Perioperative considerations in patients with non small cell lung cancer and metastases in mediastinal lymph nodes

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Since the latest revision of the TNM system reclassified T3N0 tumours into the ⅡB stage, N2 lesions became the major determinant of the ⅢA stage. Concerning the minority of patients with T3N1 tumours in this stage, their prognosis depends on characteristic of T3 tumours: localised chest wall invasion is associated with more favourable prognosis compared to those T3 tumours that either directly invade the mediastinum, or have the proximal propagation < 2 cm from the central carina.

The significance of preoperative confirmation of metastases in mediastinal lymph nodes was recognized long ago, based on survival differences depending on whether N2 lesions were confirmed preoperatively or not (Tab 1).

Tab 1 Survival differences between operated patients with cN2 and pN2

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<tr>
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<th>5-year survival (%)</th>
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<tbody>
<tr>
<td>cN2</td>
<td>pN2</td>
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<tr>
<td>Martini</td>
<td>9</td>
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<td>Pearson</td>
<td>9</td>
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<tr>
<td>Patterson</td>
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<td>Cybulsky</td>
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1 Imaging techniques in nodal assessment

Despite the continuous improvements in CT techniques and resolution, the accuracy of CT for mediastinal staging has not improved during the past decade. A wide range of variations in sensitivity, specificity and accuracy can be found through the literature (41%–95%, 25%–99% and 53%–99%) respectively; similarly, positive and negative predictive values varied between 14%–95% and 79%–96% respectively. This variation in results is probably due to different methods of nodal measurement. Currently, the consensus is that the short nodal axis more accurately predicts nodal size than the long axis and that nodes >10 mm in short axis can be considered abnormal.

There are two main problems with the nodal size as the only criterion for N2 disease: first, lymph nodes may be enlarged due to reactive hyperplasia to either tumours or specific or nonspecific infections; second, normal sized nodes may contain microscopic metastases, especially in patients with adenocarcinoma or undifferentiated carcinoma. Similarly, micrometastases in small nodes without enlarged lymph nodes are reported to occur in 8%–60% of patients with N2 lesions.

In general, most authors agree that enlarged nodes on CT should not be considered positive without a biopsy specimen, either by mediastinoscopy, or by US guided transbronchial needle–biopsy. By the other hand, may be that the widespread opinion that small nodes on CT obviate the need for lymph node sampling, could be restricted only to T1N0M0 squamous cell carcinoma. Such a statement is supported by the results of Watanabe et al, who demonstrated that the majority of patients with peripheral NSCLC and proven multilevel N2 lesions, in presence of small nodes on CT, had adenocarcinomas.

Many earlier and recent studies and meta–analyses have shown that PET was more reliable in the mediastinal nodal assessment than CT. These studies demonstrated the sensitivity, specificity and accuracy of PET scan 84, 89 and
89\% respectively. Positive and negative predictive values of PET, according to these studies were 79\% and 93\% respectively. Despite evident advantages of PET compared to CT, the limited spatial resolution of PET often requires correlation with CT findings. That is why the recent concept of integrated PET–CT scanners is expected to achieve a higher accuracy than each of these techniques alone.

2 Practical aspects of the clinical staging of the mediastinum

In clinical praxis, the assessment of the need for invasive mediastinal staging depends on whether the particular institution has a PET or not. It should be mentioned that, if cIII stage is determined by CT only, extrathoracic metastases are found on PET in 24\%–28\% patients. In cII and cI stages determined by CT, distant metastases are found in 18\% and 1\%–9\% patients respectively.

So, having these facts in mind, what should be done in the absence of PET, not only related to N2 disease, but in general? One option is to intensify the assessment of the extrathoracic spread even in the absence of symptoms and to rely upon CT and mediastinoscopy (if performed routinely or selectively) for mediastinal staging. Another option, especially for centers where mediastinoscopy is not routinely done, is to perform neoadjuvant treatment either because of local extent of the tumour, or because of tumour pathology, poorly differentiated tumours or because of N2 lesions suspicious on CT. To simplify things, with CT being definitely insufficient and PET being quite better than CT (but still not absolutely reliable in mediastinal staging), mediastinoscopy still remains actual.

In brief, N2 lesions can represent a part of the following clinical scenarios. First, they can be a part of the extensive mediastinal involvement either by the tumour, or by confluent nodes. In this situation, it suffices to perform the least invasive procedure in order to make a diagnosis (sputum cytology, bronchoscopy, FNAB).

The second situation (Fig 1) represents the existence of discretely enlarged N2 or N3 nodes, where the extent of the intrathoracic spread of the disease is not so clear. In this situation, false positive results of mediastinal nodes assessment on CT reach 40\%, whilst false positive and false negative results on PET scan were found in 13\% and 8\%–30\%\(^{[11]}\). So, biopsies of mediastinal nodes should be attempted either by TBNA or EUSNA. In case of negative results, one should proceed with mediastinoscopy. Or, mediastinoscopy can be the initial diagnostic procedure.

The third situation exists when CT is not indicative of N2 lesions, but in presence of centrally located Adenocarcinoma (Fig 2). It was demonstrated that false negative rate of CT was 20\%–25\% and some reports (on limited number of patients) indicated that false negative rate of PET could probably be very high\(^{[12,13]}\). In such a situation, the procedure of choice is mediastinoscopy, not TBNA or EUSNA, as they are associated with 30\% false negative rates.

Finally, if CT and PET are negative in terms of N2 lesions in presence of peripheral cI tumour, mediastinoscopy is not necessary, as false negative rates of CT and PET are 10\% and 3\%–4\%.

3 Invasive staging of the mediastinum

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**Fig 1** Indications for mediastinoscopy in presence of discretely enlarged N2 or N3 nodes

**Fig 2** Indications for mediastinoscopy in presence of centrally located tumours
3.1 Mediastinoscopy  It sounds paradoxically that the first surgical exploration of the mediastinum was performed 50 years ago with the idea whose actuality was not denied till today: the idea of Harken and coworkers was that that the involvement of mediastinal nodes could make the operation for lung cancer useless. By using a supraventricular approach, they used to introduce Jackson’s laryngoscope into the mediastinum and biopsied lymph nodes. Cervical mediastinoscopy by using a cervical pretracheal incision was introduced by Carlens and was subsequently perfected and popularized by Pearson in the USA.

By mediastinoscopy, it is possible to perform biopsies of the following lymph node groups, according to Mountain-Dressler’s modification (1997) of Naruke/ATS lymph node map: 2R, 2L, 4R, 4L, 7 (right and left upper paratracheal, right and left lower paratracheal and subcarinal nodes).

In some centers extended mediastinoscopy is performed by introducing a mediastinoscope between brachiocephalic trunk and common carotid artery, so that biopsies of the anterior mediastinal lymph nodes become possible. This procedure is much more technically demanding than anterior mediastinoscopy. It can be an alternative to left parasternal mediastinotomy aimed to sample subaortic and anterior mediastinal lymph node groups (lymph nodes 5 and 6).

Recently, a new concept of maximally invasive staging of the mediastinum was proposed in form of transcervical extended mediastinal lymphadenectomy (TEMLA)\(^{[14]}\). This procedure, representing the combination of surgical dissection of the nect and videodiagnosis, enables biopsies of all mediastinal lymph node stations except pulmonary ligament nodes. The main drawbacks of this procedure – technically demanding, duration up to two hours – are balanced by the maximally reliable mediastinal staging. Moreover, it was recently shown that long term survival of patients selected for operation or neoadjuvant therapy after the TEMLA procedure was longer compared with patients without this procedure.

In many centers where mediastinoscopy is performed routinely, mortality is 0. In one recent analysis on 20 000 mediastinoscopies, complications occurred in 2.5% patients and procedure-related mortality was 0.5%\(^{[15]}\). The most serious complication is bleeding. On the right side, azygos vein and anterior branch of the pulmonary artery can be injured. Other major complications are lesions of the esophagus, recurrent laryngeal nerve, trachea or major bronchi.

3.2 Bronchoscopic techniques  In experienced hands, ultrasound guided transbronchial biopsies (EBUS) of interlobar and mediastinal nodes can reach comparable accuracy as mediastinoscopy. In 1999, transeosophagally ultrasound guided biopsies (EUS) of posterior mediastinal lymph nodes was also reported as useful additional tool, in many European centers. Although it is true that lymph node samples obtained by mediastinoscopy are more reliable owing to the quantity of the tissue, properly performed needle biopsy can collect material throughout the axis of the node, not only from one point within the node. Three years ago, at the annual meeting of the ERS, it was reported that, for different reasons, routine high level performance of these bronchoscopic techniques was performed in not more than 5% of European pulmonological centers. It means that, at present, these techniques can be alternative for mediastinoscopy, but only if expertly done.

4 Subgroups of N2 lesions

Depending on the way of confirmation of metastases in the mediastinal lymph nodes, the stage III of the disease can be divided into three subgroups:

4.1 IIIA1 This subgroup includes operated patients without preoperative confirmation of N2 lesions (CT, PET, mediastinoscopy), with negative ex tempore biopsies of mediastinal nodes during thoracotomy, but in whom confirmation of positive mediastinal lymph nodes was obtained after definitive pathological report of the operative specimens, usually several days after thoracotomy.

4.2 IIIA2 This subgroup includes operated patients in whom, like in the previous subgroup, N2 lesions were not confirmed preopratively, but in whom ex tempore biopsies of mediastinal nodes during thoracotomy confirmed the existence of N2 lesions.

4.3 IIIA3 This subgroup includes operated patients with metastases in mediastinal lymph nodes confirmed by cytology or histology before the operation.

It is clear that confirmation of N2 disease in patients operated in stages IIIA1 and IIIA2 does not influence the planned
operation – in the former N2 lesions are confirmed after the operation and in the latter, if tumour is resetable, despite positive \textit{ex tempore} biopsies of lymph nodes, the operative procedure will not be aborted\cite{18,19}. Only in patients belonging to IIIA3 stage surgical treatment is not justified as initial therapeutic procedure. Even with adjuvant radiation therapy, 5-year survival of patients with preoperatively confirmed N2 lesions, does not reach 25%. Only in case of "minimal" involvement of mediastinal nodes (only one node without capsule invasion), 5-year survival can reach 20%–25%.

5 Therapeutic approach in stages IIIA1 and IIIA2

5.1 Adjuvant (postoperative) radiation therapy  Although it is well known that postoperative radiation therapy (RT) can eliminate microscopic residual tumour tissue thus decreasing the rate of the local relapse, there is still no evidence to confirm any survival benefit. In fact, the maximal effect of this kind of therapy in patients with residual disease can be expected only in the absence of occult distant metastases. Practically, it is impossible to determine the exact percentage of such patients. The LCSG trayal (mostly N1, minority with N2/T3N0), demonstrated that local relapse, as the first site of relapse, exists in about 20% operated patients without adjuvant treatment vs 1% local relapse in a group with postoperative RT. However, like some other randomized studies, neither this one showed the survival benefit that could be attributed to this treatment modality.

Although some studies addressed the problem of the harmful effect of the postoperative RT, these results should be accepted cautiously. In fact, one major meta analysis on 9 randomized studies (2 128 patients), clearly indicated the increased risk of mortality in postoperatively irradiated compared to non irradated patients\cite{20}. But, this analysis also included 26.4% patients in pI stage in which RT is usually not incicated. Moreover, it was just in the stage I where the increased risk of mortality was the most evident, not in patients with N2 lesions.

Taking account the above data, postoperative RT in this stage is not justified from the standpoint of the expected prolonged survival of the operated patients. This therapy can be justified in patients with multilevel metastases in the mediastinal lymph nodes, in presence of extracapsular nodal involvement and positive resection margins, but only with the aim to lower the risk of the local relapse. In order to avoid serious cardiac complications, the use of scanner is advisable while planning the irradiation.

5.2 Adjuvant (postoperative) chemotherapy  This therapeutic approach is based on the fact that systemic dissemination represents the most frequent form of cancer relapse in the stage IIIA.

The meta analysis on 14 randomized clinical trials comparing operation followed by platinum based chemotherapy with operation alone, demonstrated the 5% improvement of the 5-year survival in patients with adjuvant therapy. The same meta analysis revealed harmful effects of alkylizing drugs (15% increase of the risk of the lethal outcome) and the favourable effects of platinum based treatment (13% decrease of the same risk).

Similarly, meta analysis of randomized trials in 1998. (Le Chevalier), confirmed the survival benefit of only 5%\cite{21}.

The role of this treatment modality in the stage III is still being assessed in several multicentric randomized trials.

6 Therapeutic approach in stage IIIA3

6.1 Neoadjuvant therapy  It was demonstrated that after neoadjuvant therapy, the operation becomes possible in up to 50% patients initially assessed inoperable. The drawbacks of such an approach are delayed removal of the primary tumour and increased operative morbidity and mortality.

When discussing this treatment modality, it should be pointed out that, in patients with pN2 lesions, extracapsular and multilevel nodal involvement represent unfavourable prognostic factors.

The prognostic significance of the topography of metastatic mediastinal nodes is not so clear. Some studies indicated the less favourable prognosis if upper mediastinal nodes were involved (nodes accessible by mediastinoscopy) compared with patients in whom N2 lesions were revealed only at thoracotomy. Other studies found the involvement of subcarinal nodes, either isolated or in combination with other nodal groups, as less favourable compared to the involvement of other nodal groups\cite{22}.

There are also studies that found the involvement of lower mediastinal nodes (No 8, 9) as prognostically unfavourable, beside subcarinal nodes\cite{23}.
Concerning the significance of tumor localisation in presence of N2 lesions, rare studies that analysed this problem, indicated that the involvement of upper mediastinal nodes in presence of upper lobe tumors, was associated with better prognosis compared with the involvement of subcarinal nodes\textsuperscript{24}.

It seems that only multilevel nodal involvement, not the localisation of the involved nodes, represents the unfavourable prognostic sign.

Several nonrandomized phase II trials indicated the advantage of such a combined treatment modality compared with operation only, that was manifested in the increased resectability rate and survival, with similar operative morbidity and mortality\textsuperscript{25}. The 65% complete resections rate after induction CT (Mitomycin, Vinblastin, Cisplatin) for confluent of multilevel N2 lesions, as published by Martini (15% operative mortality, 28% 3-year survival), was confirmed by other phase II studies\textsuperscript{26}. This survival rate is better than 8% 3-year survival, that is classically reported for the same form of mediastinal nodal involvement without such approach.

In eight small nonrandomized trials that appeared till 2003, beside small number of patients, patients with T3N0 tumours were also included. Besides, stage III B was analysed together with lower stages, whilst surgical staging of mediastinal nodes was different. That is why trials from Barcelona (Rossel) and MD Anderson Center are the most reliable.

The Rossel s trial included 60 patients in III A stage, a part of whom had operation only and the rest underwent operation after three cycles of CT (Mitomycin, Ifosfamid, Cisplatin). All patients were irradiated postoperatively. Mediastinoscopy was performed preoperatively in 3/4 of patients, 27% patients had T3N0 or T3N1 tumours. Two and 5-year survival in a group with neoadjuvant treatment was 29% and 17% respectively, vs 2% and 0 in a group with operation only.

The MD Anderson trial included 60 patients in the stage III A (26% T3N0/1, preoperative mediastinoscopy in 83% pts), subjected either to operation only, or to three cycles of preoperative CT (Ciklofosamid, Etoposid, Cisplatin), followed by three cycles of postoperative CT. In the induction CT group, 3- and 5-year survival was 46% and 36% respectively, vs 19% and 15% in the operation only group. This survival difference may be attributed to downstaging in the CT group.

Among patients who underwent induction CT, candidates for surgical treatment should be only those with clear response to therapy (~60%—75% patients). In the SWOG trial, 22% patients had pathologically complete response to treatment, with 27% 3-year survival. The mean survival of patients with complete response was 30 months vs. 10 months in patients with N2 lesions\textsuperscript{27}. In the Bueno’s study, in 28% patients with complete response to CT (N0), 5-year survival was 35.8% vs 9% in operated patients with involved lymph nodes\textsuperscript{28}.

One of the main questions related to the extent of the lung resection after induction CT is whether the extent of resection should be tailored according to initially (before treatment) assessed local extent of the tumour, or according to local extent after the treatment. Although the explicit answer to this question did not exist 7-8 years ago, based on the accumulated experience, it is likely that the minimally possible extent of resection is justified if healthy resection margins are confirmed on frozen section during the operation.

Concerning restaging after induction CT, even with the use of PET, around 33% false positive and 15% false negative results were reported, with only ~52% correct findings\textsuperscript{29}. That is the reason for performing of remediastinoscopy in some centers. In this situation, mediastinoscopy is technically more difficult than first mediastinoscopy.

6.2 Preoperative radiation therapy Advantages of this treatment modality are: possible effect to the part of the tumour whose spread, although clinically silent, already reached the predicted resectional margins; better tissue clivage plan owing to demarcation of the tumour tissue; unresectable tumour becomes resectable. Disadvantages are clearly increased risk of operative morbidity and unclear limits of diseased tissue.

Not only lacking in survival benefit, this form of treatment was also sometimes reported as associated with worsening of survival, due to increased operative morbidity.

In patients with marginally resectable tumours, the effects of this form of treatment are contradictory. In a group of 53 patients in III A stage, operated after irradiation with 30 Gy during two weeks, Sherman reported the resectability rate of 72% with 17% 5-year survival. In LCSG phase II study, one month after irradiation with 45 Gy during 4.5 weeks, resectability rate was 34%, but the treatment related toxicity was high.

Preoperative irradiation therapy was suggested for Pancoast
tumours 30 years ago. Although in the Paulson’s series with such therapeutic approach 34% 5-year survival was achieved, similar results were reported also with postoperative irradiation or with irradiation only.

Today, preoperative radiation therapy is justified only inside controlled protocols of preoperative chemo and/or radiation therapy.

7 Specific considerations related to N2 disease

7.1 N2 lesions and sleeve pneumonectomy Until recently, broad consensus about the significance of nodal stage, as the key point of patient selection in patients undergoing this operation, did not exist. The attitudes varied from not accepting suspected N2-lesions as contraindication to surgery, through performance of mediastinoscopy only in presence of tracheal compression above the anticipated line of resection, to routine mediastinoscopy in all candidates for this operation\(^{[30,31]}\). In our recently published series of 42 patients with SP, pN2 lesions existed in 47.6% of patients. The reason for such a high percentage of pN2 lesions, (beside the mediastinoscopy related policy), was a high proportion (33.4%), of preoperatively unexpected sleeve–pneumonectomies after the preoperative work up. Similar policy existed in some other published series where detailed systematic lymphadenectomy, not a mediastinoscopy, was found as essential in terms of survival, because all 5-year survivors with pN2 lesions had systematic lymphadenopathy.\(^{[32]}\) The analysis of prognostic significance of nodal stage is additionally complicated by attitudes of some authors, for whom the presence of intracapsular N2 lymphadenopathy does not represent a contraindication for surgery, just as for standard pneumonectomy\(^{[33,34]}\); that is the reason why they perform mediastinoscopy only when N3 nodes are suspected.

The structure of patient groups reported in the literature is different related to N2–lesions, probably due to different patient selection. The percentage of pN2 in our series is higher than 24.5% and 29.6% as reported by Roviaro and Mezzetti on 49 and 27 patients respectively\(^{[35]}\). By the other hand, it is almost equal to 48% reported by Politi on 48 patients\(^{[36]}\) and lower than in a series of Porhanov where, in a subgroup of 23 patients with preoperatively diagnosed T3 tumours, 61% of them had N2–lesions.

The significant survival difference in favor of patients without pN2 vs patients with pN2 lesions clearly supports actual widely accepted attitude that this operation should not be done in patients with N2 lesions confirmed either before or during thoracotomy. The only exception could be made in case of isolated metastasis in the lymph nodes at the level 7, because they can be resected en block with the carina\(^{[37]}\).

7.2 N2 lesions in patients with COPD undergoing a lung resection. It is now well established that a curative operation is possible in a great proportion of patients with lung cancer and even moderate to severe COPD, if properly selected. The explanation is that the delayed FEV1 deficit after lobectomy can often be smaller than in operated non–COPD patients\(^{[38]}\). In a study on 42 COPD and 45 non–COPD patients, the fall in FEV1 six months after the operation in the COPD and in non–COPD groups was 3.2% and 14.9% respectively\(^{[39]}\).

By the other hand, most studies confirmed that COPD patients were exposed to the increased risk of postoperative complications. In one of biggest studies of this problem (181 COPD patients), operative morbidity and mortality were 42.3% and 7.9% respectively. Of interest for such patients with N2 lesions, undergoing lung resection after induction chemotherapy is the fact that, sometimes, cardiopulmonary complications, even without induction chemotherapy, can be more frequently associated with lobectomy than with pneumonectomy\(^{[40]}\). Having in mind the fact that lobectomy after induction chemotherapy can be technically more difficult than without it, especially in patients with incomplete lung fissures, preoperative selection of COPD patients for such a treatment should be cautiously done.

In COPD patients undergoing pneumonectomy, the overall operative risk should be counterweighted by the expected survival benefit. That is why one should be aware that in a certain proportion of COPD patients with pN2 lesions confirmed after pneumonectomy, postoperative radiation therapy will not be possible for different reasons. In these patients, postoperative chemotherapy may be safer and acceptable, especially in patients with adenocarcinomas and poorly differentiated carcinomas. So, in COPD patients undergoing pneumonectomy, systematic lymphadenectomy has also a role in the relapse prevention.

7.3 N2 lesions in the elderly undergoing a lung resection
The incidence of lung carcinoma diagnosed in elderly patients is rising worldwide, and the overall population in the developed countries is aging. The widespread belief that the life expectancy of an octogenarian with lung cancer is limited by death from natural causes is not supported by recent data. In fact, the average life expectancy for an 80-year-old living in the United States is now around 8.6 years. That means an overall 5-year survival of 80%. As the majority of this time is anticipated to be active and independent life. It seems likely that the greatest impact on an octogenarian’s survival and quality of life will be their cancer-related mortality rather than their age.

Although the age limit for surgery has even been pushed upwards to 80 years more recently, pneumonectomy has always carried a higher mortality compared with lobectomy. Rare stage adjusted studies are in line with these data, demonstrating the increasing mortality with higher stages (4.8%, 6.2%, 12%, and 20% for stages I, II, IIIA, and IIIB, respectively). In the elderly, especially in octogenarians, whenever possible, lobectomy is the preferable operative procedure, with survival rates that are higher than for pneumonectomy, demonstrating the increasing mortality with higher stages (4.8%, 6.2%, 12%, and 20% for stages I, II, IIIA, and IIIB, respectively).

In the elderly, especially in octogenarians, whenever possible, lobectomy is the preferable operative procedure, with survival rates that are higher than for conservative resection and morbidity rates lower than for pneumonectomy. As N2 lesions usually exist in more advanced tumors requiring pneumonectomy, in the elderly patients with centrally located neoplasms, sleeve lobectomy whenever technically possible should be preferred to pneumonectomy, particularly for right-sided tumors. Care should be taken of the frequent impossibility to perform adjuvant treatment in these patients, mainly due to their age and associated comorbidity.

### 7.4 Lung resection after previous pleural empyema in presence of N2 lesions

Based on scarce literature data, it is likely that lung resection, including pneumonectomy, can be safely performed provided empyema is properly solved. Of course, a balance should be made between the duration of conservative treatment of empyema and the existing emergency for surgical treatment with regard to the malignant disease. Our experience is also in line with these reports. Moreover, good cleavage plain between the lung and the chest wall and absence of any signs of active infection existed in most of our operated patients. Having this in mind, in younger patients in good condition, nonconfirmed (but suspicious) N2 lesions, in presence of otherwise resectable tumor, are not an obstacle for surgical treatment. One should only be aware that in some of these patients pneumonectomy will be necessary, especially in patients with long lasting empyema. If pneumonectomy is necessary after induction chemotherapy, a surgeon should be aware that extrapleural pneumonectomy can be the only possible solution.

### References


