What to do with "Surprise" N2?

Intraoperative Management of Patients with Non-small Cell Lung Cancer

Frank Detterbeck, MD

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.

Key Words: Surprise, Non-small cell lung cancer, Mediastinal lymph node dissection, N2, Stage IIIa, Surgery.

(*J Thorac Oncol.* 2008;3: 289–302)

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

Division of Thoracic Surgery, Department of Surgery, Yale University, New Haven, Connecticut.
Disclosure: The author declares no conflict of interest.
Address for correspondence: Frank C. Detterbeck, MD, Yale University, New Haven, CT. E-mail: frank.detterbeck@yale.edu

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]

TABLE 1. Survival of pN2 Patients According to Preoperative Staging

Study	n	CStage by CT	N1,2 Bx Done?	Med Result	R1,2 (%)	Survival 5-yr R0	All	Adj Ther	Continent
Pearson et al.[23]	79	?	All	Pos	40	15	9	RT	NA
Coughlin et al.[22]	36	?	All	Pos	22	18	14[a]	?	NA
Vansteenkiste et al.[27]	19	?	All	Pos	36	?	15	±RT	Eu
Average					**33**	**17**	**13**		
Régnard et al.[25]	254	cN2[b]	No[c]	—	25	23	18	RT	Eu
Ichinose et al.[46]	164	cN2	Few	—	Excl	27	—	None	Asia
Watanabe et al.[32]	106	cN2	No	—	50	20	16	None	Asia
Tanaka et al.[34]	84	cN2	Few	—	23[d]	—	27	±RT ± Ch	Asia
Suzuki et al.[24]	87	cN2	No[d]	—[c]	36	—	7	Few	Asia
Cybulsky et al.[55]	63	cN2	13[d]	—[c]	41[d]	—	7	±RT ± Ch	NA
Inoue et al.[91][e]	60	cN2	Sel	±	Excl	12	—	±Ch ± RT	Asia
Tanaka et al.[96]	45	cN2	Few	—	Excl	26	—	±RT ± Ch	Asia
Martini et al.[45][f]	33	cN2[g]	No	—	Excl	(8)[f,h]	—	RT	NA
Average (subtotal)[i]					**35**	**22**	**15**		
Andre et al.[29]	354	cN0,1[j]	Few	—	16	31[a]	29	±RT	Eu
Ichinose et al.[46]	242	cN0,1	Few	—	Excl	34[a]	—	None	Asia
Suzuki et al.[24]	135	cN0,1	No[d]	—[c]	18	—	43	sFew	Asia
Martini et al.[45][f]	118	cN0,1[g]	No	—	Excl	(33)[f,h]	—	RT	NA
Goldstraw[41]	86	cN0,1	No	—	15[d]	—	27	None	Eu
Tanaka et al.[34]	71	cN0,1	Few	—	23[d]	—	30	±RT ± Ch	Asia
Cybulsky et al.[55]	61	cN0,1	13[d]	—[c]	41[d]	—	14	±RT±Ch	NA
Tanaka et al.[96]	54	cN0,1	Few	—	Excl	42	—	±RT ± Ch	Asia
Watanabe et al.[32]	47	cN0,1	No	—	34	33	17	None	Asia
Daly et al.[98]	33	cN0,1	Few	—[c]	15	31	28	RT	NA
Sakao et al.[99]	30	cN0	Few	—	Excl	52	—	None	Asia
Average[i]					**23**	**37**	**27**		
Vansteenkiste et al.[27]	68	cN0,2	100	Neg	15	—	32	±RT	Eu
Goldstraw et al.[41]	62	cN0,2	100	Neg	15[d]	—	23	None	Eu
Pearson et al.[23]	62	cN0,2	100	Neg	35	41	24	±RT	NA
Average					**22**	**41**	**26**		

Inclusion criteria: studies reporting on ≥30 operated pN2 patients in whom preoperative characteristics are well defined by CT, mediastinoscopy, or both (≥15 patients for the category of positive mediastinoscopy); published from January 1980 to June 2007.

[a] Estimated from data provided.
[b] In the vast majority.
[c] <5% Mediastinoscopy-positive patients included.
[d] Proportion for all patients in study, not necessarily for each subgroup.
[e] Excluded operative mortality (<2%).
[f] Lung cancer-specific survival.
[g] As defined by chest radiograph (not CT).
[h] 4-yr survival.
[i] Excluding values in parentheses.
[j] All patients were either radiographically N0,1 or had negative mediastinoscopy.

Adj. ther., adjuvant therapy; c, clinical staging; Ch, chemotherapy; Eu, Europe; excl, excluded from study; NA, North America; p, pathologic; R₀, complete resection (negative margin); RT, radiotherapy; Select pts, mediastinoscopy performed in at least all patients with radiographic N2 disease (in most series also in patients with T3 tumors and central tumors); ?, unknown; ± both negative and positive.

Survival is more acceptable in patients with pN2 disease that are cN0,1 by CT. In series where limited confirmation of the mediastinal nodes was done, the 5-year survival for all patients is approximately 27%. Similarly, in series in which all patients had a negative mediastinoscopy (and cN0-2 disease by CT) the 5-year survival is 26%. Series involving less rigorously selected patients (cN0-2 by CT and "selec-tive" [negative] mediastinoscopy) have reported somewhat inferior survival (22% for all patients, 19% for R0 patients).[26,28,30,40–42] These outcomes suggest that resection of fairly rigorously staged patients with cN0,1 disease is justified even if pN2 involvement is found ("incidental N2"). The survival of patients who have more selective staging and are found to be pN2 is slightly inferior.

Patients with "underappreciated N2" disease probably fall within this group. The survival of this group indicates that resection is reasonable, although it also suggests that more diligent preoperative staging may be worthwhile.

Across all studies the 5-year survival in series from North America seems to be approximately half that of European of Asian series (7 versus 18 versus 17% for cN2; 14 versus 28 versus 30% for cN0,1 with limited preoperative invasive staging, respectively). This is important to keep in mind, as there are regional differences in lung cancer on different continents (high proportion of squamous cancers in Europe, higher proportion of adenocarcinoma, bronchioloalveolar carcinoma, and endothelial growth factor receptor abnormalities in Asia). There also seem to be cultural differences in how specific lymph nodes are classified, and a node near the pleural reflection is more likely to be classified as N2 by Japanese surgeons and N1 by European surgeons.[43] It is unclear how this compares with classification practices in North America. A revised node map that seeks to reconcile continental differences is being developed.[44]

Specific Situations

It is difficult to define how a specific factor should influence the intraoperative decision of whether to proceed with resection, because one factor can really not be viewed in isolation from others. The importance of the extent of preoperative staging has already been discussed. Furthermore, there are geographic variations in outcomes. Finally, it is unclear how well postoperative criteria that define subgroups with good or poor survival can be extrapolated to factors that can de determined intraoperatively. Each of these issues confounds the ability to define prognosis relative to a single factor accurately enough to dictate how such a patient should be managed when surprise N2 is found.

Several studies have performed multivariate analyses of multiple factors, which is the necessary approach when there are multiple interrelated factors (Table 2). These studies indicate that an incomplete resection, multilevel N2 involvement, clinical N2 stage (by CT), and subcarinal node involvement are independent markers of poor prognosis in more than half of the studies. The presence of T3,4 tumors, pN1 disease, and increasing age are less consistent negative prognostic markers of a worse prognosis. The histologic type of NSCLC, or whether the tumor involves a lower or upper lobe does not seem to be important. Similarly whether a pneumonectomy or lobectomy is needed has little independent prognostic significance.

The clinically relevant issue is whether any intraoperative findings preclude proceeding with a resection because the outcome is likely to be very poor. An analysis of all larger series reporting survival data on particular patient subgroups is shown in Tables 3 and 4. The inclusion criterion for this review was chosen so that there would be sufficient numbers of patients in each group to have reasonably reliable survival estimates. Furthermore, it was chosen to focus on studies reporting on a variety of factors (as opposed to smaller studies that focused on a specific factor) in an effort to reduce publication bias. However, this review is compared with another systematic review involving any study reporting on ≥20 patients in a particular subgroup.[40]

The available data suggests that resection is not justified if it is incomplete. The long-term survival is

TABLE 2. Multivariate Analyses of Factors Predicting Poor Survival in pN2 Patients[a]

Study	n	Multilevel	cN2	R1,2	N1+	Node Level 7	5	1,2	T3,4	Larger Size	Lower Lobe	Pneum	Adeno/ Large	Older Age
Andre et al.[29]	702	<0.0001	<0.0001	NS	—	—	—	—	<0.0001	—	—	—	NS	—
Ichinose et al.[46]	406	<0.0001	NS	—	<0.03	—	—	—	<0.05[b]	—	—	NS	NS	0.02
Riquet et al.[31]	237	<0.05	—	<0.05	NS	NS	NS	NS	NS	NS	NS	NS	NS	—
Suzuki et al.[24]	222	<0.001	**<0.001**	0.02	—	—	—	—	NS	0.001	—	NS	NS	NS
Miller et al.[28]	167	<0.05	—	NS	—	<0.05	NS	(NS)[c]	NS	—	—	<0.05	NS	<0.05
Thomas et al.[33]	163	<0.02	—	—	—	NS	—	NS	NS	—	—	—	NS	—
Tanaka et al.[34]	155	NS	NS	0.001	—	—	—	—	0.03	—	—	—	NS	NS
Inoue et al.[91]	154	0.005	**<0.001**	—	—	—	—	—	NS	—	<0.04	—	**0.002**	0.007
Iwasaki et al.[93]	142	NS	—	—	NS	0.002	—	—	NS	—	—	NS	NS	NS
Vansteenkiste et al.[27]	140	0.03	0.04	NS	—	NS	NS	(NS)[c]	0.003	—	NS	NS	0.03	NS
Tanaka et al.[96]	99	**0.01**	**<0.04**	—	—	—	—	—	NS	—	—	—	NS	NS
Ohta et al.[97]	94	—	NS	—	0.03	**<0.001**	—	NS	**<0.001**	NS	NS	—	NS	NS
Prognostic value[d]		**High**	**Mod**	**Mod**	**Mod**	**Mod**	—	—	**Low**	**Low**	**Low**	—	—	**Low**

Inclusion criteria: studies reporting multivariate analysis of >90 patients with pN2 disease, 1980–2007.

[a] Values given are *p* values by multivariate analysis (plain: relative risk >1.0–<2.0; The values given in bold are relative risk 2.0–<3.0; The values given in bold-underlined are relative risk >3.0). Factors analyzed by less than three studies are omitted.

[b] T2,3 vs. T1.

[c] Stations 1–4 vs. others.

[d] Scale, high: ≥75% positive; moderate: 50–74% positive; low: 25–49% positive (excluding values in parentheses).

Adeno/large, adenocarcinoma, in some cases also including large cell carcinoma (not squamous); cN2, clinical N2 by CT; mod, moderate; N1+, N1 nodes involved (nonskip metastasis to N2 nodes); NS, not statistically significant; pneum, pneumonectomy; R1,2, incomplete resection; T3,4, T3, or T4 primary tumor.

TABLE 3. Survival of pN2 Patients with Particular Negative Prognostic Factors

Study	n	5-Yr Survival (%)									
		R1,2	cN2	Multi	T3	Pneum	7	1,2	Ad/Lg	LL	N1+
Survival of all operated patients (R0-2 resections)											
Andre et al.[29]	702	10	7	7	13[a]	—	—	—	13	—	—
Naruke et al.[21]	545	8[b]	—	—	14	—	—	—	21	—	—
Maggi et al.[30]	278	0	—	15	10	—	8	—	—	—	—
Régnard et al.[25]	254	0[c]	18	9	11	—	18[d]	—	—	—	—
Riquet et al.[31]	237	8	—	8	—	—	—	—	—	—	—
Suzuki et al.[24]	222	0[e]	7	19	13[a]	13	—	—	31	—	—
Wada[48]	214	—[e]	—	—	15	—	—	—	—	—	—
Watanabe et al.[32]	199	0	—	9	—	—	23[d]	—	—	—	—
Miller et al.[28]	167	5	—	—	—	18	13	3	—	—	—
Thomas et al.[33]	163	—[e]	—	—	—	—	14	8	—	—	—
Tanaka et al.[34]	155	6[e]	25	25	15	—	—	—	27	—	—
Watanabe et al.[35]	153	0	16	7	15	—	—	—	24	—	—
Goldstraw et al.[41]	149	—	—	—	—	21	27	—	4	—	—
Vansteenkiste et al.[27]	140	4	15	22	2	22	14	—	18	20	—
Cybulsky et al.[55]	124	—[c]	7	—	—	—	—	—	—	—	—
Ishida et al.[36]	115	9[b]	16	—	0	—	—	—	19	—	—
Average (all patients)		**4**	**14**	**13**	**11**	**19**	**17**	**(6)[f]**	**20**	**(20)[f]**	**—**
Survival limited to R0 resected patients											
Ichinose et al.[46]	402	—	27	17	30	17		—	28	23[g]	26
Mountain[101][h]	307	—	—	(21)[h,i]	(29)[h]	—	—	(25)[h]	(26)[h]	—	—
Régnard et al.[25]	191	—	23	—	—	—	—	—	—	—	—
Maggi et al.[90]	157	—	—	18	14[j]	—	9[d]	—	—	—	—
Inoue et al.[91][k]	154	—	—	16	—	—	—	—	24	21	—
Rea et al.[92]	154	—	—	0	—	—	—	—	—	—	—
Martini et al.[45][h]	151	—	(8)[h,l]	(27)[h]	(22)[h]	—	(25)[h]	—	(36)[h]	—	—
Iwasaki et al.[93][k]	142	—	—	10	—	—	0[d]	—	—	—	—
Okada et al.[94]	141	—	—	11	—	26	—	—	—	—	—
Conill et al.[95]	113	—	—	3	—	—	16	—	—	—	—
Tanaka et al.[34]	94	—	—	—	28	—	—	—	32	—	—
Ohta et al.[97]	94	—	—	—	—	—	—	—	—	—	20
De Leyn et al.[42]	90	—	—	25	0	—	—	—	20	—	—
Average (R0 patients)[m]	**—**	**(25)[f]**	**13**	**18**	**(22)[f]**	**(8)[f]**	**—**	**26**	**(22)[f]**	**(23)[f]**

Inclusion criteria: studies of ≥90 pN2 patients reporting survival by prognostic factor.

[a] T3 and T4.
[b] Defined as positive margin (R1,2) or no complete node dissection performed.
[c] No definition provided.
[d] Single level involvement.
[e] Defined as positive margin (R1,2) or highest node positive.
[f] Data from less than three studies.
[g] Data reported in Ichinose 2001.[100]
[h] Cancer-specific survival (death from unrelated causes excluded).
[i] Estimated from reported data.
[j] Reprinted with permission from Maggi G. Results of radical treatment of stage IIIa non-small-cell carcinoma of the lung. *Eur J Cardiothorac Surg* 1988;2:329–335.
[k] Excluded operative mortality.
[l] 4-Yr survival.
[m] Excluding values in parentheses.

7, Nodal station 7; 1,2, nodal station 1,2; Ad/Lg, adenocarcinoma, in some cases also including large cell carcinoma (not squamous); cN2, clinical N2 by CT; LL, lower lobe; multi, multilevel node involvement; N1+, N1 nodes involved (nonskip metastasis to N2 nodes); pneum, pneumonectomy; R1,2, incomplete resection, defined as microscopic or gross residual except as indicated; T3, T3 primary tumor.

consistently poor (average 5%, range 0–10%). This is true in this review and in others (involving different inclusion criteria).[40] The definition of an incomplete resection varies, being defined by some as a microscopically positive margin,[27–31,35,41,45,46] whereas others also include patients with extracapsular involvement of a mediastinal node,[47] and others include patients in whom the most distant (highest) node was positive.[24,33,34,48] However, the survival of incompletely resected patients seems to be consistently poor, regardless of the definition. Extracapsular extension

TABLE 4. Survival of pN2 Patients with Particular Positive Prognostic Factors

Study	n	5-Yr Survival (%)								
		R0	cN0,1	Single	T1,2	Lobe	Sq	UL	N1-	5
Survival of all operated patients (R0-2 resections)										
Andre et al.[29]	702	23	29	25	22	—	20	—	—	—
Naruke et al.[21]	545	23	—	—	21[a]	—	31	—	—	—
Maggi et al.[30]	278	18	—	22	20	—	—	—	—	—
Régnard et al.[25]	254	23	—	24	29[a]	—	—	—	—	—
Riquet et al.[31]	237	20	—	26	—	—	—	—	—	—
Suzuki et al.[24]	222	36	43	35	31	31	21	—	—	—
Wada et al.[48]	214	—	—	—	34	—	—	—	—	—
Watanabe et al.[32]	199	20	—	35	—	—	—	—	—	—
Miller et al.[28]	167	24	—	—	—	31	—	—	—	24
Tanaka et al.[34]	155	34	30	37	33[a]	—	27	—	—	—
Watanabe et al.[35]	153	24	33	35	33	—	22	—	—	—
Goldstraw et al.[41]	149	20	—	21	14	21	30	—	—	—
Vansteenkiste et al.[27]	140	25	22	20	29[a]	14	22	24	—	20
Cybulsky et al.[55]	124	—	14	—	—	—	—	—	—	—
Ishida et al.[36]	115	26	24[a]	—	23[a]	—	15	—	—	—
Average (all)		**24**	**28**	**28**	**26**	**24**	**24**	**(24)[b]**	**—**	**(22)[b]**
Survival limited to R0 resected patients										
Ichinose et al.[46]	402	31	34[a]	43	31[a]	33	37	37[c]	46	—
Maggi[90]	157	23	—	25	22[d]	—	—	—	—	—
Inoue et al.[91e]	154	28	—	43	—	—	40	35	—	—
Rea et al.[92]	154	13	—	18	—	—	—	—	—	—
Iwasaki et al.[93e]	142	24	—	37	—	—	—	—	—	—
Okada et al.[94]	141	26	—	39	—	26	—	—	—	—
Conill et al.[95]	113	10	—	16	—	—	—	—	—	0
Tanaka et al.[34]	94	35	42	42	43	—	44	—	—	—
Ohta et al.[97]	94	27	—	—	—	—	—	—	33	—
De Leyn et al.[42]	90	22	—	24	34	—	26	—	—	—
Average (R0)		**24**	**(38)[b]**	**32**	**33**	**(30)[b]**	**37**	**(36)[b]**	**(40)[b]**	**(0)[b]**

Inclusion criteria: studies of ≥90 pN2 patients reporting survival by prognostic factor.

[a] Estimated from reported data.
[b] Data from less than three studies.
[c] Data reported in Ichinose 2001.[100]
[d] Data reported in Maggi 1988.[54]
[e] Excluded operative mortality.

5, Nodal station 5; Ad/Lg, adenocarcinoma, in some cases also including large cell carcinoma (not squamous); cN0,1, clinical N0 or N1 by CT; lobe, lobectomy; N1-, N1 nodes not involved (skip metastasis to N2 nodes); R0, complete resection, defined as negative margins; single, single-level node involvement; Sq, squamous cell cancer; T1,2, T1, or T2 primary tumor; UL, upper lobe.

was not of prognostic significance in multivariate analyses,[27,31] and neither was involvement of the highest lymph node (Table 2). The only study to investigate some aspects of the definition of incomplete resection concluded that only a mere lack of a complete lymph node dissection did not confer a poor outcome and should not be used as a definition of incomplete resection (as opposed to a positive margin or the most distant node being positive).[7] Therefore, it seems reasonable to conclude that there is little justification for proceeding with a resection if it can be determined that it will be incomplete, with the most robust definition being a positive margin.

Several factors listed in Table 3 can be grouped as relatively negative prognostic factors, namely clinical N2 by CT, multilevel N2, T3 tumors, or subcarinal node involvement (5-year survival of 14, 13, 11, and 17% respectively, as shown graphically in Figure 1A). These data are in close agreement with a previous systematic review (5-year survival rates of 15, 13, and 15% for multilevel N2, T3 tumors, or subcarinal node involvement, respectively).[40] However, the range of reported results varies quite widely from values that would quite clearly argue against proceeding with resection (<5% 5-year survival), to values that would argue for resection (>20% 5-year survival). This is likely because of the confounding factors. For example, the subcarinal node results are likely confounded by inclusion of patients with multilevel or nonregional node involvement, because more lung cancers
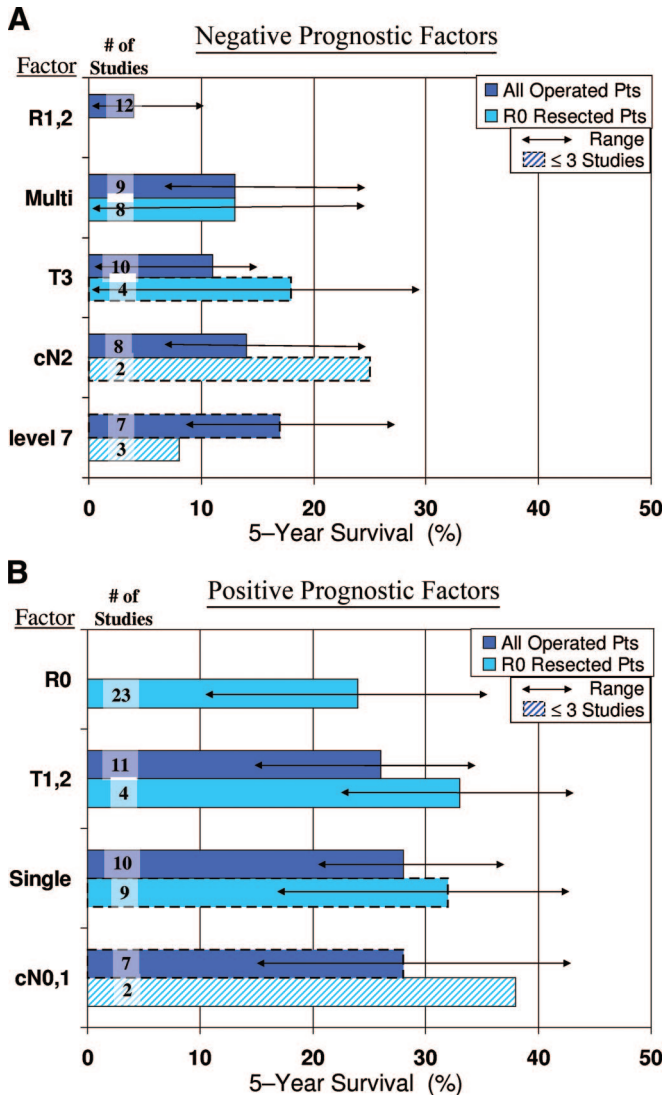
FIGURE 1. *A*, **Negative prognostic factors for patients with pN2 NSCLC.** Inclusion criteria: studies of ≥90 pN2 patients reporting survival by prognostic factor. cN2, clinical N2 by CT; level 7, nodal station 7; multi, multilevel node involvement; pts, patients; R0, complete resection; R1,2, incomplete resection; T3, T3 primary tumor. R1,2[21,24,25,27–32,34–36]; multi, all patients[24,25,27,29–32,34,35]; R0 resections[42,46,90–95]; T3, all patients[21,24,25,27,29,30,34–36,48]; R0 resections[42,46,54,96]; cN2, all patients[24,25,27,29,34–36,55]; R0 resections[25,46]; station 7, all patients[25,27,28,30,32,33,41]; R0 resections[90,93,95].

B, **Positive prognostic factors for patients with pN2 NSCLC.** Inclusion criteria: studies of ≥90 pN2 patients reporting survival by prognostic factor. cN0,1, clinical N0 or N1 by CT; level 7, nodal station 7; pts, patients; R0, complete resection; single, single-level node involvement; T1,2, T1 or T2 primary tumor. References R0[21,24,25,27–32,34–36,41,42,46,90–97]; T1,2, all patients[21,24,25,27,29,30,34–36,41,48]; R0 resections[42,46,54,96]; single, all patients[24,25,27,29–32,34,35,41]; R0 resections[42,46,90–96]; cN0,1, all patients[24,27,29,34–36,55]; R0 resection.[46,96]

originate in the upper lobes, which predominately spread to paratracheal nodes. The large International Association for the Study of Lung Cancer (IASLC) staging revision database confirmed worse survival for multilevel pN2 involvement with a 5-year survival of 20% (other factors such as T stage were not able to be analyzed).[49]

Several factors stand out as relatively consistent positive prognostic factors (Figure 1*B*). These include a R0 resection, a T1,2 tumor, single-level N2 involvement, and patients staged as clinical N0,1. Although the reported survival ranges are broad (Table 4), they do quite consistently support resection for surprise N2 discovered at thoracotomy. These results are consistent with that of other reviews.[40,49,50]

Factors that seem to have limited value in differentiating patients with good or poor prognosis include the histology, extent of resection, and in more limited data the location of the tumor (upper versus lower lobe), and the presence of involved N1 nodes (5-year survivals of 20% for adenocarcinoma, 26% for squamous cancer, 19% for pneumonectomy, 24% for lobectomy, 20% for lower lobe, 24% for upper lobe [among operated patients], and 23 versus 40% for nonskip and skip N2 [among completely resected patients]). These results are all consistent with another systematic review,[40] and the IASLC staging project did not define a consistent difference with respect to skip N2 involvement.[49] A limited amount of data in the analysis presented here suggests that survival is poor (6%) if there is involvement of the highest mediastinal nodes (stations 1 and 2). However, another systematic review found an average 5-year survival of 18% in such patients (involving three studies of >20 such patients, primarily completely resected).[40] Finally, multivariate analyses have not found this factor to be important.

Tumors in the left upper lobe (LUL) with involvement of aortopulmonary window (APW) lymph nodes deserve specific mention. A number of authors have reported particularly good results (>40% 5-year survival) in these patients, but have done so by reporting on only selected patients (only completely resected, often with other node stations negative).[51–53] Results applicable prospectively to patients as they are encountered in the clinic or operating room demonstrate approximately 20 to 30% 5-year survival for patients with station 5 nodal involvement.[40] These results are not clearly different than those of tumors in other lobes involving only a single mediastinal node station. Furthermore, multivariate analysis has not demonstrated that APW nodes carry any particular significance. A previous review of studies involving ≥20 patients found similar survival among pN2 patients with or without APW node involvement, with conflicting trends and no statistically significant difference in any of the studies analyzing this.[40] The IASLC staging revision project found no difference in survival for single-level pN2 involvement of subcarinal versus APW nodes for left-sided lung cancers.[49] Therefore, although the data suggests that LUL resection should proceed if APW node involvement is found, the preponderance of data does not support that the LUL and the APW represent a biologically different situation than other lobes and regional nodal areas.

A few studies have investigated the prognostic value of involvement of only "regional" N2 nodes,[24,27,32,53] with conflicting and unclear results. Okada et al. suggested that survival is dramatically better for patients with upper lobe tumors involving only stations 1 to 6 versus 7 to 9, for lower lobe tumors involving stations 7 to 9 versus 1 to 4, and to a lesser extent left upper lobe tumors involving stations 5 and 6 versus any others.[53] Another study has qualitatively reported very poor outcomes with involvement of nonregional nodes.[27] However, a third study found no survival difference in patients with upper lobe tumors involving stations 1 to 4 versus 7 to 9, and found significantly worse survival with lower lobe tumors involving stations 7 to 9 versus 1 to 4.[24] Finally, Watanabe et al. found no difference in 144 completely resected patients.[32]

What conclusions can be drawn? First, application of the data regarding a specific factor should be done with caution, because of confounding variables such as the extent of preoperative staging, clinical node status, geographic variation, and other factors. Second, it seems fairly clear that there is little point in proceeding with a resection that is expected to be incomplete. Third, if it seems likely that a complete resection can be accomplished it is generally appropriate to proceed, given that the morbidity and mortality of the thoracotomy and its effect on the feasibility of delivering chemoradiotherapy in a timely fashion has already been incurred. This is fairly clearly true in the case of a T1,2 tumor, single-level node involvement, and patients with a cN0,1 tumor based on careful preoperative staging. This is probably also true for patients with upper lobe tumors involving only regional nodes (LUL and station 5 or right upper lobe and R4). One should not hesitate to carry out a pneumonectomy if necessary (provided the patient is able to tolerate this), and should not change the approach based on the histologic subtype. The situation is less clear in patients with multilevel N2, clinical N2 by CT, T3 tumors, or subcarinal node involvement. However, although these patients seem to have worse survival (around 15%), in general resection is justified unless there are significant comorbidities or multiple poor prognostic factors.

HOW MUCH RESECTION IS NEEDED?

Lobectomy versus Pneumonectomy

Controversy exists about whether a lobectomy or pneumonectomy should be performed if N2 disease is encountered. Some surgeons believe that a pneumonectomy should always be performed if N2 disease is encountered, to more completely remove tumor-bearing lymphatics. Unfortunately, this issue has not clearly been addressed by any study. Most studies have shown worse survival after pneumonectomy than lobectomy,[26,28,37,54,55] although some found the opposite.[27,41] This is almost certainly confounded by more extensive tumors (higher T stage) in patients requiring pneumonectomy.[37,54] Nevertheless, these data undermine the argument that there is something to be gained from a pneumonectomy, and the data in Table 3 suggest that survival is reasonable even if pneumonectomy is required. Furthermore, the meta-analyses in Table 2 do not demonstrate the extent of resection to be of prognostic significance. Finally, although

the lymph nodes in stations R4, 7, and 5 are adjacent to the mainstem bronchi, it is not clear how pneumonectomy and MLND actually result in a more complete resection of involved N2 nodes compared with a lobectomy and MLND.

Occasionally, a central tumor is amenable to a sleeve resection (involving the bronchus, pulmonary artery, or both) as an alternative to a pneumonectomy. An average 5-year survival of 27% has been found among studies reporting specifically on patients with pN2 disease undergoing sleeve resection.[56–62] This does not seem to be noticeably different than the survival of pN2 patients undergoing a standard lobectomy, and is not worse than the survival of pN2 patients undergoing pneumonectomy (Tables 3 and 4). Therefore, the data support sleeve resection as a reasonable alternative to pneumonectomy even in the face of N2 disease.

THE VALUE OF MLND

Role of MLND in Staging

Intraoperative handling of the mediastinum can involve a complete MLND, a systematic node sampling, or a selective sampling. A formal MLND involves removal of all of the node-bearing tissues, leaving only the skeletonized trachea, phrenic nerves, aorta, and superior vena cava behind.[35] A systematic mediastinal node sampling means that the pleura overlying each ipsilateral node station is opened, explored, and representative biopsies of nodes are obtained. A selective sampling, on the other hand, involves biopsy of only selected mediastinal nodes that are felt to be abnormal. Some authors advocate a lobe-specific systematic node dissection, which consists of a complete dissection of those nodal regions most often involved by tumors in a particular lobe.[63]

It is well established that a complete MLND can be carried out safely with only a minor impact on operative times or morbidity (Table 5).[10,64–68] The standard of care for surgical management of lung cancer in general is to perform either a systematic lymph node sampling, a complete MLND, or a lobe-specific MLND.[63,69,70] The issue to be considered here is whether a particular approach can be recommended when surprise N2 disease is encountered.

The accuracy of staging seems to be improved by diligent intraoperative attention to mediastinal staging. Several controlled and randomized studies have shown that systematic sampling approximately doubles the rate of discovery of N2 node involvement relative to a selective mediastinal node sampling.[10,64,68] However, a systematic node sampling detects essentially the same number of patients with pN2 node involvement as a complete MLND.[65,67,71] A MLND may detect more patients with multilevel N2 involvement than systematic sampling,[65,71] even though the stage classification is the same (59% versus 17%, $p < 0.01$ in one study of cI–IIIa patients,[71] but no difference in another involving cIa patients[67]). This staging data suggest that less extensive node removal at thoracotomy might leave tumor behind in some instances.

THERAPEUTIC ROLE OF MLND

The therapeutic role of MLND is unclear at this time. Four randomized trials have been conducted (Table 6),[10,66–68]

TABLE 5. Mediastinal Lymph Node Dissection: Safety and Staging Data from Randomized Studies

Study	n	Elig Crit	Sampl Method	Addit'l OR Time (min)	p	Oper Mort LND	Sampl	p	Surg Morb LND	Sampl	p	pN2 (%) LND	Sampl	p	ML of N2 (%) LND	Sampl	p
Allen et al.[10]	1023	cN0,1	Select	15	<0.0001	2	1	NS	38	38	NS	4[a]	0[a]	—	—	—	—
Wu et al.[68]	471	cI-IIIa	Select	—	—	0.3	0	NS	—	—	—	48	28	—	—	—	—
Izbicki et al.[71]	182	cI-IIIa	Syst	—	—	—	—	—	—	—	—	27	23	NS	59	17	0.007
Sugi et al.[67]	115	cT1N0	Syst	42	<0.05	0	0	NS	27	3	<0.05	12	14	NS	43	38	NS

Inclusion criteria: randomized studies of lymph node dissection vs. a method of lymph node sampling in patients with NSCLC undergoing surgical resection.

[a] Any patients with N2 involvement identified intraoperatively were excluded.

Addit'l OR time, additional operative time for LND in minutes; elig crit, eligibility criteria; min, minutes; LND, lymph node dissection; ML, percent of patients with multilevel N2 involvement among those with N2 involvement; NS, not statistically significant; oper mort, operative mortality (in hospital or within 30 d); *p*, *p* value; sampl, node sampling; select, selective sampling (only abnormal appearing nodes); surg morb, surgical morbidity (complications); syst, systematic sampling (exploration of each ipsilateral node station with representative biopsy).

TABLE 6. Mediastinal Lymph Node Dissection: Survival and Recurrence Data from Randomized Studies

Study	n	Elig Crit	Sampl Method	5-Yr Survival (%) LND	Sampl	p	Local Recurrence (%) LND	Sampl	p
Allen et al.[10]	1023	cN0,1	Select	—	—	—	—	—	—
Wu et al.[68]	471	cI-IIIa	Select	48	37	<0.0001	3	5	—
Izbicki et al.[66]	182	cI-IIIa	Syst	(71)[a]	(60)[a]	NS	41	79	<0.04
Sugi et al.[67]	115	cT1N0	Syst	81	84	NS	—	—	—

Inclusion criteria: randomized studies of lymph node dissection vs. a method of lymph node sampling in patients with NSCLC undergoing surgical resection.

[a] 3-yr survival.

Elig crit, eligibility criteria; LND, lymph node dissection; NS, not statistically significant; *p*, *p* value; sampl, node sampling; select, selective sampling (only abnormal appearing nodes); syst, systematic sampling (exploration of each ipsilateral node station with representative biopsy).

but survival data are not available yet from the largest one (American College of Surgeons Oncology Group Z0030).[10] A smaller study of stage cIa patients found no survival difference, but is probably less applicable to the topic of this review.[67] The other two trials are somewhat suggestive of a benefit either in overall survival or in local control.[66,68] A systematic review of these trials carried out by the Cochrane collaboration found better 4-year survival with MLND versus node sampling (hazard ratio 0.78, *p* = 0.005).[72] A retrospective review of data from a large trial of adjuvant therapy (355 patients, pII–IIIa) suggested a survival benefit with MLND,[73] but another retrospective study (125 patients, pIa) suggested worse survival.[74]

An extended mediastinal node dissection involving bilateral mediastinal node dissection by means of a sternotomy has been advocated by some to more completely remove all nodal disease.[52] In a study of 44 patients with cI–IIIa LUL tumors, 32% were found to be pN2, of which half had involvement of stations 1, 2R, 4R, 2L. However, although survival was good for those patients with pN2 limited to the usual nodal regions assessed during LUL resection (stations 4L. 5–7), none of the patients with involvement of nodes in the extended field of resection survived 5 years. The patients in this study were treated with surgery alone in the vast majority (no neoadjuvant or adjuvant chemo- or radiotherapy).[52] Thus there seems to be little benefit to such extended node dissection, at least in the absence of additional treatment modalities.

Therefore the available data does not clearly define whether there is a therapeutic benefit to MLND. However, it seems reasonable to recommend that in general a MLND be done if intraoperative N2 disease is found. This recommendation is based on the trend to better survival and decreased local recurrence in the randomized studies. Furthermore, the randomized studies involved a broader group of patients of which only a minority had pN2 disease. If intraoperative N2 disease is found, it seems prudent to try to remove the ipsilateral nodal areas as completely as possible.

POSTOPERATIVE (ADJUVANT) THERAPY

A full discussion of the role of adjuvant therapy for pN2 patients is beyond the scope of this article. In general, adjuvant chemotherapy has become standard for resected stage II–IIIa NSCLC patients. Specific evidence-based recommendations for resected stage pIIIa patients are addressed by the recently revised ACCP guidelines.[69] These guidelines recommend postoperative chemotherapy, and suggest that consideration be given to subsequent postoperative radiotherapy (RT) as well. Concurrent adjuvant chemoradiotherapy is not recommended.[69]

A stage-specific meta-analysis of adjuvant chemotherapy for patients with stage IIIa disease published in 2005 found a hazard ratio strongly in favor of chemotherapy of 0.85 (95% confidence interval 0.69–1.04).[75] This did not quite meet criteria for statistical significance. It is probably significant that this meta-analysis did not include the more recently reported results of the Adjuvant Navelbine International Trialist Association trial, which were strongly positive in favor of adjuvant chemotherapy.[76] Taken in the broader

context of adjuvant therapy studies including such more recent results there is little doubt that adjuvant chemotherapy is beneficial. This is reflected in the guideline statements mentioned above.

The role of adjuvant RT for patients with stage IIIa disease is not clear. Systematic reviews of adjuvant RT for completely resected (R0) stage pI–IIIa NSCLC have generally found that there is a detriment to survival, although local control seems to be improved.[77–79] The survival detriment was manifest primarily in patients with stages I and II NSCLC. The available data did not allow a specific recommendation for patients with stage IIIa tumors in these reviews. A retrospective review in 2006 of Surveillance, Epidemiology and End Results (SEER) data in 7465 patients suggested that patients with pN2 disease have a survival benefit with adjuvant RT.[80] It was suggested that modern RT techniques may have decreased the toxicity of treatment to the point where a survival benefit in stage III was realized. This leaves it unclear whether RT should be used in completely resected patients with pIIIa tumors.

Adjuvant RT is generally given to incompletely resected (R1) patients. The argument for this is that the trend to better local control with adjuvant RT justifies its use in patients suspected to be at high risk for local failure such as those with an incomplete resection. However, there is little data to substantiate (or refute) this argument.[78] Nevertheless, this seems to be a rational approach, and should probably be followed sequentially by chemotherapy. In the case of gross residual disease (R2), it seems best to treat the patient as if they had undergone a large biopsy rather than a resection. These patients should be managed with concurrent chemoradiotherapy once they have sufficiently recovered from surgery (although direct data to substantiate this strategy is not available).

Does the delivery of adjuvant therapy affect the intraoperative management when N2 disease is discovered? There is no data that directly examines this. One must keep in mind that the ability to deliver adjuvant therapy postoperatively has consistently been relatively poor (approximately 65%).[69,78,88] Nevertheless, the data reviewed in this article comes from studies in which many patients did receive adjuvant therapy (Table 1). Therefore, it would seem that the data presented and conclusions reached in this review apply to patients in the current setting, in which adjuvant therapy is generally recommended for pN2 patients.

ALTERNATIVE TREATMENT APPROACHES

Primary Alternative Treatment Approaches

A full discussion of alternative treatment approaches other than primary surgery for patients with pN2 disease is beyond the scope of this article. Nevertheless, a brief summary is necessary to place the results with primary surgery in the proper perspective.

The standard of care for stage IIIa NSCLC is concurrent chemoradiotherapy.[69] The 5-year survival rates in these studies has been approximately 15 to 20%.[81,82] It is important to note that these trials have included patients with much more extensive stages IIIa and IIIb disease than the patients that are the focus of this article. Induction therapy followed by surgical resection is a reasonable alternative, although at the present time it should ideally be done in the context of a clinical trial.[69] This has been compared with chemoradiotherapy alone in a randomized trial, with no statistical difference in overall survival.[83,84] Significantly better progression-free survival in the surgical arm was offset by an increase in initial (perioperative) mortality. The 5-year survival seems to be approximately 25% for such trimodality approaches in preoperatively proven cN2 involvement.[69,84,85] More aggressive chemoradiotherapy approaches are also being explored, with survival rates of 25 to 30% in phase II studies (in a broad group of stages IIIa and IIIb patients).[13,86,87] Although direct comparisons are not possible because of differences between the patients included in these studies and patients with "surprise" pN2 disease, these results must be kept in mind when considering the role of primary resection.

Effect of Exploration on Alternative Approaches

Should an alternative treatment strategy be considered when surprise N2 disease is encountered at thoracotomy? The outcomes of alternative treatment approaches just discussed pertain to patients that have not been subjected to an exploratory thoracotomy. No data are available that specifically defines the ability to carry out such an alternative approach after a thoracotomy. However, there are extensive data that adjuvant chemotherapy can be administered as planned in only about 65% of patients after a resection.[69,78,88] It is possible that a higher percentage of patients can tolerate and complete chemotherapy after an exploratory thoracotomy compared with after a resection, but this is speculative and not supported by the similar perioperative mortality of exploration and resection. Furthermore, definitive chemoradiotherapy treatment approaches for stage III NSCLC have involved more intense treatment than those of adjuvant therapy. This makes it likely that any better tolerance of alternative treatment that might be realized after an exploratory thoracotomy compared with resection would probably be offset by worse tolerance of more intensive therapy than the 65% reported in adjuvant chemotherapy studies. In summary, speculative extrapolation of existing data suggests that only about two-thirds of patients are likely to complete definitive chemoradiotherapy after an exploratory thoracotomy.

The likelihood of completing the planned treatment seems likely to be worse if the alternative therapy under consideration is neoadjuvant chemotherapy followed by a second thoracotomy, this time with resection. The same concerns about the ability to complete the neoadjuvant treatment in a postoperative patient apply as was discussed in the preceding paragraph. In addition, studies of neoadjuvant treatment followed by resection have consistently found that only about 65% of patients are well enough to undergo resection after the induction therapy.[81] Thus, only about 50% of patients who are closed after finding surprise N2 disease at thoracotomy can be expected to complete neoadjuvant therapy and subsequent surgical resection. It is highly likely that those patients not completing the planned alternative therapy will experience very poor survival. Unfortunately, no direct data to confirm or refute these extrapolative estimates are available.

SUMMARY: APPROACH TO PATIENTS

What conclusions can be drawn? First, any suspicion of N2 disease warrants careful and thorough invasive staging, and documentation of N2 involvement should preclude initial thoracotomy and resection. Such patients with pN2 disease who are cN2 by imaging studies have a 10 to 15% survival rate (despite adjuvant RT). Given the morbidity of surgery, and the fact that other curative-intent treatment options are available, surgical resection as the initial treatment does not seem justified. The nodal involvement should be identified using a less invasive method than a thoracotomy. It is not entirely clear whether these patients should be managed by chemoradiotherapy alone or in some instances by neoadjuvant treatment followed by resection, although the most recent guideline recommendation is for chemoradiotherapy alone outside of a clinical trial.[69]

Some patients will be found to have N2 involvement at the time of resection, even if appropriate preoperative staging has been done ("unsuspected N2"). The only clear reason to abort the planned operation is if it is apparent that a complete resection is not possible. Aside from this, it seems in general to be appropriate to proceed with resection (especially if careful preoperative staging demonstrated cN0,1 disease). Survival of some subgroups may be slightly better and of others slightly worse, but the outcomes are nevertheless good enough to proceed with resection. This argument is based on data that a 5-year survival of 10 to 50% can be anticipated and on data that there is little difference in the operative mortality or QOL whether the procedure is aborted or carried out. Furthermore, the ability to give an alternative treatment (definitive chemoradiotherapy or neoadjuvant therapy followed by resection) is somewhat questionable in a postoperative patient.

Defining particular factors that might influence the intraoperative decision to resect should be done very cautiously, because the reported results vary and are likely confounded by multiple undefined additional factors. Proceeding with resection is clearly justified in the case of a T1,2 tumor, single-level node involvement, and patients with a cN0,1 tumor based on careful preoperative staging. This is probably also true for patients with upper lobe tumors involving only regional nodes (LUL and station 5, or RUL and R4). One should not hesitate to carry out a pneumonectomy if necessary (provided the patient is able to tolerate this), and should not change the approach based on the histologic subtype. Worse outcomes (around 15% 5-year survival) are seen in patients with multilevel N2, clinical N2 by CT, T3,4 tumors, or subcarinal node involvement, but in general resection is still justified unless there are significant comorbidities or perhaps multiple poor prognostic factors.

It seems appropriate to proceed with resection even when faced at the time of thoracotomy with N2 involvement and an expected 15% 5-year survival (with negative prognostic factors), whereas at the same time it seems appropriate to avoid surgery altogether for patients with cN2 as defined preoperatively (because of 10–15% expected survival). This is because there is much more to be gained from avoidance of the morbidity of a thoracotomy than from aborting a resection once the thoracotomy has been done. Furthermore, alternative treatment is easily available if thoracotomy is avoided, but is more difficult once it has been done.

This conclusion is in conflict with an earlier study using mathematical modeling, which concluded that it was always better to close on finding surprise N2 and to administer neoadjuvant therapy and then resection.[89] However, this model was based on several assumptions that are not borne out by current literature: a 2.6-fold improvement in survival after neoadjuvant therapy and resection versus chemoradiotherapy alone, a 100% ability to deliver neoadjuvant therapy after exploratory thoracotomy, no benefit to adjuvant therapy after resection, and an operative mortality for exploratory thoracotomy of 0.5%. Countering these assumptions is the data from the only randomized study, which found no difference between neoadjuvant therapy and resection versus chemoradiotherapy alone.[83,84] Meta-analyses have demonstrated a benefit to adjuvant chemotherapy for resected IIIa patients.[69] The ability to deliver chemoradiotherapy seems to be poor, as discussed in the Effect of Exploration on Alternative Approaches section. The preponderance of data documents a much higher operative mortality than was assumed in the mathematical model.[1–7] In addition, the actual data for outcomes are dependent on details of the patient cohort, as is discussed in this review. An admitted limitation of the mathematical modeling was that estimates for the various treatment approaches were derived using different patient cohorts.[89] Finally, the mathematical model lumps all surprise N2 patients together, whereas the data reviewed here leads to the conclusion that poorly staged patients ("ignored N2") should not be subjected to an exploratory thoracotomy in the first place, whereas well-staged patients should be resected even if "unsuspected N2" involvement is found.

There seems to be little benefit to frozen section analysis of lymph nodes at the time of thoracotomy in patients who are well-staged preoperatively. This follows from the conclusion that no specific characteristics of N2 involvement preclude proceeding with resection. The role of frozen section is primarily to demonstrate tumor that cannot be resected. An argument can be made that a surprise N2 node by frozen section indicates that a MLND should be done if this was not already planned.

In summary, careful preoperative staging is important, and resection as the first step for patients with cN2 disease does not seem justified. If unanticipated N2 involvement is encountered in a well-staged patient, resection is justified unless it is apparent that disease will be left behind. This seems to be reasonable even in the face of negative prognostic factors. Resection of patients with pN2 disease should probably include a formal MLND, although conclusive data to prove this are not available. Adjuvant therapy should be given, with the data being most clear for adjuvant chemotherapy.

REFERENCES

1. Kiser AC, Detterbeck FC. General aspects of surgical treatment. In FC Detterbeck, MP Rivera, MA Socinski, et al. (Eds.), Diagnosis and Treatment of Lung Cancer: An Evidence-Based Guide for the Practicing Clinician. Philadelphia, PA:W.B. Saunders, 2001. Pp. 133–147.

2. Kohman LJ, Meyer JA, Ikins PM, et al. Random versus predictable risks of mortality after thoracotomy for lung cancer. *J Thorac Cardiovasc Surg* 1986;9:551–554.

3. Deneffe G, Lacquet LM, Verbeken E, et al. Surgical treatment of bronchogenic carcinoma: a retrospective study of 720 thoracotomies. *Ann Thorac Surg* 1988;45:380–383.

4. Duque JL, Ramos G, Castrodeza J, et al. Early complications in surgical treatment of lung cancer: a prospective, multicenter study. *Ann Thorac Surg* 1997;63:944–950.

5. Van den Bosch JMM, Gelissen HJ, Wagenaar SS. Exploratory thoracotomy in bronchial carcinoma. *J Thorac Cardiovasc Surg* 1983;85:733–737.

6. Steinbaum SS, Uretzky ID, McAdams HP, et al. Exploratory thoracotomy for nonresectable lung cancer. *Chest* 1995;107:1058–1061.

7. Rami-Porta R, Mateu-Navarro M, Freixinet J, et al. Type of resection and prognosis in lung cancer. Experience of a multicentre study. *Eur J Cardiothorac Surg* 2005;28:622–628.

8. Fang D, Zhang D, Huang G, et al. Results of surgical resection of patients with primary lung cancer: a retrospective analysis of 1,905 cases. *Ann Thorac Surg* 2001;72:1155–1159.

9. Watanabe S, Asamura H, Suzuki K, et al. Recent results of postoperative mortality for surgical resections in lung cancer. *Ann Thorac Surg* 2004;78:999–1002, discussion 1002–1003.

10. Allen MS, Darling G, Pechet T, et al. Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ACOSOG Z0030 trial. *Ann Thorac Surg* 2006;81:1013–1020.

11. Dales RE, Belanger R, Shamji FM, et al. Quality-of-life following thoracotomy for lung cancer. *J Clin Epidemiol* 1994;47:1443–1449.

12. Nõu E, Aberg T. Quality of survival in patients with surgically treated bronchial carcinoma. *Thorax* 1980;35:255–263.

13. Detterbeck F, Socinski MA, Gettinger S. Lung neoplasms. In J Norton, PS Barie, RR Bollinger, et al. (Eds.), Surgery: Basic Science and Clinical Evidence. New York: Springer-Verlag, 2008. In press.

14. Wang J, Olak J, Ultmann RE, et al. Assessment of pulmonary complications after lung resection. *Ann Thorac Surg* 1999;67:1444–1447.

15. Boysen PG, Harris JO, Block AJ. Prospective evaluation for pneumonectomy using perfusion scanning: follow-up beyond one year. *Chest* 1981;80:163–166.

16. Zieren HU, Muller JM, Hamberger U, et al. Quality of life after surgical therapy of bronchogenic carcinoma. *Eur J Cardiothorac Surg* 1996;10:233–237.

17. Myrdal G, Valtysdottir S, Lambe M, et al. Quality of life following lung cancer surgery. *Thorax* 2003;58:194–197.

18. Handy JR Jr, Asaph JW, Skokan L, et al. What happens to patients undergoing lung cancer surgery? Outcomes and quality of life before and after surgery. *Chest* 2002;122:21–30.

19. Detterbeck F, Jantz M, Wallace M, et al. Invasive mediastinal staging of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007;132:202S–220S.

20. Detterbeck F. Integration of mediastinal staging techniques for lung cancer. *Semin Thorac Cardiovasc Surg* 2007;19:217–224.

21. Naruke T. Significance of lymph node metastases in lung cancer. *Semin Thorac Cardiovasc Surg* 1993;5:210–218.

22. Coughlin M, Deslauriers J, Beaulieu M, et al. Role of mediastinoscopy in pretreatment staging of patients with primary lung cancer. *Ann Thorac Surg* 1985;40:556–560.

23. Pearson FG, DeLarue NC, Ilves R, et al. Significance of positive superior mediastinal nodes identified at mediastinoscopy in patients with resectable cancer of the lung. *J Thorac Cardiovasc Surg* 1982;83:1–11.

24. Suzuki K, Nagai K, Yoshida J, et al. The prognosis of surgically resected N2 non-small cell lung cancer: the importance of clinical N status. *J Thorac Cardiovasc Surg* 1999;118:145–153.

25. Régnard JF, Magdeleinat P, Azoulay D, et al. Results of resection for bronchogenic carcinoma with mediastinal lymph node metastases in selected patients. *Eur J Cardiothorac Surg* 1991;5:583–587.

26. Nakanishi R, Osaki T, Nakanishi K, et al. Treatment strategy for patients with surgically discovered N2 stage IIIA non-small cell lung cancer. *Ann Thorac Surg* 1997;64:342–348.

27. Vansteenkiste JF, DeLeyn PR, Deneffe GJ, et al. Survival and prognostic factors in resected N2 non-small cell lung cancer: a study of 140 cases. *Ann Thorac Surg* 1997;63:1441–1450.

28. Miller DL, McManus KG, Allen MS, et al. Results of surgical resection of patients with N2 non-small cell lung cancer. *Ann Thorac Surg* 1994;57:1095–1101.

29. Andre F, Grunenwald, D, Pignon JP, et al. Survival of patients with resected N2 non small cell lung cancer (NSCLC): heterogeneity of prognosis and evidences for a subclassification (Abstract). *J Clin Oncol* 2000;18:2981–2989.

30. Maggi G, Casadio C, Cianci R, et al. Results of surgical resection of stage IIIA (N2) non small cell lung cancer, according to the site of the mediastinal metastases. *Int Surg* 1993;78:213–217.

31. Riquet M, Manac'h D, Saab M, et al. Factors determining survival in resected N2 lung cancer. *Eur J Cardiothorac Surg* 1995;9:300–304.

32. Watanabe Y, Hayashi Y, Shimizu J, et al. Mediastinal nodal involvement and the prognosis of non-small cell lung cancer. *Chest* 1991;100:422–428.

33. Thomas PA, Piantadosi S, Mountain CF. Should subcarinal lymph nodes be routinely examined in patients with non-small cell lung cancer? *J Thorac Cardiovasc Surg* 1988;95:883–887.

34. Tanaka F, Yanagihara K, Ohtake Y, et al. Time trends and survival after surgery for p-stage IIIa, pN2 non-small cell lung cancer (NSCLC). *Eur J Cardiothorac Surg* 1997;12:372–379.

35. Watanabe Y, Shimizu J, Oda M, et al. Aggressive surgical intervention in N2 non-small cell cancer of the lung. *Ann Thorac Surg* 1991;51:253–261.

36. Ishida T, Tateishi M, Kaneko S, et al. Surgical treatment of patients with nonsmall-cell lung cancer and mediastinal lymph node involvement. *J Surg Oncol* 1990;43:161–166.

37. van Klaveren RJ, Festen J, Otten HJAM, et al. Prognosis of unsuspected but completely resectable N2 non-small cell lung cancer. *Ann Thorac Surg* 1993;56:300–304.

38. Little AG, Rusch V, Bonner J, et al. Patterns of surgical care of lung cancer patients. *Ann Thorac Surg* 2005;80:2051–2056.

39. Zielinski M. Transcervical extended mediastinal lymphadenectomy: results of staging in two hundred fifty-six patients with non-small cell lung cancer. *J Thorac Oncol* 2007;2:370–372.

40. Detterbeck FC, Jones DR. Surgical treatment of stage IIIa (N2) non-small cell lung cancer. In FC Detterbeck, MP Rivera, MA Socinski, et al. (Eds.), Diagnosis and Treatment of Lung Cancer: An Evidence-Based Guide for the Practicing Clinician, Philadelphia, PA: W. B. Saunders, 2001. Pp. 244–256.

41. Goldstraw P, Mannam GC, Kaplan DK, et al. Surgical management of non-small-cell lung cancer with ipsilateral mediastinal node metastasis (N2 disease). *J Thorac Cardiovasc Surg* 1994;107:19–28.

42. De Leyn P, Schoonooghe P, Deneffe G, et al. Surgery for non-small cell lung cancer with unsuspected metastasis to ipsilateral mediastinal or subcarinal nodes (N2 disease). *Eur J Cardiothorac Surg* 1996;10:649–655.

43. Watanabe S-I, Ladas G, Goldstraw P. Inter-observer variability in systematic nodal dissection: comparison of European and Japanese nodal designation. *Ann Thorac Surg* 2002;73:245–248.

44. Zielinski M, Rami-Porta R. Proposals for changes in the Mountain and Dresler mediastinal and pulmonary lymph node map. *J Thorac Oncol* 2007;2:3–6.

45. Martini N, Flehinger BJ, Zaman MB, et al. Results of resection in non-oat cell carcinoma of the lung with mediastinal lymph node metastases. *Ann Surg* 1983;198:386–397.

46. Ichinose Y, Kato H, Koike T, et al. Overall survival and local recurrence of 406 completely resected stage IIIa-N2 non-small cell lung cancer patients: questionnaire survey of the Japan Clinical Oncology Group to plan for clinical trials. *Lung Cancer* 2001;34:29–36.

47. Mountain CF. Expanded possibilities for surgical treatment of lung cancer: survival in stage IIIa disease. *Chest* 1990;97:1045–1051.

48. Wada H, Tanaka F, Yanagihara K, et al. Time trends and survival after

operations for primary lung cancer from 1976 through 1990. *J Thorac Cardiovasc Surg* 1996;112:349–355.

49. Rusch VW, Crowley J, Giroux D, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the N descriptors in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol* 2007;2:603–612.

50. Vansteenkiste JF, DeLeyn PR, Deneffe GJ, et al. Clinical prognostic factors in surgically treated stage IIIA-N2 non-small cell lung cancer: analysis of the literature. *Lung Cancer* 1998;19:3–13.

51. Patterson GA, Piazza D, Pearson FG, et al. Significance of metastatic disease in subaortic lymph nodes. *Ann Thorac Surg* 1987;43:155–159.

52. Sakao Y, Miyamoto H, Yamazaki A, et al. The spread of metastatic lymph nodes to the mediastinum from left upper lobe cancer: results of superior mediastinal nodal dissection through a median sternotomy. *Eur J Cardiothorac Surg* 2006;30:543–547.

53. Okada M, Tsubota N, Yoshimura M, et al. Prognosis of completely resected pN2 non-small cell lung carcinomas: what is the significant node that affects survival? *J Thorac Cardiovasc Surg* 1999;118:270–275.

54. Maggi G. Results of radical treatment of stage IIIa non-small-cell carcinoma of the lung. *Eur J Cardiothorac Surg* 1988;2:329–335.

55. Cybulsky IJ, Lanza LA, Ryan MB, et al. Prognostic significance of computed tomography in resected N2 lung cancer. *Ann Thorac Surg* 1992;54:533–537.

56. Detterbeck FC, Egan TM. Surgery for stage II non-small cell lung cancer. In FC Detterbeck, MP Rivera, MA Socinski, et al. (Eds.), Diagnosis and Treatment of Lung Cancer: An Evidence-Based Guide for the Practicing Clinician, Philadelphia PA: W. B. Saunders 2001; 191–197.

57. Van Schil PE, de la Riviere AB, Knaepen PJ, et al. TNM staging and long-term follow-up after sleeve resection for bronchogenic tumors. *Ann Thorac Surg* 1991;52:1096–1101.

58. Mehran RJ, Deslauriers J, Piraux M, et al. Survival related to nodal status after sleeve resection for lung cancer. *J Thorac Cardiovasc Surg* 1994;107:576–583.

59. Naruke T. Bronchoplastic and bronchovascular procedures of the tracheobronchial tree in the management of primary lung cancer. *Chest* 1989;96:53S–56S.

60. Gaissert HA, Mathisen DJ, Moncure AC, et al. Survival and function after sleeve lobectomy for lung cancer. *J Thorac Cardiovasc Surg* 1996;111:948–953.

61. Rendina EA, Venuta F, De Giacomo T. Sleeve resection and prosthetic reconstruction of the pulmonary artery for lung cancer. *Ann Thorac Surg* 1999;68:995–1002.

62. Okada M, Yamagishi H, Satake S, et al. Survival related to lymph node involvement in lung cancer after sleeve lobectomy compared with pneumonectomy. *J Thorac Cardiovasc Surg* 2000;119:814–819.

63. Lardinois D, De Leyn P, Van Schil P, et al. ESTS guidelines for intraoperative lymph node staging in non-small cell lung cancer. *Eur J Cardiothorac Surg* 2006;30:787–792.

64. Gaer JAR, Goldstraw P. Intraoperative assessment of nodal staging at thoracotomy for carcinoma of the bronchus. *Eur J Cardiothorac Surg* 1990;4:207–210.

65. Bollen ECM, van Duin CJ, Theunissen PHMH, et al. Mediastinal lymph node dissection in resected lung cancer: morbidity and accuracy of staging. *Ann Thorac Surg* 1993;55:961–966.

66. Izbicki JR, Passlick B, Pantel K, et al. Effectiveness of radical systematic mediastinal lymphadenectomy in patients with resectable non-small cell lung cancer. *Ann Surg* 1998;227:138–144.

67. Sugi K, Nawata K, Fujita N, et al. Systematic lymph node dissection for clinically diagnosed peripheral non-small-cell lung cancer less than 2 cm in diameter. *World J Surg* 1998;22:290–294.

68. Wu Y, Huang ZF, Wang SY, et al. A randomized trial of systematic nodal dissection in resectable non-small cell lung cancer. *Lung Cancer* 2002;36:1–6.

69. Robinson L, Ruckdeschel J, Wagner H, et al. Treatment of non-small cell lung cancer—stage IIIA: ACCP evidence-based guidelines (2nd edition) *Chest* 2007;132:243S–265S.

70. Scott W, Howington J, Feigenberg S, et al. Treatment of non-small cell lung cancer—stage I & II: ACCP evidence-based clinical practice guideline (2nd edition) *Chest* 2007;132:234S–242S.

71. Izbicki JR, Passlick B, Karg O, et al. Impact on radical systematic

72. Manser R, Wright G, Hart D, et al. Surgery for early stage non-small cell lung cancer. *Cochrane Database Syst Rev* 2005;25:CD004699.

73. Keller SM, Adak S, Wagner H, et al. Mediastinal lymph node dissection improves survival in patients with stages II and IIIa non-small cell lung cancer; from the Eastern Cooperative Oncology Group. *Ann Thorac Surg* 2000;70:358–365.

74. Funatsu T, Matsubara Y, Ikeda S, et al. Preoperative mediastinoscopic assessment of N factors and the need for mediastinal lymph node dissection in T1 lung cancer. *J Thorac Cardiovasc Surg* 1994;108:321–328.

75. Berghmans T, Paesmans M, Meert AP, et al. Survival improvement in resectable non-small cell lung cancer with (neo)adjuvant chemotherapy: results of a meta-analysis of the literature. *Lung Cancer* 2005;49:13–23.

76. Douillard J-Y, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. *Lancet Oncol* 2006;7:719–727.

77. PORT Meta-analysis Trialists Group. Postoperative radiotherapy in non-small-cell lung cancer: systemic review and meta-analysis of individual patient data from nine randomised controlled trials. *Lancet* 1998;352:257–263.

78. Socinski MA, Detterbeck FC, Rosenman JG. Adjuvant therapy of resected non-small cell lung cancer. In FC Detterbeck, MP Rivera, MA Socinski, et al. (Eds.), Diagnosis and Treatment of Lung Cancer: An Evidence-Based Guide for the Practicing Clinician. Philadelphia, PA: W. B. Saunders, 2001. Pp. 206–219.

79. Okawara G, Ung YC, Markman BR, et al. Postoperative radiotherapy in stage II or IIIA completely resected non-small cell lung cancer: a systematic review and practice guideline. *Lung Cancer* 2004;44:1–11.

80. Lally BE, Zelterman D, Colasanto JM, et al. Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results database. *J Clin Oncol* 2006;24:2998–3006.

81. Hensing TA, Halle JS, Socinki MA. Chemoradiotherapy for stage IIIa, b non-small cell lung cancer. In FC Detterbeck, MP Rivera, MA Socinski, et al. (Eds.), Diagnosis and Treatment of Lung Cancer: An Evidence-Based Guide for the Practicing Clinician. Philadelphia, PA: W. B. Saunders, 2001. Pp. 291–303.

82. Jett JR, Schild SE, Keith RL, et al. Treatment of non-small cell lung cancer—stage IIIb: ACCP evidenced-based clinical practice guidelines. *Chest* 2007;132:266S–276S.

83. Albain K, Scott CB, Rusch VR, et al. Phase III comparison of concurrent chemotherapy plus radiotherapy (CT/RT) and CT/RT followed by surgical resection for stage IIIA(pN2) non-small cell lung cancer (NSCLC): initial results from intergroup trial 0139 (RTOG 93–09) (Abstract). Proc Am Soc Clin Oncol 2003;22:621.

84. West H, Albain KS. Current standards and ongoing controversies in the management of locally advanced non-small cell lung cancer. *Semin Oncol* 2005;32:284–292.

85. Detterbeck FC, Socinski MA. Induction therapy and surgery for I–IIIa, b non-small cell lung cancer. In FC Detterbeck, MP Rivera, MA Socinski, et al. (Eds.), Diagnosis and Treatment of Lung Cancer: An Evidence-Based Guide for the Practicing Clinician. Philadelphia, PA: W. B. Saunders, 2001. Pp. 257–266.

86. Socinski MA, Rosenman JG, Halle J, et al. Dose-escalating conformal thoracic radiation therapy with induction and concurrent carboplatin/paclitaxel in unresectable stage IIIA/B nonsmall cell lung carcinoma. *Cancer* 2001;92:1213–1223.

87. Socinski MA, Morris DE, Halle JS, et al. Induction and concurrent chemotherapy with high-dose thoracic conformal radiation therapy in unresectable stage IIIA and IIIB non-small-cell lung cancer: a dose-escalation phase I trial. *J Clin Oncol* 2004;22:4341–4350.

88. Alam N, Sheherd F, Winton T, et al. Compliance with post-operative adjuvant chemotherapy in non-small cell lung cancer: an analysis of National Cancer Institute of Canada and intergroup trial JBR. 10 and a review of the literature. *Lung Cancer* 2005;47:385–394.

89. Ferguson MK. Optimal management when unsuspected N2 nodal

disease is identified during thoracotomy for lung cancer: cost-effectiveness analysis. *J Thorac Cardiovasc Surg* 2003;126:1935–1942.

90. Maggi G, Casadio C, Mancuso M, et al. Resection and radical lymphadenectomy for lung cancer: prognostic significance of lymphatic metastases. *Int Surg* 1990;75:17–21.

91. Inoue M, Sawabata N, Takeda S, et al. Results of surgical intervention for p-stage IIIA (N2) non-small cell lung cancer: acceptable prognosis predicted by complete resection in patients with single N2 disease with primary tumor in the upper lobe. *J Thorac Cardiovasc Surg* 2004;127:1100–1106.

92. Rea F, Marulli G, Callegaro D, et al. Prognostic significance of main bronchial lymph nodes involvement in non-small cell lung carcinoma: N1 or N2? *Lung Cancer* 2004;45:215–220.

93. Iwasaki A, Shirakusa T, Miyoshi T, et al. Prognostic significance of subcarinal station in non-small cell lung cancer with T1–3 N2 disease. *Thorac Cardiovasc Surg* 2006;54:42–46.

94. Okada M, Tsubota N, Yoshimura M, et al. Evaluation of TMN classification for lung carcinoma with ipsilateral intrapulmonary metastasis. *Ann Thorac Surg* 1999;68:326–331.

95. Conill C, Astudillo J, Verger E. Prognostic significance of metastases to mediastinal lymph node levels in resected non-small cell lung carcinoma. *Cancer* 1993;72:1199–1202.

96. Tanaka F, Yanagihara K, Otake Y, et al. Prognostic factors in resected pathologic (p-) stage IIIA-N2, non-small-cell lung cancer. *Ann Surg Oncol* 2004;11:612–618.

97. Ohta Y, Shimizu Y, Minato H, et al. Results of initial operations in non–small cell lung cancer patients with single-level N2 disease. *Ann Thorac Surg* 2006;81:427–433.

98. Daly BDT, Mueller JD, Faling LJ, et al. N2 lung cancer: outcome in patients with false-negative computed tomographic scans of the chest. *J Thorac Cardiovasc Surg* 1993;105:904–911.

99. Sakao Y, Miyamoto H, Yamazaki A, et al. Prognostic significance of metastasis to the highest mediastinal lymph node in nonsmall cell lung cancer. *Ann Thorac Surg* 2006;81:292–297.

100. Ichinose Y, Kato H, Koike T, et al. Completely resected stage IIIA non-small cell lung cancer: the significance of primary tumor location and N2 station. *J Thorac Cardiovasc Surg* 2001;122:803–808.

101. Mountain CF. Surgery for stage IIIa-N2 non-small cell lung cancer. *Cancer* 1994;73:2589–2598.