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Which Patients with Stage III Non-Small Cell Lung Cancer Should Undergo Surgical Resection?

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ABSTRACT

The treatment of patients with stage III NSCLC remains controversial. Stage III NSCLC comprises a fairly heterogeneous group of tumors, and furthermore only sparse data from randomized clinical trials exist to guide therapy decisions. This review article proposes a management algorithm for patients with stage III NSCLC that is based upon the currently available data on surgical therapy, chemotherapy, and radiation therapy. By necessity, given the paucity of strong data, a good deal of opinion is offered. The choice to proceed with aggressive, combined modality treatment is presented in light of extent of local disease as well as patient performance status. The Oncologist 2005;10:335–344

INTRODUCTION

When presented with a patient with non-small cell lung cancer (NSCLC), the treating physician’s initial decision-making regarding therapy is very straightforward if the malignancy falls into clinical stages I or II. It has become clear from multiple studies over several decades that the primary, if not sole, therapy for stage I/II NSCLC is surgical resection. For most of these tumors, lobectomy is indicated, but if the position of the tumor is such that sleeve lobectomy or (rarely) pneumonectomy is required and it is felt that the patient can tolerate one of these procedures, then this is what should be done.

A variety of important clinical questions remain regarding the management of patients with stages I or II NSCLC. For example, there is emerging evidence that there may be a role for sublobar resection (segmentectomy or even wedge resection) for small stage I tumors [1], but there are as yet no prospective, randomized data available establishing this concept. Whether there is a survival advantage conferred by complete mediastinal lymphadenectomy versus sampling also remains unclear [2], but this question should be resolved by a randomized trial currently being carried out by the American College of Surgeons Oncology Group. Finally, there is increasingly strong evidence from prospective, randomized trials that patients in stage IB or higher with a reasonable performance status who did not receive neoadjuvant chemotherapy should receive adjuvant platinum-based chemotherapy following surgery [3-5].

At the other end of the staging spectrum lies stage IV, and here too, decision-making is relatively easy. Outside of patients with a solitary brain metastasis [6], an isolated adrenal metastasis [7], or a second nodule in a separate lobe [8], in whom some prolonged survivals can be achieved by resection of both the primary tumor and the metastatic deposit, there is no role for surgery in the vast majority of patients who present with stage IV NSCLC.

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mediastinal nodes must be confirmed by tissue acquisition. 

Stage III comprises a fairly heterogeneous group of tumors (Table 1 [9]), and within most of these subgroups there remains controversy regarding the optimal approach. Many stage III tumors lie at the borderline of what can be considered resectable, and since there is abundant evidence that an incomplete resection is of no value in NSCLC, it can be difficult to decide which of these patients should be offered an operation. For the same reason, surgery for stage III tumors has often been combined with adjuvant therapies, but after much study it remains controversial precisely which of these therapies should be employed (chemotherapy, radiotherapy, or combined chemoradiotherapy), in which cases, and in what sequence in relation to surgery (pre- or postoperatively).

Although most of the published studies that address these issues are nonrandomized, one can make reasonable recommendations on the basis of the data available and upon personal experience. This review will summarize this information and provide one approach, that is reasonable in light of current data, to determine which patients with stage III NSCLC should undergo resection, and what additional therapies should be considered. A proposed algorithm for management of these patients is described in detail in the text below.

**STAGING WORK-UP OF THE PATIENT WITH KNOWN OR SUSPECTED STAGE III NSCLC**

Certainly, given the high risk of asymptomatic metastases, all patients with pulmonary tumors that appear by initial studies to potentially be stage III should undergo a complete metastatic work-up. This includes computed tomography (CT) of the chest including the adrenals and liver, magnetic resonance imaging (MRI) of the brain, and, ideally, positron emission tomography (PET). PET, in addition to revealing distant metastases in as many as 6% of patients who otherwise stage favorably, may also play a role in staging the mediastinal lymph nodes. Although a positive PET for mediastinal nodes must be confirmed by tissue acquisition since positive predictive value in these nodes is only 56%, a negative PET in the mediastinal nodes is 87% reliable (87% negative predictive value) [10]. This approximates the negative predictive value of mediastinoscopy that has been established over many years of accumulated experience. However, it can be difficult to separate hilar N1 from N2 (mediastinal) lymph nodes by PET, and this distinction has great prognostic importance and is critical in stratification for application of adjuvant therapies. Further, PET often cannot separate centrally placed primary tumors from mediastinal node metastases. For these reasons, mediastinoscopy remains very important in this group of patients.

Where PET is not available, if PET is positive in any nodes (hilar or mediastinal), if the tumor itself is central, or if the surgeon’s preference is for mediastinoscopy, then mediastinoscopy should be performed before consideration of resection of clinical stage III NSCLC. We favor performing mediastinoscopy under the same anesthetic as possible thoracotomy. We instruct our patients that if mediastinoscopy reveals no involvement of the mediastinal nodes on frozen section examination that we will then proceed with pulmonary resection immediately, but that if the nodes are involved on frozen section, we will terminate the procedure and refer him/her for neoadjuvant or definitive chemoradiation ± radiotherapy. This approach is more convenient and less costly for the patient than staged mediastinoscopy/pulmonary resection. Although we are not aware of any studies addressing the reliability of frozen section in this setting, we have never reversed a diagnosis made on frozen section within the nodes on subsequent permanent section analysis.

**IIIA (T3 N1) Tumors**

This group of stage III tumors, which consists mainly of masses invading the chest wall but also includes tumors invading the mediastinal pleura or pericardium or the mainstem bronchus within 2 cm of the carina, is the group in which the role of surgery is most clear. The survival of
patients after complete resection of a tumor invading the chest wall but not involving mediastinal lymph nodes has been reported to range from 8% to 78.5% [11, 12], and although survival is certainly related to nodal involvement, even patients with involved N1 nodes have a 5-year survival as high as 39% [13].

Involvement of mediastinal (even N2) lymph nodes in a patient with a T3 primary tumor, on the other hand, portends a poor prognosis, and this subgroup of patients with N2 disease should be operated upon only rarely, in a combined-modality setting and if they have excellent performance status. A strong argument can be made that all patients with completely resected T3 N1 tumors should undergo adjuvant chemotherapy if they have acceptable performance status. We are unaware of any data suggesting that neoadjuvant therapies (prior to resection) are any more effective than adjuvant therapies for T3 N1 NSCLC. Since radiotherapy has been shown to favorably impact local recurrence but not survival, we believe that it is indicated after a complete resection only when the surgeon feels that the margins of resection, though pathologically negative, were somehow compromised or extremely close.

Tumors that are T3 N1 by virtue of mainstem bronchus involvement by the primary tumor within 2 cm of the carina but not involving the carina will, in expert surgical hands, most frequently undergo sleeve upper lobectomy (Fig. 1). This procedure allows preservation of pulmonary function and diminished postoperative mortality when compared with the alternative (pneumonectomy), but it offers the same oncologic resection and opportunity for cure [14]. As in the case for tumors invading the chest wall, in the absence of N2 nodal involvement there is no evidence that neoadjuvant treatment should be administered in T3 N1 patients with mainstem bronchial involvement, but there is strong evidence for the administration of postoperative platinum-based chemotherapy in fit patients. Radiotherapy, again, should be added only when the surgeon feels that his margins were unusually close though pathologically negative.

IIIA (T1-3 N2) Tumors

Tumors classified as IIIA on the basis of ipsilateral, mediastinal lymph node involvement (N2) are the subclass of stage III NSCLC to which the most attention and controversy have been directed (Fig. 2). Since N2 lymph nodes (at least on the right side) are within the field of resection of a right thoracotomy or right thoracoscopic procedure, N2 lymph nodes are considered resectable, whereas N3 nodes contralateral to the tumor or in the supraclavicular region are outside the field of the procedure and are therefore unresectable. These anatomic facts are the basis for most surgeons’ and the authors’ belief that treatment for many IIIA (N2) tumors should include surgical resection, while surgery should not be performed on IIIB (N3) tumors. It should be mentioned, however, that on the left side it is not clear, in fact, that paratracheal nodes should be considered resectable, since their removal requires extensive mobilization of the aortic arch and recurrent laryngeal nerve—procedures that are not generally performed as part of standard lymphadenectomy in North America. Certainly, if one is planning to operate on a patient with a left-sided tumor and left level 2 or 4 lymph node involvement, then these mobilization procedures should be undertaken.

The above use of the terms resectable and unresectable, however, ignores the important fact that failure of local control is less often the mode of relapse of NSCLC than is distant metastasis. Thus, the appreciation that mediastinal lymph node involvement is a marker for aggressive tumor biology and for distant disease is likely more important than its meticulous resection. It is the appreciation that N2 nodes predict distant disease and the fact that survival was so low in IIIA (N2) patients that led to the introduction of neoadjuvant chemotherapy for this subgroup of stage III.

The oft-quoted Rosell [15, 16] and Roth [17, 18] studies provided randomized, prospective data in support of neoadjuvant chemotherapy followed by surgery for selected patients with IIIA NSCLC. Although these were small, imperfect studies, and although other randomized studies did not demonstrate a benefit to neoadjuvant treatment for IIIA (N2) disease [19, 20], this approach has gained wide acceptance. With the strong theoretical underpinning for

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Figure 1. Sleeve right upper lobectomy, shown here, allows complete resection of T3 tumors involving the mainstem bronchus while avoiding the high morbidity and mortality associated with pneumonectomy. The lower lobe is preserved by anastomosing its bronchus to the remaining mainstem bronchus. From [35] Kenneth L, Franco JB. Advanced Therapy in Thoracic Surgery. Hamilton, ON: B.C. Decker, 1998:163, with permission.
neoadjuvant treatment, once positive, supportive data in the treatment of IIIA disease was available, this approach was readily accepted. But should all patients with IIIA (N2) disease undergo chemotherapy followed by surgery? And is there a role for combined induction chemoradiotherapy in some of these patients? To address these questions, a number of factors must be explored.

First, it must be recognized that not every patient has a sufficiently good performance status to safely receive induction therapy followed by a major operative procedure. This therapeutic regime can be quite debilitating, and it is not appropriate in those with major baseline comorbidities. It has been difficult to draw a line defining which patients will likely tolerate this approach and which will not; this is an area where experienced clinical judgment is important. Additionally, in our opinion, preoperative chemotherapy alone is generally better tolerated than combined chemoradiation, so we reserve the latter for patients who are in particular good condition and in whom there is reason to believe that the radiotherapy component is valuable. Note that the algorithm in Figure 2 recommends neoadjuvant chemoradiation only for more extensive N2 nodal involvement (larger nodes) and in patients with at least a moderately good performance status.

It is important to note that the randomized studies supporting neoadjuvant treatment in IIIA (N2) NSCLC utilized neoadjuvant chemotherapy alone, not chemoradiotherapy. The move towards neoadjuvant chemoradiotherapy has been supported largely by phase II studies suggesting that the addition of radiation increases the rate of nodal sterilization, and that this correlates with improved survival. However, since adding neoadjuvant radiotherapy to chemotherapy adds morbidity but is likely to impact only local control, the authors’ belief is that it should be added to neoadjuvant chemotherapy only in situations where the surgeon feels that he/she is unlikely to achieve a complete resection with clear margins.

The algorithm in Figure 3 uses nodal size by preoperative CT scan as a rough guide to determine when radiotherapy should be added to the neoadjuvant regimen. It should be clearly stated that this approach has only indirect support in the literature but has been determined to be a reasonable approach by the group of surgeons, oncologists, and radiation oncologists who treat lung cancer at our institution. This algorithm thus serves as a general guideline for the management of patients with IIIA (N2) NSCLC within the University of Pennsylvania Health System. Involved mediastinal nodal groups that are less than 1.5–2.0 cm in maximal diameter are unlikely to have complete nodal replacement or extranodal extension—findings that would render it likely that clear margins can be achieved by surgery. For this reason, we generally operate on these patients after chemotherapy alone. However, with individual nodal groups reaching the 1.5– or 2.0–3.0-cm range, we believe it is far less likely that local control can be achieved, even with a meticulous mediastinal lymphadenectomy, in the absence of preoperative radiotherapy. For this reason, if a patient appears healthy enough to be able to tolerate

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**Figure 2.** A proposed algorithm for the management of patients with stage IIIA NSCLC. *See Figure 3 for a more detailed management algorithm for patients with N2 lymph node involvement.*
trimodality therapy, we favor neoadjuvant chemoradiotherapy followed by surgery. Patients with nodal groups over 3–3.5 cm in diameter clearly fall into the bulky N2 category, where we believe that even after induction chemoradiotherapy, surgery is unlikely to achieve a complete resection with clear margins. Further, multiple studies demonstrate that these patients have very poor survival no matter what therapy they receive. We therefore rarely recommend operation for these patients and favor definitive nonsurgical therapy.

For patients with N2 nodes that fall into the 1.5–3.0-cm range, there is the occasional patient with what might be considered borderline performance status who would likely tolerate neoadjuvant chemotherapy followed by surgery reasonably well but for whom trimodality therapy might be overwhelming. Although we believe that nodes in this range should ideally be treated preoperatively with combined chemoradiotherapy, we will occasionally operate upon less sturdy patients with nodes in this range after chemotherapy alone. Although it is clearly reasonable for a patient with single-station, microscopic N2 disease (nodes less than 1 cm in size) to be operated on primarily and then undergo adjuvant chemotherapy if he/she remains in acceptable condition postoperatively (see below), we do not believe that a patient with 1.5–3.0-cm nodes should undergo surgery if unable to receive at least some form of neoadjuvant therapy.

A corollary to the concept that neoadjuvant treatment can be debilitating is the fact that it likely increases operative morbidity and mortality, and thus even neoadjuvant chemotherapy alone should not be applied indiscriminately. Although it has been difficult to establish increased surgical morbidity after induction therapy with statistical significance in prospective studies (e.g., [20]), several retrospective surgical series and one as yet unpublished prospective, randomized study strongly suggest that this is the case [21–23]. Of particular importance is the finding of the Memorial Sloan-Kettering group that patients who undergo right pneumonectomy after neoadjuvant chemotherapy have a 24% postoperative mortality rate [22]. This extraordinary number suggests that: A) parenchyma-sparing sleeve resections (Fig. 1) should be performed in preference to pneumonectomy whenever possible in those who have received neoadjuvant treatment, and B) although it is difficult to make this judgment on the basis of preoperative studies, those in whom it is felt highly likely that a right pneumonectomy will be required should receive neoadjuvant treatment only after much thought and discussion. This 24% mortality rate for right pneumonectomy after induction therapy makes a strong argument that patients with lung cancer be treated by surgeons who are subspecialized in pulmonary surgery. The ability to perform challenging sleeve resections in situations that would result in pneumonectomy in less experienced hands is absolutely essential to the optimal care of these patients.

It is also important to realize that not all N2 lymph node involvement portends the same prognosis. That is, microscopic and/or single-station involvement of the N2 nodes appear to be associated with a significantly better survival than macroscopic and bulky N2 involvement [24]. Further, there is strong but nonrandomized evidence that involvement of a single, left level 5 mediastinal lymph node in patients with a left upper lobe tumor portends no worse of a prognosis than N1 disease [25, 26].

The results of surgery alone are sufficiently good in these patients to show that it is quite reasonable for those with
microscopic, single-station N2 disease, particularly those with less than excellent performance status, to undergo primary surgery. If these patients tolerate the procedure well and are in reasonable condition postoperatively, then the addition of chemotherapy should be considered at that time. This approach is rendered even more reasonable by the recent prospective, randomized data in support of the effectiveness of postoperative adjuvant chemotherapy [3–5]. It is, in fact, unknown at this time whether preoperative chemotherapy is of greater benefit than postoperative chemotherapy in situations where the surgeon does not feel that complete resection will be an issue. A randomized trial addressing this issue is currently in the planning stages.

It should be noted that, as shown in Figure 3, those patients with poor performance status with IIIA (N2) NSCLC should rarely be offered surgery, particularly with greater than microscopic N2 disease. Although this is a difficult decision to come to with any individual patient since resection remains the most effective single-modality therapy in NSCLC, the overall survival data support this approach. The 5-year survival (cure) rate for clinical IIIA (N2) NSCLC after surgical resection alone is 13% [8], and this value likely excludes patients with bulky N2 tumors. A patient with a poor performance status will likely not tolerate neoadjuvant therapy followed by surgery, so it is this surgery-alone survival data that one must consider in these patients. Operative mortality in the poor performance status patient can certainly reach the 5% range. When the surgical mortality rate approaches the chances for cure, one should look askance at surgery. We believe, then, that these patients should be offered palliative chemotherapy or definitive chemoradiation if it is felt they can tolerate these modes of therapy. Although even these nonsurgical therapies are not without morbidity and mortality, they can generally be administered in a fashion that minimizes risk.

An important study presented at the American Society of Clinical Oncology Meeting in 2003 [23] sheds additional light on the role of neoadjuvant therapy followed by resection for stage IIIA (N2) NSCLC and merits discussion. This study, intergroup 0139, randomized 429 patients with IIIA (N2) disease after two cycles of cisplatin/etoposide and concomitant radiotherapy to either two additional cycles of chemotherapy alone or surgical resection followed by two additional cycles of chemotherapy. In the surgical arm, there was significantly better progression-free survival, but the difference in overall survival, although slightly favoring the surgical arm, did not reach statistical significance. The treatment-related death rate in the surgical arm was 7%, versus 1.6% in the nonsurgical arm, but the surgical arm deaths occurred mainly in those undergoing right pneumonectomy. Although the results of this study can be interpreted differently depending upon one’s bias, a surgeon’s conclusion is that if one could avoid right pneumonectomy in these patients by aggressive use of sleeve lobectomy, there is a good chance that not only progression-free survival, but overall survival as well would favor the surgical arm.

INT 0139, like many other studies before it, demonstrated that sterilization of lymph nodes to N0 portends the best prognosis (50% survival at 3 years). However, several studies report a reasonable number of long-term survivors following surgery even in patients with residual N2 disease after neoadjuvant therapy. This finding has dissuaded the authors from performing mediastinoscopy routinely after induction therapy in order to determine who should go on to surgical resection. Most of these patients have had a preoperative mediastinoscopy. We believe that redo mediastinoscopy is hazardous, and thus in our opinion it should be employed only if its benefit becomes clear in future studies. One such situation would be if it appears likely that a right pneumonectomy will be required at the time of surgery. Certainly, a right pneumonectomy after induction therapy, given its high mortality rate, should be assiduously avoided unless there is clear evidence that N2 disease has been eradicated.

We have, because of our hesitance to perform redo mediastinoscopy, employed a policy of resecting patients in whom there is no radiographic progression during induction therapy. Although we are skeptical of their potential in this situation, particularly after radiotherapy, there is some hope that PET response or endoscopic ultrasound-guided needle biopsy will be proven useful in the future to identify complete pathological responders to neoadjuvant regimens.

A final point to discuss is when additional postoperative therapy should be added in patients who have received neoadjuvant therapy. There are less data available on this issue than on the other issues outlined above. A reasonable approach is that hardy patients with residual N2 disease in the resected specimen that is either multistation or extracapsular should in general undergo adjuvant radiotherapy if they did not receive it preoperatively. Additional chemotherapy is considered unlikely to be of benefit if it did not initially provide a dramatic downstaging. On the other hand, we tend to administer additional chemotherapy postoperatively in hardy patients who have been downstaged, as this downstaging suggests that their tumors are sensitive to the chemotherapy and that therefore additional chemotherapy may be more likely to have benefit. There is certainly more art than science in making these decisions about additional postoperative therapy.

IIIB (T1-4 N3) Tumors

Mainly on the basis of the Southwest Oncology Group (SWOG) 8805 study, which had a 0% 3-year survival following induction chemoradiation and surgery for N3 patients [27], we continue to believe that IIIB (N3) tumors
should be treated nonsurgically. Common sense dictates that since N3 lymph nodes are out of the field of surgical resection, surgery is unlikely to improve outcome significantly over what can be achieved with chemoradiation. Until the unlikely appearance of phase III data demonstrating that neoadjuvant treatment followed by surgery in patients with IIIB (N3) disease results in better survival than treatment with chemoradiotherapy alone, we believe that these patients should continue to be managed nonsurgically.

IIIB (T4 N2) Tumors

Although surgery is certainly indicated in selected T4 N0–1 patients (see next section), the addition of N2 disease to any T4 status renders the chances of cure so low that the risks of surgery are rarely worth taking. If all patients with clinical N2 disease have a 5-year survival rate of 13%, then T4 tumors with N2 disease certainly have a survival rate below this value, and the mortality rate of surgery after neoadjuvant therapy will certainly approach this cure rate. Only T4 N2 patients with the best performance status and those with minimal N2 nodal involvement (e.g., single-station, microscopic disease) should be considered for induction therapy followed by surgery. This will be a very rare patient.

IIIB (T4 N0–1) Tumors

Certain T4 categories are clearly amenable to complete surgical resection, and patients with these tumors and limited (N0–1) nodal disease should be considered primary surgical candidates. These include T4 by virtue of satellite tumors within the primary tumor lobe and T4 by virtue of limited carinal invasion. T4 satellite nodule tumors can be resected by standard pulmonary lobectomy, with 5-year survival of approximately 20% [28, 29]. It is to be hoped that the addition of adjuvant chemotherapy will improve these results further. We are aware of no data available to support neoadjuvant treatment in this situation.

Tumors that are T4 by virtue of carinal involvement, though requiring careful and expert surgical management, can be resected with an operative mortality of approximately 10% in the current era. Although this surgical mortality rate after carinal resections including carinal pneumonectomy (Fig. 4) is significant and demands a fearless surgeon and patient, the reported 5-year survival rate of 51% with resected T4 N0 carinal tumors and 32% for T4 N1 carinal tumors [30] justifies this approach in patients with excellent performance status and mediastinoscopically negative lymph nodes. We believe that these patients should not undergo neoadjuvant therapy given the tenuous nature of the carinal reconstruction anastomoses in the best of circumstances. Most will receive postoperative adjuvant therapy if able to tolerate it.

Several small series also report resection of tumors that are T4 by virtue of limited involvement of vertebral body, left atrium, great vessels (usually superior vena cava), and esophageal muscularis, with acceptable surgical mortality rates of 0%–8% and long-term survival in 8%–42% of patients [31]. Since involvement of these structures presents difficulty obtaining wide margins of resection and it is therefore often unclear preoperatively whether negative margins will be obtainable, we believe that optimal management includes neoadjuvant chemoradiation to shrink the tumor and sterilize margins. This approach is extrapolated from the management of Pancoast tumors—the tumor that epitomizes a situation in which the key problem is one of local control due to limited margins of resection. SWOG study 9416 [32] has demonstrated impressive preliminary results with resection of Pancoast tumors following neoadjuvant chemoradiation. We believe it is reasonable to expect similar results in patients with these T4 tumors. If these patients are felt not to be able to tolerate trimodality therapy, then bimodality therapy with radiation followed by surgery is a reasonable approach. If even this is felt to be too morbid in an individual patient, then a nonsurgical approach is most appropriate.

It bears mention that CT and MRI are not particularly reliable in determining whether these T4 structures are truly invaded by a tumor. These studies often suggest invasion that at exploration is found to represent mere abutment, or they suggest abutment that at exploration is found to represent actual invasion. Thus, one must use clinical judgment to determine which of these patients should be subjected to neoadjuvant therapy in the absence of definitive evidence that this treatment has benefit over postoperative adjuvant therapy.

Figure 4. Depiction of right carinal pneumonectomy, the most common procedure performed for a T4 tumor involving the carina. The right lung and carina are removed and the trachea is anastomosed to the left mainstem bronchus. From [36] Mitchell JD, Mathisen DJ, Wright CD et al. Clinical experience with carinal resection. J Thorac Cardiovasc Surg 1999;117:45, with permission.
The final category of T4 disease that should be considered is NSCLC that is T4 by virtue of pleural involvement and malignant pleural effusion. This subclass of IIIB disease is incurable, with median survivals of 6–9 months. Most patients with symptomatic malignant effusion will be treated by pleurodesis. It should be mentioned, however, that a few small phase II studies have reported novel combined-modality approaches to these patients that may be worthy of additional study. For example, one group has employed resection of the primary tumor and all gross pleural disease followed by intraoperative photodynamic therapy, with a median survival of 21.7 months [33]. Another group has reported a thoracoscopic approach involving resection of the primary tumor and pleural perfusion by warm cisplatin-containing solution, with a median survival of 18 months [34]. These experimental approaches should remain limited to the clinical trial setting.

**SUMMARY**

We have seen that although a minority of the data available to guide decisions regarding surgical therapy for stage III NSCLC is of randomized or even prospective quality, combining this data and personal experience allows one to propose a reasonable algorithm for the management of these patients. Our algorithms (Figs. 2, 3, 5) recommend that most patients with less than bulky stage IIIA (N2) NSCLC should be managed by neoadjuvant therapy followed by surgical resection in the absence of disease progression. We recommend adding induction radiation to neoadjuvant chemotherapy only when mediastinal node size reaches approximately 1.5 cm and only in patients who are sufficiently fit to tolerate this demanding trimodality approach. Patients with microscopic N2 disease can be reasonably operated on without induction therapy, and this is particularly appropriate in settings where it is thought that right pneumonectomy may be required. Patients with T3 N1 NSCLC should be treated with primary surgical resection followed by chemotherapy, with radiotherapy reserved for those with compromised margins.

Patients with IIIB (N3) NSCLC should generally be treated nonsurgically, as should nearly all patients with T4 N2 disease. Those with T4 N0–1 tumors, however, are optimally treated by primary surgical resection followed by adjuvant chemotherapy and/or radiotherapy, or by neoadjuvant treatment to shrink tumors prior to surgery in those cases where limited margins of resection are anticipated. For all of these patients, performance status is critically important in decision-making about approaches to therapy. Although bimodality and trimodality therapies appear to improve outcomes in most cases of stage III NSCLC, they incur significant morbidity and must be applied to carefully selected patients.

**DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST**

The authors indicated no potential conflicts of interest.
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