Operative Results of Non-small Cell Lung Cancer Clinically Presenting Mediastinal Lymph Adenopathy

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Operative Results of Non-small Cell Lung Cancer Clinically Presenting Mediastinal Lymph Adenopathy

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Abstract
Objective: Selection of treatment for operable N2 non-small cell lung cancer (NSCLC) is still controversial. If considered resectable, we have actively performed surgery even for clinical stage IIIA-N2 disease. In this retrospective study, surgical results in NSCLC with clinically presenting mediastinal lymph adenopathy examined to investigate its indication.

Methods: Consecutive 202 patients who were preoperatively diagnosed or suspected of mediastinal lymph adenopathy and underwent operation were investigated for such as pathological judgement of nodal metastasis, completeness of operation and prognosis. Perioperative chemotherapy and/or radiotherapy was performed in 56 patients.

Results: Pathological diagnosis of nodal status was NO in 64 patients, N1 in 27, N2 in 104 and N3 in 7. Complete resection was performed in 109 patients (54%). In 111 patients with pathologically proven N2 (pN2), only 40 (36%) were completely resected. The reason of incomplete resection included extranodal extension of mediastinal nodal metastasis in 31 patients, pleural dissemination in 18, extension of primary tumor to mediastinum in 11. Median post-operative survival time was 553 days, and survival rates at 2- and 5-years were 43% and 22%, respectively. In all pN2, survival rates at 2- and 5-years were 33% and 11%, respectively. In 40 patients of completely resected pN2, survival rates at 2- and 5-years were 42% and 22%, respectively, whereas those were 17% and 5% in 64 patients with incompletely resected pN2. The positive effect of perioperative treatment on survival was not apparent.

Conclusions: If resectable, surgical approach to N2 might be approved, however, extensive examination is required prior to therapy to avoid incomplete resection.

Key words: non-small cell lung cancer, mediastinal node metastasis, clinical stage, TNM classification.

Introduction
It has been still controversial whether surgical treatment for non-small cell lung cancer (NSCLC) with ipsilateral mediastinal node metastasis (stage IIIA-N2 disease) is indicated or not. Patients with the first defined N2 at thoracotomy or pathological examination show a 5-year survival rate of approximately 20 to 30%[1-3], whereas surgical outcome of those with radiologically obvious N2 (clinical N2: cN2) is miserable, 5-year survival rate of which cannot reach...
10% (4,5). More than 60% of recurrence in N2 patients is observed at distant organs, therefore, it is considered that clinical N2 disease is almost systemic disease and contraindication for surgery(4,5). Shields and colleagues advocated routine mediastinoscopical examination before treatment in order to avoid vain surgery(5). Watanabe et al., however, reported that resection for cN2-NSCLC resulted more than 20% of a 5-years survival rate if completely resected(6). Thus if resectability was exactly judged preoperatively, subpopulation of cN2 would be indicated for surgery as long as there is no definitively effective modality for N2 disease other than resection established yet. Preoperative induction chemotherapy has been paid an attention as an effective modality for N2 disease since several randomized phase III trials showed survival benefit as compared with surgery alone(7-9). However, the modality is still under investigation because several studies had several problems such as marginal difference, small cohort size or far poor prognosis of control group.

Recent series of chemoradiotherapy trials for unreseatable N2-NSCLC have shown favorable results with 2-year survival rates of 20 to 37%, and this modality has become an alternative for radiation alone(10-12). Now it is crucial point to investigate standard modality for clinically manifested but operable N2-NSCLC. Until now, there have been limited information in surgical results for clinical N2 disease since objects in most studies concerning operative results of cN2 were patients who had undergone complete resection(11-6). We had performed operation with or without adjuvant therapy for NSCLC with N2 manifested on preoperative computed tomography (CT) and considered resectable, and have investigated the outcome of all patients who underwent thoracotomy along with this strategy in the present study.

Patients and Methods

Patients

During the period between 1980 and 1998, a consecutive series of 895 NSCLC patients underwent at the Department of Surgery II, Kyushu University Hospital. In them, a total of 202 patients had presented ipsilateral mediastinal node swelling (a short axis of more than 1 cm) in preoperative computed CT, but no apparent extranodal invasion, contralateral node swelling, pleural dissemination or mediastinal invasion of primary tumor, and were considered resectable. The histologic diagnosis of the tumors was based on the criteria of the World Health Organization(13), and the TNM stage was determined according to the criteria revised in 1997(14). Age of them comprised 35 to 82 years old with a mean of 64 ± 4.4 years old. They included 158 male and 44 female, 96 adenocarcinomas, 79 squamous cell carcinomas, 19 large cell carcinomas and 8 others. All of them were diagnosed as N2 whereas there were 27 T1, 119 T2, 41 T3 and 15 T4. All patients had no distant metastasis (cM0). Standard operations such as a lobectomy or pneumonectomy with a complete dissection of the hilar and mediastinal lymph nodes were intended in all patients. In a preoperative adjuvant setting, chemotherapy and radiotherapy were performed in 10 and 3 patients, respectively. In a postoperative adjuvant therapy, chemotherapy and radiotherapy were performed in 19 and 24 patients, respectively. A follow-up examination was, in general, done every 2 months for the first 2 years and thereafter every 3 to 4 months, and mean observation period was 858 days. The follow-up includ-
ed a physical examination, complete blood count, blood chemistry, and chest radiography. Although a few patients routinely received screening examinations by CT or radionuclide bone scanning once or twice per year after their operation, the majority of patients underwent CT or a radionuclide bone scan only when symptoms related to recurrence appeared. The recurrent disease was then confirmed by biopsy if clinically feasible. In patients for which that was not feasible, radiographic evidence (roentogenography, CT, or radionuclide scan) was accepted. However, imagings obtained by CT or detailed pathological findings were also referred.

Statistical analysis

The number of days from the detection of the first recurrent site until death constituted the length of post-recurrent survival. Survival curves were prepared by the Kaplan-Meier method\(^{15}\), and comparisons among the survival curves were made using the logrank test\(^{16}\). The difference in resectability among subgroups was examined by a t-test. Multivariate analysis was performed to analyze which factor had an influence on postoperative prognosis in patients with pathologically defined N2 (pN2) using a Cox proportional hazard model\(^{17}\). The data were considered as significant when the p value did not exceed 0.05.

Results

Operation and overall survival in patients with clinically manifested mediastinal node swelling

Performed operations were pneumonectomy in 37 patients, bi-lobectomy in 18, lobectomy in 99, segmentectomy in 6, partial resection in 2, and exploratory thoracotomy in 40. Incomplete resection that included exploration was performed in 103 patients. Overall survival rates at 2 years and 5-years were 42.7 % and 21.7 %, respectively.

Pathologic examination for nodal metastasis and analysis of pN2-3 subgroup

Pathologic examination revealed N0 in 64 patients, N1 in 27, N2 in 104, and N3 in 7, thus 91 patients with pathological N0-1 (45 %) had been overestimated in preoperative CT scan. Complete resection among pN0-1 and pN2-3 was achieved in 76 % (69/91) and 36 % (40/111), respectively. Ipsilateral intrapulmonary metastasis was detected in 18 patients (M1). The reasons of incomplete resection were residual primary tumor in 15, pleural dissemination in 14, inadequate pulmonary reserve for pneumonectomy in 6, and incomplete dissection due to inflammatory lesion in 5 among the pN0-1 patients whereas, among the pN2-3 patients, the reasons were extranodal invasion in 31, pleural dissemination in 18, residual primary tumor in 11, distant metastasis in 7, unresectable N3 disease in 3 and incomplete dissection of metastatic lymph node due to accompanied inflammatory lesion in 1. The survival rates at 2 / 5 years among each pN status were 57 % / 39 % in pN0, 51 % / 27 % in pN1, 33 % / 11 % in pN2 and 1 % / 0 % in pN3, and the differences between them were statistically significant (p < 0.0001) (Fig. 1). In 111 pN2-3 patients, postoperative survival rates at 2 / 5-years were 42 % / 22 % in 40 completely resected patients whereas 17 % / 5 % in 71 patients of incomplete resection (Fig. 2). There was significant difference between them (p = 0.0004), although no difference was observed between survival of 27 patients who underwent exploratory thoracotomy and that of 44 patients who had
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Fig. 1 Postoperative survival curves of each pN group. The postoperative outcome was significantly related to pN factor (p < 0.0001).

Analysis of therapeutic factor influencing prognosis

To analyze prognostic factors in patients with pN2–3, multivariate analysis was performed for therapeutic variables (Table 1). Complete resection was the most influencing factors with a relative risk of 0.442 (p = 0.0002). There was no significant effect found in preoperative chemotherapy, postoperative chemotherapy, or postoperative mediastinal radiotherapy.

Relationship between clinical factors and operative result of incomplete resection

Expectedly the above results clearly showed the positive relationship between survival and pathological N status or complete resection. We examined preoperative factors predicting incomplete resection. As shown in Table 2, neither histology, cT

Table 1 Multivariate analysis of factors associated with postoperative outcome in pN2–3 patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard ratio</th>
<th>95% confidence interval</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>Resection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete / Incomplete (40 / 71)</td>
<td>0.442</td>
<td>0.286–0.684</td>
<td>0.0002</td>
</tr>
<tr>
<td>Preoperative chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes / No (10 / 101)</td>
<td>0.899</td>
<td>0.384–2.107</td>
<td>0.8051</td>
</tr>
<tr>
<td>Postoperative chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes / No (19 / 92)</td>
<td>1.393</td>
<td>0.913–2.125</td>
<td>0.1236</td>
</tr>
<tr>
<td>Postoperative radiotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes / No (24 / 87)</td>
<td>0.914</td>
<td>0.569–1.478</td>
<td>0.7214</td>
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</table>
factor or subjective symptom did not exhibit a positive relationship to resectability.

**Comments**

The stage IIIA-N2 NSCLC comprises various extension of disease, and there still have been several inquiries for selection of therapeutic approach. Recently, concurrent chemoradiotherapy has been accepted as the best modality for locally advanced NSCLC including N2 disease, by which 2-years survival rate of 20 to 37% was achieved\(^{10}-^{12}\). Although the objects were unresectable cases in most series of the bimodality, no obvious standard was situated to make a decision whether it was resectable or unresectable. It is still controversial whether surgery alone for the resectable N2 case should be performed or not. Recent clinical trials suggest survival benefit of induction chemotherapy followed by surgery in locoregionally advanced NSCLC\(^{8,9}\), and National Institute of Health advocated that surgery alone should not be performed in practice although obvious consensus has not been established\(^{18}\). Surgical results in pN2 disease reported from several surgeons were various in that a survival rate was less than 10 to 30% at 5 years after surgery\(^{11}-^{36}\), however, the objects analyzed in those studies included substantial population of pathologically first defined N2 patients and excluded patients with incomplete resection. For exact review of the surgical indication for N2 NSCLC, selection of a cohort should be based on clinical stage but not pathological stage, and should include all patients who underwent surgery.

From a point of view that complete resection is one of the best therapies, otherwise at least or not worse than others, for operable N2 disease, we have performed active surgery for patients with NSCLC presenting mediastinal node swelling but considered operable in CT. The justice of our selection is to be evaluated by a randomized control study, however, there has been no such clinical trial completed ever. Therefore, in the present study, we analyzed the outcome of our active surgery to discuss a proper strategy for operable N2 disease.

True (pathologically defined) N2 was only

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Relationship between complete resection and clinicopathologic factors in pN2-3 patients</th>
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<tbody>
<tr>
<td>Factors</td>
<td>Complete resection (N=40)</td>
</tr>
<tr>
<td>Symptom</td>
<td></td>
</tr>
<tr>
<td>Yes (N=16)</td>
<td>4</td>
</tr>
<tr>
<td>No (N=95)</td>
<td>36</td>
</tr>
<tr>
<td>Cell type(^a)</td>
<td></td>
</tr>
<tr>
<td>Adeno (N=58)</td>
<td>21</td>
</tr>
<tr>
<td>Squamous (N=35)</td>
<td>13</td>
</tr>
<tr>
<td>Others (N=18)</td>
<td>6</td>
</tr>
<tr>
<td>T factor</td>
<td></td>
</tr>
<tr>
<td>T1 (N=15)</td>
<td>5</td>
</tr>
<tr>
<td>T2 (N=64)</td>
<td>23</td>
</tr>
<tr>
<td>T3 (N=22)</td>
<td>8</td>
</tr>
<tr>
<td>T4 (N=10)</td>
<td>4</td>
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\(^a\)Adeno: adenocarcinoma; Squamous: squamous cell carcinoma.
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51 %, and 64 % of patients with pN0-1 were resulted in overestimation. These results were expected since, in general, accuracy of diagnosis for mediastinal node metastasis by CT is approximately 60 % with a criteria that a short axis of more than 1 cm is positive. Since another rational of our active surgery for NSCLC presenting mediastinal node swelling is that a case of even false positive N2 (pN0-1) was automatically rescued from false judgement of inoperation, such overestimation was not negative factor for our strategy. On the other hands, several surgeons who have a point of view that N2 disease is contraindication for surgery advocated that preoperative biopsy through mediastinoscopy is mandate to avoid a vain surgery5). However, mediastinoscopy requires systemic anesthesia, is traumatic, and sometimes shows false negative. Moreover, mediastinoscopy had 21 % of false negative that underwent surgery19). Nakano et al. reported that mediastinal ultrasonography is useful for detection of a swollen mediastinal node, especially for a subcarinal node, and suggested that such a diagnostic tool might increase the diagnostic efficacy of mediastinoscopy20). If operable N2 disease is properly selected by imaging, and survival of resected patients is comparable with other modality, mediastinoscopy can be skipped and active surgery would be approved.

In 104 patients with pN2, 2- and 5-year survival rates were 33 % and 11 %, respectively. This result would be comparable to concurrent chemoradiotherapy. Focussing 40 pN2 patients undergoing a complete resection, the respective survival rates at 2- and 5-years were 42 % and 22 %, whereas those of patients with incomplete resection were 17 % and 5 %. On considering a low respectability of 38 %, more accurate diagnostic tools is required to in order to avoid incomplete resection. The major reasons for non-curative operation were extranodal invasion from metastatic mediastinal node and carcinomatous pleurisy. To detect such condition, exploratory thoracoscopy would be the most certain method although invasive. High resolution CT or bronchoscopic sonography is also to be investigated.

We could not detect any efficacy of postoperative adjuvant therapies for N2 patients in our study. Therapeutic power of chemotherapy or radiotherapy has been reported to be very small in studies for completely resected cases21)22), therefore it might be difficult to detect the efficacy in the cohort of our study. We also performed induction chemotherapy in 10 patients using CDDP and camptotesin. Response was obtained in 8 patients, and downstaging in 6, however, obvious benefit is unclear in this study.

In conclusions, we proposed that surgery might be acceptable for operable IIIA-N2 cases, extensive evaluation for a possibility of complete resection would be mandate. Such operable IIIA-N2 cases would be almost considered as a control for other modality in clinical trials for this disease.

Acknowledgment

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臨床的に縦隔リンパ節腫大を伴う非小細胞肺癌に対する手術成績

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要約
目的：切除可能な N2 非小細胞肺癌の治療法選択は未だ議論のあるところである。我々は切除可能と判断された IIIA-N2 期非小細胞肺癌に対して積極的な切除を行ってきた。本 retrospective 研究では、縦隔リンパ節腫大の認められた非小細胞肺癌に対する外科手術成績を検討し、その適応について検討した。
方法：術前に縦隔リンパ節腫大が認められ、且つ切除された一連の患者 202 名について、病理学的リンパ節転移診断、切除率および予後について検討した。周術期の化学療法または放射線療法は 56 例に施行された。
結果：病理診断の結果は N0 が 64 例で、N1, 104 例が N2, 7 例が N3 であった。全症例中、完全切除は 109 例（54 ％）に行われたが、病理学的 N2（pN 2-3）111 例では 40 例（36 ％）のみが完全切除された。非完全切除の理由は、31 例で縦隔リンパ節転移巣からの筋外浸潤、18 例で胸膜播種、11 例で原発巣の縦隔浸潤であった。全症例の術後中間生存期間は 553 日、術後 2 年および 5 年生存率は各々 43 ％、22 ％であった。全 pN2 例では術後 2 年および 5 年生存率は各々 33 ％、11 ％であった。完全切除された pN2 40 例の術後 2 年および 5 年生存率は各々 42 ％、22 ％であったが、非完全切除に終わった pN2 64 例では 17 ％、5 ％であった。周術期補助療法の有効性は明らかではなかった。
結論：切除可能ならば N2 非小細胞肺癌に対する外科治療は許容されるかも知れないが、そのためには無用な手術を避けるために切除の可否を治療前に徹底検索することが必要であろう。