Sampling *versus* systematic full lymphatic dissection in surgical treatment of non-small cell lung cancer

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Abstract

The extent of mediastinal lymph node assessment during surgery for non-small cell cancer remains controversial. Different techniques are used, ranging from simple visual inspection of the unopened mediastinum to an extended bilateral lymph node dissection. Furthermore, different terms are used to define these techniques. Sampling is the removal of one or more lymph nodes under the guidance of pre-operative findings. Systematic (full) nodal dissection is the removal of all mediastinal tissue containing the lymph nodes systematically within anatomical landmarks. A Medline search was conducted to identify articles in the English language that addressed the role of mediastinal lymph node resection in the treatment of non-small cell lung cancer. Opinions as to the reasons for favoring full lymphatic dissection include complete resection, improved nodal staging and better local control due to resection of undetected micrometastasis. Arguments against routine full lymphatic dissection are increased morbidity, increase in operative time, and lack of evidence of improved survival. For complete resection of non-small cell lung cancer, many authors recommend a systematic nodal dissection as the standard approach during surgery, and suggest that this provides both adequate nodal staging and guarantees complete resection. Whether extending the lymph node dissection influences survival or recurrence rate is still not known. There are valid arguments in favor in terms not only of an improved local control but also of an improved long-term survival. However, the impact of lymph node dissection on long-term survival should be further assessed by large-scale multicenter randomized trials.

Introduction

The prognosis of lung cancer patients remains poor, and one of the targets of surgical treatment is to achieve radical (R0) excision and the most accurate staging. Among intra-operative findings, the role of lymph node involvement remains fundamental for these targets to be achieved.

The optimum extent of lymphadenectomy remains controversial. The purpose of this review is to evaluate the effectiveness of mediastinal lymph node dissection (MLND) *versus* sampling (MLNS) in staging accuracy, the overall survival and the impact of the procedure on mortality and morbidity in patients with non-small cell lung cancer (NSCLC).

In 2004, the council of the European Society of Thoracic Surgeons set up a workshop to standardize definitions and surgical procedures regarding lymph node dissection in NSCLC patients.[1]

According to these guidelines, *lymph node sampling (LNS)* is the removal of one or more lymph nodes that are thought to be representative; removal is guided by pre-operative or intra-operative findings. In order to select the suspicious lymph node, the surgeon focuses on the macroscopic appearance and visual and tactile evaluation, frequently through an unopened mediastinal pleura. *Systematic sampling* means that the surgeon performs routine pre-determined selection of lymph nodes at specific levels.

Systematic nodal dissection (LND) is the procedure of complete removal of the mediastinal tissue containing the lymph nodes, in a systematic manner within anatomical landmarks. Besides the mediastinal lymph nodes, dissection of the hilar and the intrapulmonary lymph nodes completes the resection. The technique ideally demands *en bloc* removal of all tissue that may contain cancer cells, including lymph nodes and surrounding fatty tissue with anatomic landmarks, as well the trachea, bronchus, superior vena cava, the aorta and its branches, pulmonary vessels, and pericardium.

Methods of research

A Medline search was conducted to identify articles in the English language that address the role of mediastinal lymph node resection in the treatment of NSCLC. Search terms included: lung, cancer, medi-

astinal lymph nodes, metastasis, sampling, dissection, mortality, complication, morbidity, survival. Search terms were selected on the basis of common key words identified during an initial literature search. The authors reviewed all relevant original and review articles published up till November 2011. Reference lists were also checked to ensure that all relevant articles had been identified.

Results

Stage accuracy

Worldwide, computed tomography (CT) is the accepted approach to determine the extent of the primary tumor, but it has limited potential in the assessment of mediastinal lymph nodes. Diameter larger than 1 cm in the short axis is generally considered to be the standard criterion for a suspicious lymph node. Several meta-analyses have reported low sensitivities and specificities of CT in the assessment of mediastinal lymph-node involvement, ranging from 50% to 65% and from 65% to 85%, respectively.[2] Positron emission tomography (PET) when combined with CT checks not only the size of mediastinal nodes but also their metabolic activity. Most available studies analyzing nodal staging with PET define sensitivity, specificity, and predictive values in reference to mediastinoscopy. We may conclude that a negative PET is accredited with a high diagnostic accuracy, matching with a negative mediastinoscopy.[3] However, the false negative rate of mediastinoscopy is close to 10%. There is no clear threshold to detect malignant tissue within lymph nodes by PET as this technique does not recognize tumor foci measuring less than 4 mm in diameter.[4] Consequently, medical imaging is unable to provide adequate staging of the mediastinal lymph node status.

MLND improves staging accuracy by increasing lymph node harvest and improving the identification of occult N2 disease. Skip transfer and occult lymph node metastasis are two theoretical reasons in favor of extensive mediastinal dissection.[5-7] Asamura and colleagues demonstrated that, *skip metastasis phenomenon* (which is the incidence of N2 disease without N1 involvement) occurred in 42 (25%) of 166 patients with NSCLC who underwent at least lobectomy with hilar and mediastinal lymphadenectomy.[8] Massard and colleagues conducted a multicenter cross-sectional study comparing lymph node sampling and dissection in each individual patient.[9] They reported on 208 patients with operable primary NSCLC who underwent mediastinum exploration prior to the lung resection, and in whom biopsies were taken from any suspicious node. Subsequently, the usual formal lymph node dissection was performed. Lymph node sampling adequately identified only 31 patients with N2 disease. However, after the MLND, 60 patients (including the 31 identified by MLNS) were confirmed to have N2 disease. In addition, MLND identified 25 patients with multilevel N2 disease, whereas only 10 were recognized through MLNS. Formal lymph node dissection provides both adequate nodal staging and complete resection, as the sensitivity of MLNS is limited to 51.6%. MLND is recommended in all cases for complete resection of NSCLC.

Survival benefit and disease-free period

The impact of MLND *versus* MLNS on overall survival is unclear as reports are conflicting.[9-13] A prospective randomized control trial conducted by Izbicki and colleagues in 169 patients with stage I, II or IIIA NSCLC found no survival benefit after a median follow up of 47.5 months.[14] The patients in the MLND group underwent lymphatic dissection from stations 12, 11, 10, 7, 4, and 5, whereas in the sampling group, mediastinal lymph nodes were removed only if they appeared suspicious. The authors failed to show any difference in overall and disease-free survival except in the sub-group of patients with limited

lymph node involvement (pN1 or single-station pN2 nodes). The application of immunohistochemical staining allowed micro-metastases on lymph nodes to be identified in 94 patients. In this group of patients, MLND appears to prolong relapse-free survival (P=0.037) with a borderline effect on overall survival (P=0.058). Because current pre-operative staging procedures cannot precisely identify these patients, the authors recommend that all patients with apparently resectable NSCLC should undergo MLND.

Sugi and colleagues evaluated radical systematic lymphadenectomy on early-stage NSCLC.[15] They conducted a prospective randomized study in 115 patients with peripheral NSCLC smaller than 2 cm in diameter and no evidence of suspicious lymph nodes on pre-operative CT (short axis diameter <1 cm). Pre-operative mediastinoscopy was not performed. The patients were randomly assigned into a lobectomy+MLNS group (n=56) or a lobectomy+MLND group (n=59). Patients in the first group underwent longitudinal incision of the mediastinal pleura, and any suspected nodes from regions 2 to 9 were removed. The nodes of regions 4, 5, and 7 were removed routinely from all patients. In patients undergoing MLND, resection was combined with a radical *en bloc* mediastinal lymphadenectomy as described by Naruke and Martini.[16,17] All patients with N2 disease received 50 Gy of radiation to the entire mediastinum post operatively. The numbers of patients with N1 or N2 disease were practically identical between the two groups. No significant difference was found in recurrence rate between the 3- and 5-year survival in the sampling group (89.2% and 83.9%, respectively *vs* 88.1% and 81.4%, respectively, in the dissection group). The authors concluded that MLND is not required in patients with clinically diagnosed peripheral non-small-cell lung cancers less than 2 cm in diameter.

Keller and colleagues reported improved survival after MLND in patients with tumors localized in the right lung.[18] A total of 373 eligible patients were enrolled to the study and divided in the MLND group (n=186) and the MLNS group (n=187). Only patients with pathological stages II (T1-2N1M0) or IIIA (T1-2N2M0) were included. Median follow up was 44 months. The survival rate of the 186 patients after MLND was significantly better than that of those patients who had undergone MLNS. However, this advantage was limited to patients with right lung tumors. Sub-group analysis demonstrated improved median survival after complete MLND in the 125 patients with right upper lobe tumors (median survival 57.5 months *vs* 29.2 months; P=0.006) as well as in the 66 patients with right lower lobe tumors (50.7 months *vs* 24.1 months; P=0.029). The survival advantage in patients with right lung tumors was 66.4 months when MLND was performed *versus* 24.5 months in the MLNS group (P<0.001). The weak point of the study was that only patients with N1 or N2 disease were included and the non-randomized choice of performing MLND *versus* MLNS which was based on surgeon preference. Also, of the 190 surgeons who had entered patients to the study, 131 of them entered only one patient.

Wu and colleagues designed a randomized, prospective clinical study to investigate the possible benefits of MLND *versus* MLNS in long-term survival and prevention of local recurrences in clinically staged I-IIIA NSCLC patients.[19] A total of 532 patients aged 70 years or under were enrolled in the study (although 471 were eligible for follow up) after surgical restaging. Of these, 268 patients were assigned to lung resection combined with MLND and 264 were assigned to lung resection combined with MLNS. In the latter group, nodes with suspected cancer metastases (diameter >1 cm or hard to palpation) were removed and submitted for histological examination. Nodes of the station number 7 were removed routinely in all patients. The median survival was 43 months in the MLND group and 32 months in the MLNS group (P=0.0001). The incidence of local recurrences and distant metastases seemed to be reduced in the MLND group. It should be noted that the patients were only clinically staged before randomization, thus 48% of the patients in the MLND group had pIIIA disease in comparison to 28%

of the patients in the MLNS group. Furthermore, there were no other data available related to any post-operative adjuvant therapy.

Lardinois and colleagues conducted a prospective study to compare MLND *versus* MLNS in two groups (n=50 patients each).[20] All patients underwent complete resection for stage T1-3N0-1 NSCLC without mediastinal lymph-node involvement, as assessed by mediastinoscopy. The study was not randomized and the technique of mediastinal lymph node assessment applied in a specific patient was related to the preference of the surgeon involved. No patient underwent induction therapy. The MLNS consisted of systematic sampling of the lymph-node stations 2, 3, 4, 7, 8, 9 on the right side and 4, 5, 6, 7, 8, 9 on the left side. The median overall survival time was 51.7±5.7 months after MLND and 50.9±4.9 months after MLNS (P=0.4). Disease-free survival was 46.2±5.3 months after MLND and 41.1±5.7 months after MLNS (P=0.3). Patients with pathological stage I NSCLC had a longer disease-free survival after MLND (60.2±7 months) than after MLNS (44.8±8.1 months) (P<0.03). Patients with pathological N0 status also revealed a longer disease-free survival after MLND (52.8±6.9 months) than after MLNS (41.3±7.7 months; P=0.08). Overall, local and distal recurrence for pathological stage I, II, and IIIA disease was observed during follow up in 59% (13 of 22), 82% (9 of 11), and 90% (9 of 10) of patients after MLNS and in 38% (9 of 24), 75% (9 of 12), and 62% (8 of 13) after MLND, respectively. A local recurrence was observed in 40% (17 of 43) of patients after MLNS and in 16% (8 of 49) after MLND. Although MLND does not lead to improved survival, local tumor control may be enhanced in patients with nodal negative mediastinum.

Ma and colleagues focused their retrospective two-institute study on those patients with early stage IA NSCLC.[21] The study enrolled 105 patients with post-operatively proved T1 tumor. Of these, 42 underwent MLND and 63 underwent MLNS. Significantly higher 5year overall survival in the MLND group was reported for patients with lesions between 2 cm and 3 cm (81.6% *vs* 55.8%; P=0.041). A higher incidence of post-operative complications was also reported in the MLND group (26.2% *vs* 11.1%; P=0.045). Considering the limitations inherent to the retrospective and non-randomized design of the study, MLNS should be performed if the tumor size is less than 2 cm and MLND if tumor size is 2-3 cm, for a potentially better survival. The study of Takizawa and colleagues failed to prove any significant difference in overall survival between the MLND and the MLNS groups in 119 patients with clinical stage I NSCLC.[22] After the median follow up of 79 months, the survival rate was 78% in the MLND group and 76.2% in the MLNS group (P=0.6).

Recently, a randomized multi-institutional prospective trial in 1111 patients, with early stage NSCLC (T1-2, N0-1) was reported by Darling and colleagues.[23] In the end, 1023 patients satisfied inclusion criteria. A rigorous mediastinal and hilar lymph node sampling per protocol was performed before randomization. For tumors in the right lung, lymph node stations 2R, 4R, 7, and 10R were sampled. For tumors in the left lung, stations 5, 6, 7, and 10L were sampled. Any suspicious lymph nodes were also biopsied. The surgeon had the option of taking samples by mediastinoscopy, thoracotomy, or video-assisted thoracic surgery. If none of the lymph nodes sampled showed evidence of cancer on frozen-section examination, patients were subjected to intra-operative randomization to MLNS, only with no further lymph node removal (n=498), or to complete MLND (n=525). The median survival was 8.1 years [95% confidence interval (CI): 7.0-9.0] in the MLNS group and 8.5 years (95% CI: 7.4-not achieved) in the MLND group (P=0.25). The 5-year disease-free survival was 69% (95% CI: 64-74) in the MLNS arm and 68% (95% CI: 64-73) in the MLND arm (P=0.92). There was no difference among local (P=0.52), regional (P=0.10), or distant (P=0.76) recurrence between the two treatment arms. It should be noted that the protocol required a detailed examination of lymph nodes from all mediastinal stations before randomization. This process eliminated many patients with possible occult micrometastases in mediastinal lymph nodes. The low incidence of unsuspected N2 disease (4%) in patients

who underwent complete MLND is not, therefore, surprising. The participation of many surgeons (n=102) from 63 institutes creates potential problems of standardization. In conclusion, the latter and latest study does not prove survival benefit after MLND in patients with early stage NSCLC. However, these results should not be generalized to other patients with either radiographically only based staging or those with higher stage tumors.

Cost of extensive mediastinal dissection

Many authors have examined the impact of MLND on the length of hospital stay and on the rate of patient complications. Radical lymphadenectomy requires major dissection that interrupts and damages neurogenic, vascular and lymphatic structures in the mediastinum. Potential complications may arise from injuries to the bronchial arteries and nerves, the tracheobronchial tree itself, and recurrent nerves. Neurogenic interruption can cause pulmonary vascular spasm. Cardiac output and cardiac rhythm may also be impaired.

The impact of the procedure on the operative time, on blood loss and the need for blood transfusions, the duration of the chest tube drainage, the rate of wound complications and the quality of healing are also important factors that should be taken into consideration. Prolonged air leaks, atelectasis and nerve palsies (due to injuries on recurrent or on the phrenic nerve) are also complications that concern many thoracic surgeons. Keller and colleagues found no difference between the MLND and the MLNS groups regarding operative time, blood loss and transfusion requirements.[18] Izbicki and associates prospectively compared the morbidity and mortality associated with MLNS and MLND and found that the radical approach was associated with a longer operation time (MLND 207 min *vs* MLNS 185 min), but no increase in blood loss, mortality, or the need for further surgery were observed.[24] The rate of chylothoraces and sustained recurrent laryngeal nerve injuries, the duration of chest tube drainage and overall hospital stay were similar in both groups. The same argument was also put forward in the study by Bollen and colleagues.[25] However, 3 patients in their study (5%) who underwent complete MLND suffered unintentional left recurrent laryngeal nerve injury, and 2 additional patients developed chylothoraces. Hata and associates reported two left recurrent laryngeal nerve injuries and one phrenic nerve paralysis in 50 patients who underwent extensive mediastinal dissection.[26] Doddoli and colleagues demonstrated in 465 patients with stage I NSCLC that lymphadenectomy (defined as the removal of at least 10 lymph nodes and a minimum of two stations) did not improve rates of operative morbidity and mortality.[27] The occurrence of respiratory complications, *i.e.* pneumonia and adult respiratory distress syndrome (ARDS), was very similar in the two groups who underwent lymph node sampling (n=207) and lymph node dissection (n=258). Fifty major complications (10.8%) occurred and resulted in 13 post-operative fatalities (2.8%). The post-operative mortality rate was 2.4% (n=5) and 3.1% (n=8), respectively, and all causes of death were related to ARDS.

There seemed to be a higher incidence in the elderly population of the study. In a retrospective and non-randomized study, Aoki and colleagues evaluated the efficacy of lobectomy without mediastinal lymphadenectomy in patients aged over 80 years with stage I NSCLC.[28] They performed lobectomy without MLND or MLNS in 27 patients and lobectomy with MLND in 22 patients. The authors reported significantly longer operative times in the MLND group, and intra-operative blood loss, but no difference in the length of post-operative hospital stay. There were no deaths in the first group, but one (4.5%) of the 22 patients in the MLND group died within 30 days after surgery. The overall morbidity rate was 41% (11 of 27 patients) and 41% (9 of 22 patients), respectively. Post-operative pul-

monary complications were more frequent in those patients with radical dissection, although the difference was not significant. The frequency of post-operative complications in octogenarians was also investigated by Chida and colleagues.[29] Forty-eight patients were divided into two groups: those who received an anatomical lung resection and mediastinal lymph-node dissection (MLND group, n=23), and those who received an anatomical lung resection and regional (hilar) lymph node dissection and/or sampling (MLNS group, n=25). There was no significant difference in the rate of death from cancer extension during the observation period between the groups (MLND 52.3% *vs* MLNS 53.8%). On the other hand, 9 of 21 patients (42.8%) died from other diseases in the MLND group, while only 2 of 13 (15.3%) died in the MLNS group (P=0.092). Thus, more patients in the MLND group tended to die from a disease other than cancer extension. No difference in pulmonary complications between the groups was found. Arrhythmia occurred in a total of 12 patients after surgery (9 MLND patients *vs* 3 MLNS patients). Thus, a mediastinal lymph-node dissection procedure was associated with a significantly greater incidence of cardiac complications as compared to a regional lymphadenectomy (P=0.004). In Okasaka's study[30] in 160 patients aged over 70 years, common complications of radical systematic mediastinal lymphadenectomy (such as recurrent nerve palsy and chylothorax) occurred in 4.2% in the MLND group (n=76), but did not occur in the non-MLND group (n=94). The patients of the latter group underwent simple pulmonary resection, with only a hilar lymph node resection, or selective mediastinal lymph node dissection. A trend for a higher rate of post-operative complications, including atrial arrhythmia, prolonged air leakage and pneumonia was found in the MLND group. Ishiguro and colleagues reported shorter operative time, less blood loss and shorter hospital stay in the MLNS patient group compared with the MLND group.[31]

These findings suggest that avoiding radical lymphadenectomy could be justified in resections for elderly patients. Thoracic surgeons should, therefore, carefully select the most appropriate, least invasive procedure of treatment, as these patients are more sensitive to the invasive nature of the operation than younger patients.

Discussion

Many authors have discussed the best management of the mediastinal lymphatic tissue during the surgical treatment of NSCLC. However, we should be more skeptical about the formality of the surgical resection in routine clinical practice. Little and colleagues found that the majority of the surgeons do not follow the *standard* approach of MLND, and only 57.8% of patients who had surgery at their initial treatment of lung cancer had any mediastinal lymph nodes sampled or removed. In community hospitals, the rate was even lower at only 48.1%.[32]

The definition of lymph node dissection may differ among authors and this may produce systematic study design bias in trials comparing MLND with MLNS. Practice patterns among surgeons may vary widely. Watanabe reported that there is considerable discordance in the designation of nodal station between Japanese and European surgeons, and thus more detailed nodal charts and precise, easily understood definitions of nodal stations are needed for intrathoracic staging.[33] There is also no common consensus on the minimum quantity of the lymph nodes that should be removed for pathological evaluation. Another issue is that the number of the lymph nodes may have been increased artificially when pieces have been fragmented during or after the dissection. At least six lymph nodes from hilar and mediastinal stations (one of them should be subcarinal) is the minimum requirement for accurate staging. Others recommended examination of a minimum of ten lymph nodes and at least three lymph node stations.[34-36]

The decision to perform MLND adds approximately 25-30 min to the operative time. The main concern of thoracic surgeons is the impact on mortality and morbidity. Most reports demonstrate that MLND is a relatively safe procedure, with no statistically significant difference in the frequency or severity of post-operative complications. However, the elderly population seems to be more vulnerable, and the possibility of prolonged hospitalization should be considered before making a final decision.

Whether or not a more extensive mediastinal exploration during resection for NSCLC will translate into a better local tumor control and improved survival is still controversial. The highly accurate surgical staging obtained after MLND might allow a more precise selection of the patients in adjuvant therapy protocols. The limitations of the single mode treatment may be overcome by multimodality treatment strategies, and incomplete nodal staging could potentially allow some patients to avoid adjuvant chemotherapy. A separate proportion of NSCLC patients are characterized by resectable pN2 disease, with no micrometastases to distal organs. This is a small group of patients that is impossible to identify pre-operatively. MLND offers these patients a complete R0 resection and the opportunity to obtain survival benefit from multidisciplinary therapy.

Conclusions

MLND is accepted as a standard complement of lobectomy for the surgical treatment of NSCLC. MLND is an important process for accurate staging; it increases the operative time by a few minutes, and has an acceptable impact on the rate of post-operative complications. Most studies demonstrate a trend towards better survival after MLND. However, the value of lymphadenectomy should be further assessed through such novel strategies as the use of videothoracoscopic and other endoscopic techniques. These techniques improve classification of the primary tumor according to metastatic potential in order to allow the treatment strategy parameters, including the optimum extent of lymphadenectomy, to be customized for each individual patient.

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