Long-term survival with surgery as part of a multimodality approach for N3 lung cancer

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Abstract

OBJECTIVES: The extension of non-small-cell lung cancer (NSCLC) to supraclavicular (SC) and contralateral (CL) mediastinal lymph nodes is termed N3 and usually forbids surgical resection. However, scarce surgical series have reported encouraging results, and we sought to analyse our experience with this particular subgroup of patients.

METHODS: We retrospectively reviewed the charts of 5857 patients undergoing surgery for NSCLC during the last 30 years in two French centres. Eleven patients presenting with pathological-N3 were found, and more closely analysed concerning lymphatic spread, surgical indication and prognosis.

RESULTS: N3 consisted of tumoural extension to the SC (n = 5), CL mediastinal (n = 5) or both (SC + CL, n = 1) stations. Patients underwent induction treatment with chemotherapy alone (n = 4), chemoradiotherapy (n = 3) or first-line surgery (n = 4). All patients underwent a complete surgical resection of the tumour associated with ipsilateral systematic mediastinal lymph node dissection. Additional resection of N3 lymph nodes was performed in 8 cases. Adjuvant treatment included chemoradiotherapy (n = 6), chemotherapy alone (n = 1) or radiation therapy alone (n = 1). All 5 patients with SC-N3 presented with ipsilateral disease; 3 of them survived 5 years. Four patients with CL-N3 presented with left-sided tumour and nodal extension to the 4R station, and none of them survived.

CONCLUSIONS: Some N3-patients with specific anatomical location may benefit from multimodality treatment including surgery. These results support further prospective studies for selected N3-patients.

Keywords: Non-small-cell lung cancer • N3 disease • Multimodality therapy • Surgery

INTRODUCTION

Since 1986, the supraclavicular (SC) and contralateral (CL) hilar and mediastinal lymph nodes have been assigned to an N3 designation in the International Staging System for non-small-cell lung cancer (NSCLC) [1, 2].

In 1988, Naruke et al. [3] reviewed 1479 patients undergoing a complete surgical resection of NSCLC and reported that 5-year survival rates were acceptable in patients with Stage IIIA (mainly N2) disease, but anecdotic in patients with Stage IIIB (including N3) disease. This gap could be explained by the extremely poor prognosis of N3 disease in this study, with no 5-year survivors among 55 patients. As a result, the 1991 ACCP section report stated that Stage IIIB disease was more appropriately treated with non-surgical therapy [4], and the 2007 ACCP guidelines further specified that surgery was not recommended for these patients [5].

However, some clinical trials have combined induction therapy and surgical resection with encouraging results in patients with Stage IIIA (N2) disease, questioning the relevance of such a management for patients with Stage IIIB (N3) disease. In 1994, Rusch et al. [6] reported encouraging results following multimodality treatment and surgical resection of patients with N3 disease. As contributions have been rare, this question is still open to discussion. Our purpose was to contribute to solving that problem and to analyse the particular lymphatic spread and prognosis of patients with Stage IIIB (N3) NSCLC undergoing surgical resection.

PATIENTS AND METHODS

From January 1980 to December 2009, 5857 patients underwent a surgical resection for NSCLC with curative intent at the Department of Thoracic Surgery of Georges Pompidou European Hospital (Paris), and Cedar Surgery Centre (Bois Guillaume). Data were prospectively entered since April 1984. The charts of the patients were retrospectively reviewed. The preoperative
diagnostic work-up included chest X-ray, bronchoscopy, computed tomography (CT) scan of the chest, spirometry, lung perfusion scan and a thorough search for distant metastases (including positron-emission tomography scan in recent years). The staging system was the International Staging System for NSCLC of 2009 [1]. N3 disease theoretically precluded surgery.

However, 11 patients with proven N3 involvement were found in the database, and form or constitute the basis of this report. Those patients have been presented at Tumor Board Conferences, prospectively in 10 cases, and retrospectively to confirm the emergency management in 1 case. The decision to propose a surgical resection was taken in agreement with medical and radiation oncologists, after a careful examination of the situation. In most of the cases, the first decision was to perform chemo- and/or radiotherapy, but adequate and unexpected disease control led to a proposal of second-line surgical resection in carefully selected patients.

We more particularly focused on the location of N3 stations, treatment and long-term prognosis of these patients to question the place for surgery. Follow-up was performed by the chest physician and the thoracic surgeon. No patient was lost to follow-up. This study was approved by our Thoracic Surgery Society Ethics Committee that waived the need for informed consent.

RESULTS

There were 5 men and 6 women, with a mean age of 57.4 years (range 43–69 years). Lung cancer was located in the right upper (n = 3), left upper (n = 3), left lower (n = 3) and right lower (n = 2) lobes. There were 7 adenocarcinomas and 4 squamous cell carcinomas. The N3 involvement consisted of a tumoral extension to the SC (n = 5), CL mediastinal (n = 5) or both (SC + CL, n = 1) stations.

Surgery was decided in various situations, including: (i) good response to induction treatment in carefully selected patients in 7 cases; (ii) assumed first-line treatment of left-sided NSCLC associated with pretracheal lymph nodes involvement (classified as N2 disease before 2009) in 2 cases; (iii) salvage therapy in the emergency setting of massive haemoptysis in 1 case and (iv) compassionate therapy in a patient with contraindication to chemotherapy due to terminal renal failure in 1 case.

Surgical resections consisted in 4 lobectomies, 3 pneumonectomies, 2 bilobectomies, 1 sleeve lobectomy and 1 lingulectomy. The postoperative recoveries were uneventful except for 1 patient who presented a chylothorax requiring prolonged chest drainage without reintervention. There was no postoperative death, but 1 patient died from unknown causes 3 months after a left pneumonectomy. The median survival was 62 months, and the overall 5-year survival rate was 54.5% (Fig. 1).

SC-N3 was always on the side of the lung cancer. The patients are summarized in Table 1. Regarding perioperative management, 4 patients underwent induction therapies, including, in 1 case, platinum-based chemotherapy only and in the other 3 cases, chemoradiotherapy, with good responsiveness. The fifth patient underwent a first-line surgery, as he presented with haemoptysis requiring emergency surgery. Regarding SC-N3 management, the lymph nodes were surgically removed for 3 patients, and treated with definitive chemoradiotherapy for the last 2. One patient died of N3 recurrence within 2 years; 1 died of brain metastasis at 2.9 years, and the 3 others were alive at 5 years.

CL-N3 was always in the anatomical CL mediastinum. The patients are summarized in Table 2. The primary tumour was located on the left side and the nodal extension involved the 4R station in 4 patients. In 2 cases, pN3 disease was confirmed by mediastinoscopy, induction chemotherapy resulted in complete clinical mediastinal response, and a left lung resection with left mediastinal lymphadenectomy was performed without any right lymphadenectomy. In 1 case, cN3 disease was located in the lower pretracheal zone, chemotheraphy was contraindicated by renal failure and the patient underwent a first-line surgery through a left thoracotomy allowing a complete resection of the primary tumour and the bilateral mediastinal lymph nodes. In 1 case, the patient was staged cN0 and underwent a first-line surgery through a left thoracotomy, and the N involvement was discovered during the thoracotomy. In the last 2 patients, the CL-N3 was located in the lower pretracheal zone and was removed by the same thoracic approach after division of the ductus arteriosus. None of these 4 patients was alive at 5 years. The fifth patient had a right lung cancer and a CL-N3 in the aorto-pulmonary window (Station 5). He underwent a right upper lobectomy with a complete ipsilateral mediastinal lymphadenectomy and proved to be pT3N0. After adjuvant therapy leading to a stable disease, the patient underwent a left mediastinal lymphadenectomy through a left thoracotomy and is still alive after a follow-up of 8.6 years.

The patient with both SC and CL involvement was a 51-year old female who presented with left upper lobe squamous cell carcinoma. Left SC-N3 was confirmed by biopsy, and the diagnostic work-up demonstrated a clinical right paratracheal N3. She underwent induction chemoradiotherapy, followed by a left upper lobectomy and a bilateral mediastinal lymphadenectomy through two successive approaches and then adjuvant chemotherapy. The patient is still alive after a follow-up of 5.9 years.

Figure1: Overall survival following surgical resection of Stage IIIb (N3) disease.

COMMENTS

Our series demonstrates encouraging results after surgical management of some carefully selected patients with NSCLC and N3 involvement, questioning the rarity of that disease in surgical literature, the interest in selecting such patients for multimodality treatment and the importance of distinguishing the N3 mode of spread according to anatomical criteria as a basis for selection.
The main series of patients presenting with N3 disease and managed with surgery as primary treatment are summarized in Table 3 [7–12]. These surgical series are scarce and heterogeneous, and some of them are lacking long-term follow-up, making definitive conclusions difficult to draw. However, apart from the results reported in 1994 by Hata et al. [8], long-term survival rates were particularly poor, with 5-year survival rates ranging from 0 to 5% [7, 9–12]. Better outcomes were achieved when surgery was included in multimodality treatment protocols, as summarized in Table 4 [6, 13, 14]. In three large Phase II trials, 5-year survival rates ranged from 19 to 28%. However, the management of N3 disease differed among trials: N3 resection was not attempted in the Southwest Oncology group (SWOG) and in Stamatis’ Phase II trials [6, 13], whereas bilateral mediastinal lymphadenectomy was performed in patients reported by Grunenwald et al. [14]. In these three publications, the usefulness of removing N3 stations remained unclear as the predominant form of relapse was distant metastatic disease.

The management of clinical N3 involvement has therefore been tailored in further studies. In 2007, Yokomise et al. [15] reported surgery on 17 patients with unfavourable pericardial nodal disease, achieving upstaging of the pericardial station in 10 patients with N3 disease who underwent surgery followed by adjuvant chemotherapy. In 2012, Steger et al. [16] reported surgery on 17 patients with unfavourable persistent N3 extension after tri-modal therapy. Persistent N3 disease was resected through the same approach if CL, or a different approach if SC. Non-reachable low-volume N3 disease was assumed to be sterilized by radiotherapy without...
subsequent resection. In both series, multimodal therapy was justified with an acceptable outcome if surgery could be carried out with a curative intent and a low morbidity. However, these results raise some concerns about the usefulness of removing N3 stations when down-staged.

The presence of N3 disease is nowadays commonly diagnosed preoperatively by imaging and endobronchial techniques, but occult N3 extension may still be discovered during surgery. Interestingly, when Sakao et al. [12] performed cervical and bilateral mediastinal lymph node dissection in patients with lung cancer in the right upper lobe, 51% had N2 extension, and half of them had unexpected SC or CL-N3. More recently, Kendirinan et al. [17] performed cervical ultrasound in patients with lung cancer and no palpable SC-lymph node, and found that 25% had enlarged SC-lymph nodes on ultrasound and 13% had cytological-proven N3 involvement. Both studies suggested that SC-N3 was more frequent in patients with upper N2 involvement. On the contrary, Anami et al. [18] found that, among 11 patients with occult N3 micrometastases, 75% had no N1 or N2 extension and were considered as skip N3. Therefore, occult N3 disease seems both frequent in clinical trials and underestimated in clinical practice, questioning its influence on long-term prognosis.

Apart from these prognostic considerations, the classification of lymphatic extension of NSCLC has been lacking clarity for more than three decades. One should remember that mediastinal lymph node metastases, whether ipsilateral or CL, were classified N2 before 1986 [1]. Within this N2 group, in 1978, Naruke et al. [19] demonstrated that selected patients with metastasis limited to the ipsilateral mediastinal lymph nodes could undergo complete resection with a far better outcome than those with more extensive mediastinal metastasis that obviated surgical resection. The Naruke lymph node map was adopted with some modifications by the American Joint Committee on Cancer [20] in 1979, and adapted in 1983 by the American Thoracic Society (ATS) [21] to better fit the clinical staging and description provided by cervical mediastinoscopy. As SC and CL-N2 were in the field of radiation therapy and therefore considered regional by the radiation oncologist, these lymph nodes have been assigned to a N3 designation in 1986 [2]. Thus, the current N2 and N3 classification is the consequence of theoretical demarcation between surgical and radiation oncologists, to offer adequate loco-regional treatment to a greater number of patients. All the successive classifications constantly adapted the disease to the medical practice without taking the anatomy and physiology of the lymphatic drainage of the lungs into consideration.

Furthermore, the lack of consideration regarding the lymphatic anatomy led to a certain degree of confusion when classifying N2 and N3 diseases. When considering SC-lymph node, their location outside the hemithorax indicates them as apparently forming an independent lymph node station, even if this assertion is open to discussion. On the contrary, it is difficult to define where exactly the location is, of the mediastinal CL-N3 in the ATS lymph node map. The upper mediastinum has been divided along the midline of the trachea by the ATS [21], and some N2-patients were considered as having N3 disease because the lymph node involvement transgressed the tracheal midline. This artificial boundary was renewed in the 1997 Mountain classification [22]. Thus, discrepancies became evident between the Naruke and ATS maps concerning boundaries between hilar N1 and N2 at the level of the right upper

Table 3: Main series reporting surgery as primary treatment for N3 disease

<table>
<thead>
<tr>
<th>N</th>
<th>SC-N3</th>
<th>CL-N3</th>
<th>Surgical management</th>
<th>5-year survival rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watanabe et al. [7] (1991)</td>
<td>27</td>
<td>14</td>
<td>13</td>
<td>n = 19 (T + N + N3)</td>
</tr>
<tr>
<td>Hata et al. [8] (1994)</td>
<td>25</td>
<td>12</td>
<td>13</td>
<td>n = 25 (T + N + N3)</td>
</tr>
<tr>
<td>Jassem et al. [9] (2000)</td>
<td>4</td>
<td>–</td>
<td>–</td>
<td>n = 4 (T + N + N3?)</td>
</tr>
<tr>
<td>Naruke et al. [10] (2001)</td>
<td>111</td>
<td>–</td>
<td>–</td>
<td>n = 111 (T + N + N3?)</td>
</tr>
<tr>
<td>Sakao et al. [12] (2007)</td>
<td>37</td>
<td>–</td>
<td>–</td>
<td>n = 37 (T + N + N3)</td>
</tr>
</tbody>
</table>

The surgical management is summarized as (T + N) when including anatomical lung and ipsilateral mediastinal lymph nodes resections, (T + N + N3) if N3 involvement is present, and (T + N + N3?) if N3 involvement is suspected but not confirmed. The survival rates are presented as median survival or 5-year survival rates.

Table 4: Main series reporting surgery for N3 disease in the frame of multimodality trials

<table>
<thead>
<tr>
<th>Inclusion Induction therapy</th>
<th>Surgical management</th>
<th>N3</th>
<th>Survival rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stamatis et al. [13] (1999) Stage IIIB N = 56 (CRT)</td>
<td>N = 34 (T + N)</td>
<td>N = 32 (CL only)</td>
<td>5 years 26% (N3)</td>
</tr>
<tr>
<td>Grunenwald et al. [14] (2001) Stage IIIB N = 40 (CRT)</td>
<td>N = 24 (T + N + N3)</td>
<td>N = 19 (CL &gt; SC)</td>
<td>5 years 28% (N3)</td>
</tr>
<tr>
<td>Yokomise et al. [15] (2007) Stage IIIB-N3 N = 10 (CRT)</td>
<td>N = 10 (T + N + N3)</td>
<td>N = 10 (CL + SC)</td>
<td>2 survivors &gt;5 years</td>
</tr>
<tr>
<td>Steger et al. [16] (2012) Stage IIIB-N3 N = 17 (CRT)</td>
<td>N = 17 (T + N + N3)</td>
<td>N = 17 (CL + SC)</td>
<td>Median 31 months</td>
</tr>
</tbody>
</table>

CRT: chemoradiotherapy.
mediastinum, precarinal lymph node and at the level of the tracheal bifurcation lymph node. That source of bias was corrected by the International Association for the Study of Lung Cancer lung cancer staging project [23], but confusion may have existed until now concerning Stage IIIB research and mainly the N3 prognostic value, because the 1997 lymph node mapping was still in use in recent papers [17].

To better circumscribe the lymph node involvement of NSCLC and its influence on long-term survival, N2 and N3 stations are in need of being interpreted according to their anatomical counterpart. Regarding SC-N3, Hata et al. [24] carried out lymphoscintigraphies in 179 patients with neither hilar nor mediastinal lymph node lesions. Four important routes of lymphatic drainage from the left lung were identified, and two major crossings between the right and left lymphatic channels were found. The lymphatic drainages ended in the scalene nodes (SC-lymph node). This type of ending was confirmed by an anatomical study reported in 1997 by Le Pimpec Barthes et al. [25]. Both studies demonstrated that the SC-lymph nodes were in the way of the right paratracheal lymph node chains that also include the 4R and 2R stations, and of the left paratracheal lymph node chains including the 4L and 2L stations, suggesting that SC-lymph nodes should be considered as the highest ipsilateral lymph node stations of the same anatomical lymph node chain.

In the published series, SC-N3 are excluded for surgery in some [13] or exceptionally included for unknown reasons in others [14]. SC-N3 may even have been considered as non-surgical, whereas they seemed to be associated with the best results in two studies [15, 16] and in ours. Considering ipsilateral SC-N3 as the highest level of lymphatic involvement of the paratracheal chain, multimodality treatment should be discussed in the frame of the Tumor Board Conference. Aggressive treatment could include induction chemoradiotherapy in the case of multistations N2 and N3 involvement, or induction chemotherapy only in the case of skip N3 disease, followed by complete surgical resection of the primary tumour, ipsilateral mediastinal lymph nodes, and SC-N3 in the case of partial response, and concluded by adjuvant chemotherapy according to the final pathological staging.

Regarding CL-N3, the two major crossings between the right and left lymphatic channels on the left lung mentioned by Hata et al. [24] in 1990 had already been described by Rouvière in 1932. They also exist on the right lung as demonstrated on anatomical subjects. Thus, mediastinal lymphatic crossings commonly concern the stations 4R and 2R with the left and 4L and 2L with the right. Skip metastases outside the ipsilateral mediastinum are exceptional on those crossings, but may be explained by direct anatomical pathways from the left segments to the 4R nodes. The right paratracheal nodes are more frequently infused by the lymph issuing from the lymph nodes of the tracheal bifurcation (Station 7) or the precarinal lymph nodes (now considered as 4R [23]), which was also observed by Hata et al. [24]. On the contrary, metastases from the right lungs to Stations 5 and 6 are not anatomically demonstrated, either directly or after crossing other mediastinal lymph node.

Therefore, the anatomy of the lymphatic drainage explains well the extension of NSCLC from the left lung to the right latero-tracheal chain, but fails to explain the case of subaortic lymph node metastasis from a N0 right lung cancer that we observed. As this patient also benefited from prolonged survival, it is worth considering CL-N3 to the 5–6 stations as a systemic metastasis, managing the patient as if he were presenting with oligometastatic disease and offering elective surgical resection in selected cases.

However, this study has important limitations, including its small size, retrospective design, unplanned surgical resection in most of the cases and the unknown results of patients with similar demographics and tumours characteristics treated with chemoradiation only.

With respect to these limitations, we can conclude that some carefully selected N3 patients seem to benefit from multimodality treatment including surgery, and prospective multicentre trials should be encouraged.

Conflict of interest: none declared.

REFERENCES


