cm, the N_2 metastasis increases with the long axis increases, especially in the case of adenocarcinoma. In addition, in cases of adenocarcinoma, the N_2 metastasis of low-grade differentiated is significantly higher than high-grade differentiated ($P<0.01$). These findings are of great importance for reasonable radical removal of mediastinal nodes.

The cancer infiltration by the nodes metastasized into the bronchus wall is an another feature of N_2 metastasis. It may be near the cancer even fused with the latter, or distant from the cancer. It is due to the cancerous tissue passes through the node capsule and invades directly the tunica externa of the bronchus. It is easy to be neglected and is the cause of cut end residual tumor and post-operative local cancer recurrence in part of patients. In 2 patients with peripheral lung cancer of our group, the intra-operative pathological examination revealed existence of cancerous infiltration of tunica externa of main bronchus wall by sub-prominence metastasized nodes and prompted us to do total pulmonectomy and

prominence reconstruction. These findings indicated that: when to carry out an operation for lung cancer, especially in the case of adenocarcinoma, apart from to eliminate the hilar mediastinal nodes, the cancerous infiltration to bronchial externa tunica must also be emphasized.

Extension and Mode of Mediastinal Node Dissection

Now the extended node dissection in lung cancer enabled the 5-year survival rate of patients with N_2 metastasis attained to 15-30%[4,5], but the extension and the mode of node dissection rest to be a problem of controversy both at home and abroad. According to the finding of our study, we hold that: (1)The cases suitable to operation should be selected strictly, operation must be carried out more actively for all patients whose primary cancerous lesion and mediastinal enlarged nodes, after careful pre- or intra-operative examination can be removed completely; (2) The complete removal of lymph nodes must include the hilar and upper and lower mediastinal nodes of homolateral thoracic cavity, especially those in the concentrated metastasized areas; (3) The dissection of lymph nodes should not be only done on the basis of hand contact or naked eyes observation, or is only limited within the hilar or local nodes. If not residual metastasized lymph nodes may reside; (4) For T_1 patients (TNM staging), when long axis of tumor is less than 1cm, the node dissection should be determined according to the histopathological types, the grade of differentiation and actual status of operation; (5) In case of main bronchus wall invaded by metastasized nodes, simple removal of local lymph nodes is insufficient. Radical procedure must be taken, to resect the main bronchus invaded and to select bronchoplasty pulmonectomy may be the better choice; (6) The posterio-lateral incision is the ideal incision for hilar and mediastina nodal dissection in thoracotomy. In part of patients, to cut off the arch of azygos vein for right incision and to isolate the aortic arch for left incision is helpful to the exposure and dissection of the 3rd and 4th lymph node groups. The value of the mid-line opening through the sternum for N_2 dissection is a problem to be further explored.

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