What to do with "Surprise" N2?

Intraoperative Management of Patients with Non-small Cell Lung Cancer

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There is debate about how patients should be managed when malignant involvement of mediastinal lymph nodes is encountered at the time of lung resection. A comprehensive review of the literature demonstrates that differences in which outcomes are reported and how extensively patients were staged preoperatively explain much of the conflicting data. Certain negative and positive prognostic factors can be defined, but in general the outcomes justify proceeding with resection unless it is clear that disease will be left behind. Reasonable arguments can be made that the approach should include a mediastinal lymph node dissection and adjuvant therapy.

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The subject of intraoperative assessment and management of unanticipated N2 involvement remains a confusing area. The term "surprise N2" in this article refers to any patient who is discovered to have N2 lymph node involvement that was not suspected or documented preoperatively. The data often seems to be conflicting, in part because the patient populations vary (e.g., with respect to selection or the extent of preoperative staging investigations). Because of confusion about the data, approaches are often driven more by underlying attitudes or assumptions. For example, some take a simple, existentialistic approach that staging is relatively unimportant because outcomes are determined by fate, or at least factors about biologic behavior that we are not able to predict. The implication of this attitude is that treatments other than surgery are not useful. Others believe that dissemination of lung cancer is primarily though lymphatic drainage in a progressive manner, and therefore that resection of all potentially involved nodes is crucial (and that the highest node is negative). Others believe that nodal involvement is only useful as a prognostic marker, representing a surrogate measure of whether a tumor has developed the ability to grow significantly at other sites. Proponents of this theory cite the fact that tumor cells circulating in the bloodstream are quite frequent, even in node-negative cancers, but do not always lead to disseminated metastases. The data are not currently available to clearly prove or refute such different underlying beliefs.

This article takes a purely pragmatic approach, and discusses data that pertains to a number of practical clinical questions that surgeons face. These include whether intraoperative nodal assessments should affect if resection is carried out, whether it affects the extent of pulmonary resection, including if there are special situations in which these questions should be answered differently. Finally, this article considers the question whether there is a therapeutic benefit to complete removal of all lymph nodes by means of a mediastinal lymph node dissection (MLND), or whether the extent of intraoperative node assessment merely contributes to the accuracy of pathologic staging.

DOES MEDIASTINAL NODAL STATUS AFFECT THE DECISION TO RESECT?

Mortality and Quality of Life (QOL)

Should the status of mediastinal nodes as assessed at the time of thoracotomy affect the decision to proceed with a resection? This question really comes down to an assessment of the long-term survival versus the short-term mortality and the effect on QOL. Answering the question is complex, because the long-term survival, in particular, depends on many factors and must be carefully considered.

There seems to be little difference in the perioperative mortality of an exploratory thoracotomy versus a resection. The average reported operative mortality after an exploratory thoracotomy is 4% (0–7%).[1–7] The average operative mortality for pulmonary resection is approximately 4%,[1] although more recent series suggest it has decreased to about 2%.[8–10]

The data for QOL generally suggests that both short-term and long-term QOL considerations have little impact on intraoperative decision making. Most studies of perioperative QOL have suggested that although short-term QOL is decreased by surgical resection, QOL returns to baseline by 6 months.[1,11,12] There is no formal data concerning the short-term morbidity of recovering from an exploratory thoracotomy versus a resection, but there is little reason to expect

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there to be a difference. Not undergoing a resection carries a psychologic burden of loss of hope, whereas resection is associated with loss of lung function, However, the majority of studies[11,13–16] demonstrate good long-term functional capacity even in patients with limited pulmonary reserve (with only a few exceptions).[17,18]

Long-Term Survival

Long-term survival of patients with pN2 disease (i.e., postresection N2 disease) varies markedly according to preoperative factors and the extent of preoperative staging investigations. It must be noted that pathologic staging, as officially defined, is staging done after a surgical resection. Clinical staging involves any and all information available before resection, and may be very extensive (e.g., including mediastinoscopy) or fairly limited. On one end of the spectrum are patients who were thought to have stage I or II disease after extensive preoperative staging involving imaging and invasive procedures, but are found postoperatively to have pN2 disease. The term incidental N2 has been used for such patients when the nodal involvement is discovered postoperatively, and perhaps "unsuspected N2" would be appropriate when it is found intraoperatively in such well-staged patients. On the other end of the spectrum are patients with suspicious mediastinal nodes (by computed tomography [CT] or positron emission tomography) who nevertheless undergo a resection (without further staging investigations), which then demonstrates pN2 involvement. These patients should perhaps be more appropriately called "ignored N2." In between these groups are patients with more subtle suspicion of N2,3 involvement such as those with a central tumor or with N1 node enlargement, who do not undergo an invasive staging procedure (even though there is a well-documented 20% chance of N2 involvement despite a normal CT or positron emission tomography of the mediastinum).[19,20] Such patients who are found to have pN2 disease at the time of resection should perhaps be called "underappreciated N2." These distinctions are important, because pN2 patients with minimal preoperative investigations cannot necessarily be expected to have the same survival as those undergoing extensive preoperative staging. Omitting pursuit of a biopsy is not the same as a negative preoperative biopsy result.

In assessing long-term outcomes one must be careful to avoid being misled by studies that report only the survival of the best subgroup, selected after the fact (i.e., excluding incompletely resected patients or perioperative deaths). It is best to consider the outcome for all patients who were subjected to surgery, because only these data are clinically applicable to new patients who are being considered for surgery or are undergoing surgery and are found to have "surprise" N2 disease. Whether a microscopically complete resection will be achieved cannot really be determined until after the resection has been completed. Among patients with cN2 disease by CT (and pN2 involvement), approximately one-third will undergo incomplete resection, whereas among those with cN0,1 disease (and pN2 involvement), approximately one-fourth are incompletely resected. The vast majority of studies have found extremely poor 5-year survival in incompletely resected studies (average 4%).[21–36]

Long-term survival according to how preoperative staging was done is summarized in Table 1. Only a few studies have reported outcomes in patients in whom N2 involvement was proven preoperatively. Although these studies involved very highly selected patients (generally thought to have only microscopic disease in a single-node station), 5-year survival for all patients is only 10 to 15%. This demonstrates that we have poor ability to select a favorable cohort among patients with preoperatively proven N2 disease. In other words, if N2 disease is documented preoperatively, resection does not seem to be justified because the long-term outcomes are so poor (even among highly selected patients). The results of alternative treatment approaches (i.e., neoadjuvant therapy and resection or definitive chemoradiotherapy) for patients with stage III non-small cell lung cancer (NSCLC) is generally >15%, even though these approaches have usually involved a broader group of patients with a larger disease burden in the mediastinum (see Alternative Treatments section).

In patients with cN2 disease by CT in whom minimal surgical staging was done, survival after resection is similarly poor (~15%) when pN2 involvement is found. Although the outcomes seem to be a few percentage points higher than for preoperatively proven N2 disease, this is likely because of the inclusion of many studies from Asia (Asian studies generally seem to have better outcomes, see below). The argument to forego invasive staging in cN2 patients because of good long-term outcomes after resection does not seem justified. The outcomes show that our ability to select favorable patients among those with suspected N2 disease is disappointingly poor, and suggests that it is not justified to subject patients with cN2 disease ("ignored N2") to thoracotomy (except perhaps after preoperative chemotherapy in a multimodality treatment plan). One could draw the conclusion that such cN2 patients should be closed and receive chemotherapy and radiation (with or without subsequent reoperation and resection). However, the real conclusion has to be that the N2 involvement in these patients should be identified by other means instead of a thoracotomy.

Careful preoperative staging therefore seems to be important, because outcomes of patients with cN2 disease (either biopsy proven or radiographically suspected) are poor. It is disturbing, however, that the 5-year survival was very poor (5–10%) in reported series of patients with cN2 disease (by CT) in whom the majority underwent a negative mediastinoscopy (but were nevertheless pN2 after resection).[29,37] Therefore a false-negative mediastinoscopy does not predict a better outcome. Perhaps these are patients in whom resection should be aborted in favor of an alternative approach (chemoradiotherapy or neoadjuvant therapy and later resection). The quality of how well mediastinoscopy is performed is probably important. A large series from United States found that not even a single lymph node was biopsied in approximately half of all mediastinoscopies for staging of lung cancer.[38] At the other end of the spectrum is a complete bilateral transcervical extended lymphadenectomy for staging (average of 39 nodes removed, missed mediastinal nodes in only 13%, and a negative predictive value for N2 disease of 96%).[39]