Sampling or node dissection for intraoperative staging of lung cancer: a multicentric cross-sectional study

Gilbert Massard a,*, Xavier Ducrocq a, Evgenia A. Kochetkova a, Vladimir A. Porhanov b, Marc Riquet c

a Service de Chirurgie Thoracique, Hôpital Civil, 67091 Strasbourg, France
b Cardiothoracic Center, 140 Ulitsa Rossiskaia, 350086 Krasnodar, Russian Federation
c Service de Chirurgie Thoracique, Hôpital Européen Georges Pompidou, 20 rue Louis Leblanc, 75908 Paris, France

Received 27 February 2006; received in revised form 30 March 2006; accepted 6 April 2006

Abstract

Objective: This study compares accuracy of sampling versus formal node dissection in patients with primary lung cancer. Patients and methods: During a 4-month period, 208 consecutive patients (172 men, 36 women) without bulky disease underwent resection for primary lung cancer in three centers. The surgeon first sampled the main lymph node stations, and subsequently performed a radical mediastinal dissection. Endpoints were accuracy of prediction for stage N2 and radicality of node sampling compared to dissection. Results: Resection consisted of 1 segmentectomy, 142 standard lobectomies, 6 bilobectomies, 14 sleeve-lobectomies, and 45 pneumonectomies. There were 108 squamous cell carcinomas, 621 adenocarcinomas, 18 bronchoalveolar carcinomas, 8 large cell carcinomas, 4 adenosquamous carcinomas and 8 neuroendocrine carcinomas. Primary tumor was stage T1 in 49 patients, T2 in 110, T3 in 43, and T4 in 6. Lymph node status (dissection) was N0 in 113, N1 in 35, and N2 in 60 patients. N2 disease concerned a single node in 16, a single node station in 19, and multiple levels in 25. Both N1 and N2 nodes were diseased in 36 patients. Sampling adequately recognized N2 disease in 31 patients (52%). Multiple level N2 was accurately identified in 10 patients (40%). Resection based on sampling would have been incomplete in 53 patients (88%). Conclusion: Radical mediastinal dissection is a mandatory adjunct to resection for lung cancer with curative attempt.

Keywords: Surgery; Lung cancer; Lymph node dissection

1. Introduction

For several reasons, accurate pathologic staging remains a basic recommendation for management of non-small cell lung cancer. At the individual patient’s level, staging allows to estimate prognosis and hence to define the most adequate treatment strategy. At the collective level, staging allows to evaluate new treatment modalities; further, it enables a given institution to proceed with internal audit and to check whether its results are in line with the usual standards of reference.

Medical imaging is unable to provide adequate staging. The pitfalls of CT scan have been outlined by several studies. Roughly speaking, the final message is that close to 20% of patients are at risk for understaging, and close to 50% for overstaging [1]. PET scan is an exciting new modality, especially when combined with CT scan: the combined assessment checks not only the size of mediastinal nodes but also their level of metabolic activity. Most available studies analyzing nodal staging with PET define sensitivity, specificity, and predictive values in reference to mediastinoscopy. We may conclude from these studies that a negative PET is credited a high diagnostic accuracy, matching with a negative mediastinoscopy [2]. However, we should also remember that the false negative rate of mediastinoscopy is close to 10%. A recent study has obviated a threshold for detection of malignant tissue within lymph nodes by PET; tumor foci measuring less than 4 mm in diameter were not recognized by PET [3]. On the contrary, a positive PET is subjected to a high false positive rate, justifying a pathologic evaluation in any case [2].

We should not rely on the size of the primary tumor to predict lymph node involvement: formal lymph node dissection may disclose N2 disease in up to 12% of patients with tumors measuring 1 cm in diameter or less [4]. Thoracotomy is a privileged access to a precise staging. Common sense anticipates that a complete lymph node dissection should lead to an almost absolute nodal staging. However, many authors have been frightened by the potential risks of such a dissection. Devitalization of the bronchial tree might favor bronchial stump dehiscence; the
extensive field of dissection might lead to secondary bleeding or chylothorax; resection of draining pathways might increase the risk for pulmonary edema and ARDS; removal of lymphatic tissue might decrease host defenses. Therefore, many colleagues have preferred to proceed with lymph node sampling, consisting of random biopsies at the main lymph node stages.

Our working hypothesis was that complete lymph node dissection is superior to node sampling for adequate determination of N stage; we further estimated that a complete node dissection is mandatory to ascertain a complete resection, leaving no invaded node in the mediastinum. One way to answer the question is a randomized trial comparing one group of patients undergoing sampling to another group undergoing formal dissection. However, this is an indirect approach, comparing two populations with some hazards of statistical error. Further, there is an ethical limitation: if dissection were clearly superior to sampling, it would be unethical to subject patients to sampling. Therefore, we decided to undertake a multicenter cross-sectional study, comparing sampling and dissection in each individual patient.

2. Patients and methods

2.1. Patient population

This study was conducted in three centers with four surgeons participating: Vladimir A. Porhanov in Krasnodar, Marc Riquet in Paris, Xavier Ducrocq, and Gilbert Massard in Strasbourg. We included 208 consecutive patients with operable primary non-small cell lung cancer. Patients with bulky mediastinal disease, N2 proven by mediastinoscopy, or having received preoperative chemotherapy were excluded.

None of the patients underwent PET scan; this tool was not available at the participating centers during the period of investigation; however, enlarged nodes suggestive for N2 or N3 disease were explored by mediastinoscopy. The three participating centers routinely perform complete homolateral lymph node dissection for any patient undergoing resection for primary lung cancer. Most surgical indications had been validated by a multidisciplinary discussion at the institutional tumor boards.

2.2. Methods

All operations were performed through standard or muscle sparing, posterolateral or lateral thoracotomy according to the surgeons preference. The tumor was resected with lobectomy or pneumonectomy as requested; bronchoplastic lobectomy was preferred to pneumonectomy when feasible.

Prior to lung resection, the mediastinum was explored and lymph node sampling was performed in the areas described below. Biopsies were taken following the surgeon’s impressions during inspection and palpation of nodes. Subsequently, the usual formal lymph node dissection was performed. Stations were adequately labeled. In this way, each patient has been his own control. There is no ethical concern because each patient underwent the planned routine lymph node dissection.

On the right side, we dissected the pulmonary ligament, the subcarinal space, the azygos nodes and the laterotracheal nodes.

On the left side, we dissected the pulmonary ligament, subcarinal space, aorto-pulmonary window, and paraaortic and sub-aortic nodes. In order to gain adequate access to the tracheobronchial angle, the arterial ligament was routinely transected.

We considered as N2 lymph nodes located beyond the pleural reflexion lines according to the ATS criteria. Intrapulmonary nodes were accurately dissected by the surgeon during lobectomy, and by the pathologist following pneumonectomy.

2.3. Criteria for judgment

Separate histopathological evaluation was made on sampled nodes and on the retrieved and adequately labeled dissection specimens. We calculated the true positive rate of lymph node sampling to predict N2 disease, and to adequately identify multi-level N2 disease. We also estimated the rate of complete resection based on sampling.

3. Results

We included 208 consecutive patients operated during a 4-month period in the three participating centers, by four authors: Vladimir A. Porhanov in Krasnodar group, Marc Riquet in Paris, Xavier Ducrocq, and Gilbert Massard in Strasbourg. We included 208 consecutive patients with operable primary non-small cell lung cancer. Patients with bulky mediastinal disease, N2 proven by mediastinoscopy, or having received preoperative chemotherapy were excluded.

None of the patients underwent PET scan; this tool was not available at the participating centers during the period of investigation; however, enlarged nodes suggestive for N2 or N3 disease were explored by mediastinoscopy. The three participating centers routinely perform complete homolateral lymph node dissection for any patient undergoing resection for primary lung cancer. Most surgical indications had been validated by a multidisciplinary discussion at the institutional tumor boards.

2.2. Methods

All operations were performed through standard or muscle sparing, posterolateral or lateral thoracotomy according to the surgeons preference. The tumor was resected with lobectomy or pneumonectomy as requested; bronchoplastic lobectomy was preferred to pneumonectomy when feasible.

Prior to lung resection, the mediastinum was explored and lymph node sampling was performed in the areas described below. Biopsies were taken following the surgeon’s impressions during inspection and palpation of nodes. Subsequently, the usual formal lymph node dissection was performed. Stations were adequately labeled. In this way, each patient has been his own control. There is no ethical concern because each patient underwent the planned routine lymph node dissection.

On the right side, we dissected the pulmonary ligament, the subcarinal space, the azygos nodes and the laterotracheal nodes.

On the left side, we dissected the pulmonary ligament, subcarinal space, aorto-pulmonary window, and paraaortic and sub-aortic nodes. In order to gain adequate access to the tracheobronchial angle, the arterial ligament was routinely transected.

We considered as N2 lymph nodes located beyond the pleural reflexion lines according to the ATS criteria. Intrapulmonary nodes were accurately dissected by the surgeon during lobectomy, and by the pathologist following pneumonectomy.

2.3. Criteria for judgment

Separate histopathological evaluation was made on sampled nodes and on the retrieved and adequately labeled dissection specimens. We calculated the true positive rate of lymph node sampling to predict N2 disease, and to adequately identify multi-level N2 disease. We also estimated the rate of complete resection based on sampling.

3. Results

We included 208 consecutive patients operated during a 4-month period in the three participating centers, by four authors: Vladimir A. Porhanov in Krasnodar group, Marc Riquet in Paris, Xavier Ducrocq, and Gilbert Massard in Strasbourg. We included 208 consecutive patients with operable primary non-small cell lung cancer. Patients with bulky mediastinal disease, N2 proven by mediastinoscopy, or having received preoperative chemotherapy were excluded.

None of the patients underwent PET scan; this tool was not available at the participating centers during the period of investigation; however, enlarged nodes suggestive for N2 or N3 disease were explored by mediastinoscopy. The three participating centers routinely perform complete homolateral lymph node dissection for any patient undergoing resection for primary lung cancer. Most surgical indications had been validated by a multidisciplinary discussion at the institutional tumor boards.
4. Discussion

Likewise, as in prior reports, this study clearly demonstrates that lymph node sampling is inadequate for accurate determination of N-stage. Its originality is not that much the result, than its design. This cross-sectional analysis represents in some way the final link in a chain of arguments in favor of lymph node dissection. It allows for a direct comparison of sampling to dissection in each individual patient, whereas most others studies compare two groups of patients treated differently, and finally conclude from survival data to stage migration and more or less adequate staging.

We would like to discuss two recent studies which demonstrated that prognosis of stage I is improved when more lymph nodes are dissected; both conclude to a stage migration effect.

Gajra et al. [5] have reviewed 442 patients with stage I disease. The authors studied the impact of total number of nodes dissected and of lymph node stations explored on rough and disease-free survival. Patients were classified into quartiles according to the number of nodes harvested: less than 4, 4–6, 7–9, more than 9 nodes; corresponding 5-year survival rates were 47.3%, 72.8%, 76.4%, and 79.1%, and corresponding 5-year disease-free survival rates were 43.4%, 67.3%, 76.3%, and 74.7%, respectively. Considering the number of lymph node stations explored, survival was 61.9% when no station was explored, 55.8% for 1–2 stations, 85.2 for 3–4 stations, and 87.6 for more than 4 stations. The authors adequately conclude that the observed difference is the consequence of a stage migration [5]. The more nodes are resected, the more likely is the reality of stage I; on the contrary, if few nodes are harvested, there is an obvious risk of missing involved mediastinal nodes. In our study, there were 113 patients with “true” N0 disease; if we add the 29 patients with a false negative sampling, we obtain a population of 142 patients with supposed N0 disease, of whom 20% are actually N2!

Doddoli et al. [6] reviewed 465 patients having undergone curative resection for NSCLC and pathologically staged N0. Median number of lymph nodes harvested was 10; median number of stations explored was 2. Therefore, the authors proposed to define as lymphadenectomy, a procedure harvesting more than 10 nodes, and exploring 2 or more node stations; patients were accordingly classified into sampling (N = 207) and node dissection (N = 258). Five-year survival was 59% following sampling and 64% following node dissection. In a multivariate analysis, node dissection was identified as a favorable prognostic factor (hazard risk: 1.43; 95% confidence interval: 1.00–2.04; p = 0.048) [6]. We underline that the number of lymph nodes in a given station is highly variable; therefore, a definition of lymph node dissection relying only on the number of dissected nodes is hazardous.

The myth of increased complications following formal node dissection is swept away by two recent studies. Lardinois et al. [7] showed that there was no significant difference in terms of morbidity, duration of drainage, and duration of hospital stay when comparing sampling to dissection. Doddoli et al. [6] showed that there was no difference in complications excepted for left laryngeal nerve palsy, which was more frequent following lymphadenectomy. As we noticed from our own experience, laryngeal nerve palsy may be prevented with increasing experience; we recommend to routinely sever the arterial ligament and to completely dissect out the vagous and recurrent nerves before removing the lymph nodes.

If lymph node sampling fails to recognize diseased nodes, there should be an increased incidence of local recurrence following sampling in comparison to node dissection. This hypothesis is nicely confirmed by Lardinois et al. [7], who compared two populations of patients with N0 or N1 disease, defined either by sampling or by node dissection. This study was not randomized, but each participating surgeon chose a technique at the beginning and applied it all along the duration of the study. Although there was no difference in overall survival, the disease free survival was significantly longer after node dissection (41 months vs 46 months). Local recurrence in patients with node-negative mediastinum (N0/1 disease) occurred more frequently after sampling (46%, 16 of 35 patients) than following complete dissection (13%; 5 of 38 patients).

There is an increasing body of evidence that lymph node dissection does not only improve staging, but may also increase survival. Of course, studies concentrating on stage I disease are subjected to a simple stage migration effect and do not allow to conclude.

Keller et al. [8] demonstrated a significant improvement of survival in patients with node involvement subjected to lymph node dissection when compared to sampling. The reported series included 373 patients with pathologically staged N1 or N2 disease. One hundred and eighty-seven patients underwent sampling, and 186 underwent complete node dissection; 222 were N2. Median survival was 57.2 months after dissection and 29.2 only after sampling; respective median survival rates were 66.4 and 45.2 months for stage N1, and 38.2 and 22.2 months for stage N2. The same difference was noted for right-sided tumors, where median survival was 66.4 months after dissection and 24.5 months after sampling. Surprisingly, there was no difference for left sided tumors, but we know that an exhaustive dissection is technically more demanding on the left side. In a multivariate analysis, sampling appears as a significant adverse prognostic factor (relative risk 1.502; 95% confidence interval 1.139–1.980; p = 0.0034). This series, however, suffered from two methodological drawbacks: though including patients with proven stage II or IIIa, it has been a non-randomized study; the cooperative multicenter design made that 373 patients were operated by 192 different surgeons.

A more definitive argumentation has been set by Wu et al. [9]. A randomized study including 532 patients compared sampling to node dissection. As expected, dissection staged more patients with N2 disease (sampling: 42% stage I and 28% stage IIIA; dissection: 24% stage I and 48% stage IIIA). Comparing stage by stage, 5-year survival was improved after dissection (stage I: 82% vs 57%; stage II: 50% vs 34%; stage IIIA: 27% vs 6%). Stage migration alone cannot explain this result, because the observed overall survival was considerably better in patients having undergone dissection (48% vs 37%).

Protocols of multicenter studies usually describe with extensive details criteria for chemotherapy or radiation
therapy, and define quality control for these treatment modalities [10,11]. Surprisingly, no single study mandates quality controls for surgery. It is frustrating that the surgical community has not yet defined adequate and validated quality criteria for oncologic surgery. A simple look at the area under the curve illustrates immediately that surgery is still the mainstay of treatment, and claims for a high quality surgery [10,11]!

We conclude that formal lymph node dissection should be a standard approach during surgery for non-small cell lung cancer: it ascertains both adequate nodal staging and completeness of resection. There are valuable arguments in favor of not only an improved local control of the disease but also of an improved long-term survival.

References


