Complete mediastinal lymphadenectomy: the core component of the multidisciplinary therapy in resectable non-small cell lung cancer

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Summary
There is a great deal of concern about metastasis of lung cancer to regional lymph nodes, due partly to the work of groups of thoracic surgeons in Japan and North America beginning in the 1970s. The classification of regional lymph node stations for lung cancer staging published by Mountain and Dresler has been widely adopted for more than ten years. Anatomic landmarks for 14 levels of intrapulmonary, hilar, and mediastinal lymph nodes stations are designated. Skip transfer and occult lymph node metastasis, confirmed by studies regarding the mode of spread of intrathoracic lymphatic metastasis, are two theoretical bases for complete mediastinal lymphadenectomy of lung cancer. However, whether or not the degree of the dissection influences prognosis, the role of systematic nodal dissection (SND) vs mediastinal lymph node sampling (MLD) in resectable non-small cell lung cancer (NSCLC) remains controversial. A systematic literature search was performed to identify relevant reports, making full use of the 'Cited by,' 'Related Records,' 'References,' and 'Author Index' functions in the PubMed and ISI Web of Science databases. This paper presents a review of the role of mediastinal lymph node distribution and methods of determining suitability for hilar and mediastinal lymphadenectomy based on the four subsets of stage IIIA-N2, balancing the cost vs effect of mediastinal lymph node dissection in resectable NSCLC, focusing on the stage migration bias in clinical trials comparing SND and MLS, recommending a reasonable node dissection sequence, improving the prospects for the perioperative anti-tumor therapy based on mediastinal lymphadenectomy, and evaluating the various preoperative staging techniques. Finally, we believe that, besides the role of complete resection and accurate staging, the complete mediastinal lymphadenectomy is the core component of the lung cancer multidisciplinary therapy, and suggest that the values of lymphadenectomy should be further assessed using decision-tree analysis based on large-scale prospective randomized trials and pooled analysis to evaluate the costs vs effects.

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1. Introduction
Spread through the hilar and mediastinal lymph nodes (MLNs) is a key pathway in non-small cell lung cancer (NSCLC) metastasis. The status of N2 (MLNs) and patterns of sub-N2 (IIIA1—IIIA3), determine the treatment strategies and prognosis of NSCLC [1]. Borrie, Nohl-Oser and Cahan first described the intrapulmonary lymphatic anatomy with its interconnecting network, and the radical mediastinal lymphadenectomy in the resection of lung cancer in the 1950s [2,3]. This technique is based on the role of complete surgical resection, as well as achieving clear state of N2 [4]. However, in this area, there are still many unresolved, fascinating, and controversial issues. The best evidence to resolve these problems is based on randomized controlled trials (RCTs). However, a multicenter RCT in this issue may not be possible in a strict sense. Furthermore, the so-called stage migration phenomenon between systematic nodal dissection (SND) and MLN sampling (MLS) is also an important factor that produces bias in research. Emerging methods, including positron emission tomography/computed tomography (PET—CT), mediastinoscopy, and endoscopic techniques with fine needle aspiration, may replace some roles of SND in accurate staging. In addition, the application of multidisciplinary therapeutic strategies, including perioperative anti-tumor treatment and video-assisted thoracic surgery (VATS), will vitalize related areas of research, which may lead to the development of novel alternatives to lymph node dissection.

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2. Search strategy

A systematic literature search was performed to identify relevant reports. Computerized bibliographic searches were supplemented with hand searches of conference abstracts and specialist journals, and articles were tracked by making full use of the ‘Cited by,’ ‘Related Records,’ ‘References,’ and ‘Author Index’ functions in the PubMed and ISI Web of Science databases. The following keywords and medical subject headings were analyzed to identify relevant controlled trials, guidelines, and reviews: carcinoma, non-small cell lung, mediastinum, lymphatic metastasis, lymph node excision, neoplasm staging, combined modality therapy, postoperative complications, survival rate and prospective studies.

3. Mediastinal lymph node distribution

There is a great deal of concern regarding metastasis of lung cancer to regional lymph nodes, due partly to the work of groups of thoracic surgeons in Japan and North America that began in the 1970s [5—9] (Fig. 1). Currently, the locations of MLNs are categorized based on the integration of the schema advocated by the American Joint Committee on Cancer (AJCC), adapted from the lymph node mapping Tsuguo Naruke built [6], and the American Thoracic Society regional lymph node classification system boosted by Martini et al. [7]. The classification of regional lymph node stations for lung cancer staging reported by Mountain and Dresler [10], which includes anatomical landmarks for 14 levels of intrapulmonary, hilar, and MLN stations, has been adopted widely for more than 10 years. In the forthcoming seventh edition of the TNM Classification for Lung Cancer, due to be published in early 2009, the International Association for the Study of Lung Cancer (IASLC) will state that current N0—N3 descriptors define distinct prognostic groups for both clinical and pathological staging, and should be maintained. Exploratory analyses showed that lymph node stations could be classified into six ‘zones’: peripheral (level 12—14) or hilar (level 10—11) for N1, and upper (level 1—4) or lower mediastinal (level 8—9), aortopulmonary (level 5—6), and subcarinal (level 7) for N2 nodes [11]. Nodal metastases to the lower mediastinum from upper lobe cancer were more frequently observed than the lower lobe cancer to the upper mediastinum [11,12]. Among the primary tumors that had only a single involved N2 station, the most common site of lymph node metastases was level 4R for right upper-lobe tumors, levels 5/6 for left upper-lobe tumors, and level 7 for middle and lower-lobe tumors [11], which should be routinely sampled in the lymph node dissection. Skip transfer and occult lymph node metastasis confirmed by research in the mode of spread in intrathoracic lymphatic metastasis are two theoretical bases for extensive mediastinal dissection of lung cancer [2,3,12—14].

4. When should we cut it out

In 1976, Naruke et al. [5] recognized that the presence of MLN metastasis, especially with subcarinal lymph nodes, is not a good candidate for surgical treatment. Nevertheless, patients with stage IIIA (N2) tumors that might benefit more from lymphadenectomy present substantial heterogeneity in clinical presentation, treatment, and prognosis. Presentations of N2 disease range from apparently resectable tumors with occult microscopic nodal metastases to unresectable, bulky multistation. Therefore, for the purpose of generating rational treatment guidelines, N2 tumors are classified into four subsets [1].

In patients with single-station metastases identified on the final pathological examination (IIIA1) or recognized intraoperatively (IIIA2), and when complete resection of the nodes and primary tumor is technically possible, it is rational to proceed with the planned lobectomy and mediastinal lymphadenectomy. Usually, the pathological IIIA1 and IIIA2 cases after thoracotomy are clinical stage I or stage II by imaging (short axis of the lymph node less than 1 cm in enhanced CT scan). For surgical considerations, an exploratory thoracotomy should be avoided. Patients with potentially resectable N2 disease (IIIA3) identified preoperatively by PET or...
mediastinoscopy have relatively poor prognosis when treated with surgery alone. Whenever possible, induction therapy followed by surgery for stage IIIA\(_3\) disease should be carried out in clinical trials. Patients with incomplete resection and those with residual nodal disease should be considered for postoperative radiotherapy. Finally, in cases of unresectable bulky N2 disease (IIIA\(_4\)) with favorable performance status (PS), platinum-based chemoradiotherapy would provide improved prognosis over thoracotomy or radiotherapy alone, as to what should be used for primary treatment in stage IIIB N3 disease (Fig. 2).

5. SND and MLD

Whether or not the degree of the dissection influences prognosis, the role of SND vs MLS in resectable NSCLC remains controversial [15—19]. Opinions favoring SND include complete resection, improved nodal staging, and better local control due to resection of undetected micrometastases and decreased risk of leaving residual lesions. Arguments against routine SND are increased morbidity compared with sampling and the lack of evidence for improved survival. SND requires a more extensive mediastinal exploration than MLS and may be associated with increased bleeding, longer operating time, longer duration of catheterization, longer hospitalization, and potential damage to mediastinal structures. The values concerning SND and MLS should be assessed further using decision-tree analysis with stringent data to evaluate the costs vs the effects (Table 1).

5.1. Standardized procedure

SND should be performed in a standardized manner but not dependent only on the primary lesion [5,10,20]. All the surrounding fat containing the lymph tissue is isolated and removed systematically and en bloc within anatomical landmarks. Superior mediastinal compartment is opened and trachea, azygos vein, superior vena cava and ascending aorta are completely freed from all tissue. Subcarinal, paraspinal and inferior pulmonary lymph nodes removed en bloc. Levels 1–4 and 7–9 are dissected in right-sided lung cancer. In left-sided, the subaortic compartment is cleared and nodes 5 and 6 are completely removed. Interlobar, lobar and segmental nodes should also be dissected out when lobectomy is performed. After removal, the different nodal stations are placed in different containers with separate labeling. The MLS consisted of removal of part of one node, removal of one node from a nodal station or the removal of selected stations with suspected cancer metastases guided by preoperative or intraoperative findings, which were thought to be representative of the different predetermined lymph node levels. The mediastinal fatty tissue containing the nodes was not removed en bloc [18,20—23]. Wu et al. [22] found that the number of lymph node metastases was an independent predictor of survival. Pathological evaluation of at least 10 MLNs from at least three stations should be performed at the time of surgery [24,25]. The report from the pathologist should describe the number of nodes removed, and the overall number of metastasis in each station for both techniques. Survival following resection for NSCLC is associated with the number of LNs evaluated during surgery. Ludwig et al. [26] suggested an evaluation of nodal status should include 11–16 LNs to gain better prognosis. While practice patterns among surgeons vary widely, Watanabe reported that there is considerable discordance in the designation of nodal station between the Japanese and European surgeons [27], and thus more detailed nodal charts and precise, easily understood definitions of nodal stations are needed for intrathoracic staging. In 2004, Barnard found 305 papers related to lung cancer lymphadenectomy. However, definitions of lymph node dissection according to specified authors differ from each other [28] and thus may produce systematic study design bias about the trials comparing SND with MLS.

5.2. Controlled clinical trials

Although there was study design bias in the included trials, Wright et al. suggested that SND is associated with improved survival in patients with stages I—IIIA NSCLC in a meta-analysis of three RCTs [29]. Although not all three trials found

| Table 1: The cost(cons) vs effect(pros) of mediastinal lymph node dissection |
|-----------------------------|-----------------------------|-----------------------------|
| Outcome measures | Systematic nodal dissection | Mediastinal lymph node sampling | Level of evidence* |
| Complete resection | Pros | Cons | Weak [4,22] |
| Local recurrences | Pros | Cons | Weak [22,23,31,32,35] |
| Distant metastasis | Pros | Cons | Weak [22,31,32,35] |
| Accurate staging | Pros | Cons | Strong [4,22,23,31,33,35] |
| Disease-free survival | Pros | Cons | Strong [23,32,35] |
| Overall survival | Pros | Cons | Strong [22,23,29,30,31,32,35] |
| Operative mortality | No significant difference | No significant difference | Strong [23,31,34,37] |
| Perioperative complications | No significant difference | No significant difference | Strong [23,31,34,37] |
| Damage to mediastinum | No significant difference | No significant difference | Weak [23,31,32,37] |
| Hemorrhage | Cons | Pros | Weak [23,31,34,35,37] |
| Operating time | Cons | Pros | Weak [23,31,34,35,37] |
| Duration/amount of drainage | Cons | Pros | Strong [23,31,34,37] |
| Hospitalization period | No significant difference | No significant difference | Strong [23,31,34,37] |
| Stimulate tumor growth, impaired immune response | Cons | Pros | Weak [19,32] |
| Secondary cancers | No significant difference | No significant difference | Weak [31] |

* Strong evidence implies that the sample size of the relevant trials was large enough and that the conclusions were consistent with each other. Weak evidence indicates that the sample size of the relevant trials was not large enough and/or that conflicting conclusions ensued within trials.
a significant difference, each trial tended to favor the SND arm. The larger the sample size, the more remarkable the detected difference.

Furthermore, seven original articles commended our vision, including four RCTs [17,22,30–34], two CCTs [23,35] and a multicentric cross-sectional study [4] (Table 2, Fig. 3). Keller et al. [35] showed that complete mediastinal lymph node dissection (MLND) was associated with improved survival with right NSCLC when compared with systematic sampling in non-randomized comparison. The reason for no significant difference in 5-year survival between SND and MLD in some controlled trials [23,31], despite the better HR in overall survival of SND is still unclear. One possible explanation is that the algorithm used to determine overall survival makes full use of censored data and is consequently more capable of detecting the difference. In Wu et al. [22], the trial with the largest sample size among the five finished trials comparing survival, NSCLC patients gained more benefit from SND in stage IIIA than in stage I or II. It may be that clinical stage IIIA patients have a greater chance of developing mediastinal spread of MLNs. Based on the current knowledge in stage IIIA, patients with mediastinoscopically proven N2 lymph node involvement were excluded from thoracotomy in the study by Lardinois et al. [23], which may weaken the complete resection effect of SND. It should also be noted that in the trial reported by Sugi et al. [31], only patients with cT1N0 NSCLC were randomized. Theoretically, the authors hypothesized that N0 groups may be less likely to benefit from SND. However, with their inclusion in Wright’s meta-analysis, a clear benefit of SND was still indicated [36]. One explanation might be that the current applied technologies for examining lymph nodes metastasis have broadly recognized limitations [13,30]. It may also be due to the stage migration phenomenon that would favor the SND group.

Many researchers have found a significantly higher rate of N2 disease after SND as compared with MLS [22]. Although, in Keller et al.’s [35] trial, systematic sampling was as efficacious as complete MLN dissection in tumor staging. However, complete MLND identified significantly more levels of N2 disease. Massard et al. [4] indicated that the most important benefit of SND may be accurate staging through a self-controlled, multicentric cross-sectional study, which would also create a stage-shift effect at the same time, as compared with sampling [28]. Therefore, the pathological TNM staging in the same cases with MLS or SND differs for the stage migration phenomenon, which is related to the accuracy of intraoperative staging. A more extensive MLND detected more occult N2 disease, and more patients were assigned to stage IIIA disease. Hence, a systematic bias favoring SND occurred. Survival by pathological stage based on different procedures may not reflect the truth. Nevertheless, the whole population of SND and MLD was compared in the above prospective RCTs with balanced baseline of preoperative lymph nodes clinical staging. Furthermore, the current N descriptors define distinct prognostic groups for both clinical and pathological staging [11]. When the sample size is sufficiently large, the pathological stage between the two arms should be equivalent. Therefore, a pooled analysis combining independent studies is needed to increase sample size and the statistical power to detect the difference.

With respect to progression diseases, there might be an increased tendency in local recurrence but not in distant metastasis in the MLS group [22,23,31,32,35]. Combined with perioperative complications observation in the ACOSOG (the American College of Surgeons Oncology Group) Z0030 trial, we deduced that SND has better local tumor control than MLS after thoracotomy, without leading to increased morbidity (38.6% vs 37.9%) [37]. In addition, there is no way to perform absolutely double-blind studies involving surgery, and the skill, talent, or educational backgrounds of the individual surgeons would affect the quality of surgery and prognosis. Therefore, an ideal multicenter randomized controlled study in the field of thoracic surgery may be difficult to accomplish in the strict sense.

Despite these limitations, published data suggest that resectable NSCLC patients gain benefits from SND in comparison with MLS. However, as with one to four LNs, there appears to be no incremental survival improvement after evaluating >16 LNs [26]. Local tumor control enhanced by SND in patients with N0 mediastinum could not be transformed into increased survival. There were no significant differences in distant metastasis between the two arms, and the postoperative complications between the two arms may be eclipsed by publication bias. Nevertheless, we may resolve this problem by achieving the correct balance between excessive therapy and incomplete resection. The ongoing large-scale prospective randomized trial ACOSOG Z0030 includes 1111 patients, overwhelmed the other five RCTs, and was highly cited for its postoperative complications results (Fig. 3). We expect valuable evidence provided by this trial to reveal whether SND or MLS should be performed in various individuals after decades of controversy.

5.3. Reasonable dissection sequence

In patients with resectable NSCLC, lobectomy or more extensive resection are recommended rather than sublobar
Table 2
Characteristics of the controlled trials

<table>
<thead>
<tr>
<th>Studies</th>
<th>Study design</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Izbicki et al. [32–34], finished, Passlick et al. [30], finished</td>
<td>Prospective randomized controlled trial (At thoracotomy, eligible patients were randomly allocated into two groups) The patients were followed up at 6-month intervals. The median follow-up time was 47.5 months</td>
<td>Inclusion criteria: curatively resectable NSCLC Exclusion criteria: M1 disease; N3 disease; multiple N2 disease preoperatively; after randomization, patients were excluded if they had evidence of intrapulmonary metastases, patients exhibited residual tumor at the resection margin, SCLC</td>
<td>Mediastinal lymph node sampling (LS): 93 Radical systemic lymphadenectomy (LA): 76 Three patients in each group were lost to follow-up and were censored</td>
<td>Overall survival Disease-free survival Distant metastases Local tumor recurrences Tumor staging Perioperative complications and events 30-day mortality</td>
</tr>
<tr>
<td>Sugi et al. [31], finished</td>
<td>Prospective randomized study Computer generated random numbers Intention-to-treat analysis Unblinded during follow-up at 6-month intervals. The median follow-up time was 49 months</td>
<td>Peripheral carcinoma (&lt; 2 cm in diameter) without evidence of hilar or mediastinal node involvement</td>
<td>Mediastinal lymph node sampling: 56 Radical systematic hilar and mediastinal lymph node dissection: 59</td>
<td>3- and 5-year survival Distant metastases Local tumor recurrences Tumor staging Perioperative complications and events Surgery-related death</td>
</tr>
<tr>
<td>Keller et al. [35], finished</td>
<td>Stratified, non-randomized prospective trial based on a randomized prospective trial of adjuvant therapy (ECOG 3590) Telephone communication</td>
<td>Patients with completely resected stages II and IIIA NSCLC were eligible Patients with multifocal bronchoalveolar tumors within the same lobe or different ipsilateral lobes were not eligible</td>
<td>Systematic sampling (SS): 187</td>
<td>Overall survival Disease-free survival Distant metastases Local tumor recurrences Staging</td>
</tr>
<tr>
<td>Wu et al. [22], finished</td>
<td>Prospective randomized trial Regular examinations were followed up at 3-month intervals during the first 2 years, from the third year at 6-month intervals, and from the fifth year at 12-month intervals</td>
<td>All patients who entered the trial must be &lt; 70 years old Pathologic types must be NSCLC cTNM and pTNM must be stage I–IIA The operation is a complete resection</td>
<td>Systematic nodal dissection (SND): 240 Mediastinal lymph nodal sampling (MLS): 231</td>
<td>Overall survival Distant metastases Local tumor recurrences Surgical morbidity and mortality</td>
</tr>
<tr>
<td>Lardinois et al. [23], finished</td>
<td>Prospective, non-randomized trial A mean follow-up time of 89 months was achieved in 92 patients every 3 months during the first 3 years, every 6 months from the third to the fifth year, and then yearly</td>
<td>Complete anatomical resection (lobectomy or pneumonectomy for histologically proven NSCLC) Patients with mediastinoscopically proven N2 or N3 lymph node involvement were excluded from the study</td>
<td>Mediastinal lymph node dissection (MLND): 50 Mediastinal lymph node sampling (MLS): 50</td>
<td>Overall survival Disease-free survival Distant metastases Local tumor recurrences Perioperative complications and events Surgery-related death</td>
</tr>
<tr>
<td>Massard et al. [4], finished</td>
<td>Multicentric cross-sectional study This study was conducted in three centers with four surgeons participating during a 4-month period.</td>
<td>Without bulky disease underwent resection for primary lung cancer in three centers</td>
<td>Lymph node dissection: 525 Lymph node sampling: 498</td>
<td>Accuracy of prediction for stage N2 and radicality of node sampling compared to dissection</td>
</tr>
</tbody>
</table>

The surgeon first sampled the main lymph node stations, and subsequently performed a radical mediastinal dissection in 208 consecutive patients.
resection (wedge or segmentectomy) as standard procedures [38–40]. Whereas, what is the reasonable order for surgical resection of pathologically confirmed early stage NSCLC, lobectomy after MLND or the reverse? In our experience [22], lobectomy after MLND shows greater advantages as compared with the traditional procedure. For the right mediastinum, the mediastinal pleura should first be isolated along the vagus nerve, azygos vein arch, and the phrenic nerve, the pulmonary ligament should then be released, followed by exposure of the hilar, interlobar, pulmonary ligament, and the subcarinal lymph nodes, and then lobectomy with a peanut sponge is used to dissect the lobar lymph nodes and the segmental lymph nodes are completely cleaned. For the left mediastinum, the pulmonary root is exposed after separation of the mediastinal pleura along the lower edge of the aortic arch, the frontal of vagus nerve, and the posterior of phrenic nerve. The subaortic, ascending aorta, subcarinal, hilar, and interlobar lymph nodes are resected. The subcarinal lymph nodes are more difficult to expose in the left hemithorax than in the right side. A malleable retractor is used to retract the aorta and esophagus posteriorly. Finally, lobectomy should be performed. The above sequence is based on the following considerations. First, the great vessels of pulmonary root and hilar are more fully exposed after MLND, and it may help ensure a smooth operation and improve the safety of lobectomy, avoid duplication of operations, and save time. Second, the veins and the lymphatic system are two important routes for the spread of lung cancer. According to the same principle as the procedure using pulmonary vein ligation first, lobectomy after lymph node dissection may avoid the intraoperative spread of tumor cells. Yamanaka reported that lobar lymph node metastases in nonprimary lobes were more frequent on the right side lung cancer [41]. Nonprimary N1 is resected selectively in our practice.

6. Neoadjuvant and adjuvant therapy

In accordance with the evolution of tuberculosis treatment, many scholars consider that the surgical approach to lung cancer will eventually be replaced by non-surgical therapy. However, it is likely that surgery will remain the main form of treatment for early stage NSCLC in the foreseeable future. Nowadays, there is strong evidence indicating the limitations of single-mode treatment of lung cancer. Therefore, clinical oncologists have reached a consensus that multimodality therapy should be applied in cases of lung cancer; whereas perioperative therapy could not be appropriately established in the absence of complete mediastinal lymphadenectomy.

6.1. Adjuvant chemotherapy

Until recently, the benefit of adjuvant chemotherapy in stage I–IIIA NSCLC patients was uncertain [42]. After decades of twists and turns, adjuvant cisplatin-based chemotherapy is recommended for routine use in patients with stages IIA, IIB, and IIIA NSCLC, but not for routine use in populations with stage IB disease, which did not show significantly favorable results with adjuvant treatment in subgroup analyses [40,43–44]. Nevertheless, the pooled hazard ratio of 0.78 comparing SND and MLD was superior to that in adjuvant chemotherapy meta-analyses, which have generated great enthusiasm in the field of lung cancer treatment [29,40,43–45]. Furthermore, incomplete or inaccurate nodal staging by sampling or sentinel lymph node mapping could potentially prevent some patients from receiving beneficial postoperative chemotherapy [17,46]. The above views about adjuvant chemotherapy launched by Cancer Care Ontario and American Society of Clinical Oncology should be adjusted by the physician in light of each patient’s individual circumstances for clinical application, such as the degree of lymph node dissection and the intraoperative findings. To date, very few patients with stage IA NSCLC have been enrolled in RCTs of adjuvant therapy. Adjuvant chemotherapy is inappropriate for patients with stage IA, bronchioloalveolar carcinoma, PS >2, and patients suffering from pneumonectomy or major postoperative complications. In addition, clinical trials should be designed to test innovative therapies for further research.

6.2. Neoadjuvant chemotherapy

Several trials of induction chemotherapy have yielded conflicting opinions about its effects on survival and perioperative complications in stage IIIA disease [47–51]. Patients with documented MLN disease were found to be down-staged to N0 in thoracotomy after multimodality therapy in limited cases [52]. Survival was significantly better in patients with N2 down-staged to N0, after induction chemotherapy followed by surgical resection of SND [53,54]. These studies suggest that surgical resection after induction therapy should be avoided in patients who have biopsy-proven residual tumor in the mediastinal nodes [39,55]. With regard to establishment of the roles of adjuvant chemotherapy, several phase III trials tending to favor neoadjuvant chemotherapy as compared to surgery alone were terminated in 2005 based partly on ethical principles [56,57]. After the report of preliminary results of a randomized trial of neoadjuvant chemotherapy performed in China in 2002 [52,58], patients are now being recruited for a phase III head-to-head trial to explore the roles of neoadjuvant vs adjuvant chemotherapy in early stage NSCLC (NCT00321334).

6.3. Adjuvant radiotherapy

Adjuvant radiation therapy appears detrimental to survival in stages IB and II, and may confer a modest benefit in stage IIIA with limited evidence for less local recurrence [44,59]. Patients with positive resection margin and the highest mediastinal node, inadequate systematic sampling of hilar and MLNs, extracapsular nodal extension [21], multi-station N2, and the distance between the bronchial stump and the tumor of less than 2 cm are potential candidates for postoperative radiotherapy. Conformal irradiation therapy based on the markings of silver clips in various levels of MLNs resected, combined with the positions of pathologically
confirmed IIIA-N2 may be effective. It should also be confirmed in well-designed RCTs.

6.4. Neoadjuvant EGFR-TKI therapy in stage IIIA-N2

Stage IIIA NSCLC represents a relatively heterogeneous group of patients with ipsilateral mediastinal (N2) lymph node involvement. The relative roles of chemotherapy, surgery, and radiotherapy as the local treatment modalities are not clearly defined. Therefore, patients in this subset should be referred for multidisciplinary evaluation before embarking on definitive treatment.

The epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) may provide dramatic clinical responses in some patients with pulmonary adenocarcinoma carrying EGFR activating mutations. A trial conferring neoadjuvant EGFR-TKI therapy is currently recruiting participants (NCT00600587). The purpose of this study is to evaluate the value of neoadjuvant TKI therapy before thoracotomy in IIIA-N2 (confirmed by mediastinoscopy) NSCLC selected by EGFR gene analysis and to explore a new treatment strategy for this subset. Compared with neoadjuvant chemotherapy, individual induction TKI therapy holds the advantage with shorter periods of preoperative treatment, fewer side effects, and higher response rates with the assistance of EGFR mutations analysis. Furthermore, from the whole picture, transitory preoperative TKI therapy could also be used as a reference when considering the regimen of second-line treatment after progression. Drug sensitivity tests in vivo may replace other current TKI predictors of efficacy, offering better multimodality therapy strategies.

7. Accurate preoperative staging

Identifying pathological N2 disease is of paramount concern because its presence significantly affects prognosis and therapeutic implications. Recent findings supporting the use of adjuvant or neoadjuvant therapies in these patients suggest that efforts should be made to assess the lymph node status accurately in treatment-naïve patients as well as in those that have undergone preoperative treatments [60]. Over the last several years, different techniques have emerged, which vary in accuracy and procedure-related morbidity. Consensus has since been reached by the Council of the European Society of Thoracic Surgery. For primary staging, mediastinoscopy remains the gold standard for the upper mediastinal LNs. If thorough mediastinoscopy has been performed before thoracotomy, those areas previously sampled do not require repeat biopsy. Invasive procedures can be omitted in patients with peripheral tumors and negative nodes on PET scan for its high negative predictive value. PET-positive mediastinal findings should be cytohistologically confirmed by the minimally invasive techniques, including transbronchial needle aspiration (TBNA), ultrasound-guided bronchoscopy with fine needle aspiration (EBUS-FNA) and endoscopic esophageal ultrasound-guided fine needle aspiration (EUS-FNA). Complementary with the PET, their specificity is high, but the negative predictive value is low. If they yield negative results, a mediastinoscopy remains needed. Finally, SND is recommended in all cases to ensure complete resection and accurate staging to define the most adequate treatment strategy [61]. In restaging patients with stage IIIA-N2 disease who have undergone preoperative chemotherapy, after thorough staging mediastinoscopy, post-induction remediastinoscopy had disappointing sensitivity for adhesions and fibrosis. Integrated PET—CT might yield favorable results [62]. However, for restaging, endoscopic invasive techniques are still advisable despite the encouraging results supported with the use of PET—CT imaging. If they yield a positive result, non-surgical treatment is indicated in most patients [61,63].

8. Video-assisted thoracic surgery

As many surgeons are investigating the use of VATS lobectomy in patients with peripheral lesions and as the application of SND is difficult for most surgeons with VATS, Sugi et al. [31] included peripheral NSCLC less than 2 cm in diameter in their trial and demonstrated that this subset should not require radical systematic mediastinal and hilar lymph node dissection. Furthermore, the surgical approach to stage I and II NSCLC continues to evolve in the role of sublobar resections instead of lobectomy for treatment of smaller tumors, and the use of video-assisted techniques to perform anatomic lobectomy [40]. Recently, a prospective, multi-institution feasibility study about VATS lobectomy was published, showing that a standardized approach to VATS lobectomy, defined specifically with avoidance of rib spreading is feasible [64].

At present, VATS has been used by a small group of surgeons with expertise in mediastinal staging [65]. Whether thoracoscopic lymphadenectomy harbors more advantage than mediastinoscopy is not yet confirmed. While thoracoscopic techniques allow access not only to right paratracheal nodes, subcarinal nodes, and aortopulmonary nodes, which mediastinoscopy could reach, but also the inferior pulmonary ligament and paraesophageal lymph nodes [39]. Thus, these approaches should be used as a complement to standard mediastinoscopy in assessing hilar and MLNs [66], which could help avoid unnecessary thoracotomy in lower mediastinal IIIA_3-4 [67].

9. Conclusion

Surgery is a treatment modality that relies mostly on tailored therapy. Some surgeons feel that MLS is more targeted than SND. While learning from current evidence, the survival after mediastinal lymphadenectomy shows a tendency to favor SND. In addition, perioperative anti-tumor therapy could not be appropriately established in the absence of complete mediastinal lymphadenectomy. The hilar and mediastinal lymphadenecomy is the core component of the lung cancer multidisciplinary therapy. On the other hand, with the emergence of various preoperative staging techniques, the advantages of accurate neoplasm staging by SND could be partially supplanted. The increasing improvements of VATS and endoscopic technology will inevitably minimize the surgical trauma. Would lung cancer surgery witness the development history of breast cancer...
surgery once again, from minor to extensive, then extensive to minor? The values of lymphadenectomy should be further assessed using decision-tree analysis to evaluate the costs vs effects. Thus, it may be time for a paradigm shift in lung cancer multimodality therapy. [68].

Reference


