CHEST Supplement

DIAGNOSIS AND MANAGEMENT OF LUNG CANCER, 3RD ED: ACCP GUIDELINES

Treatment of Stage III Non-small Cell Lung Cancer

Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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Objectives: **Stage III non-small cell lung cancer (NSCLC) describes a heterogeneous population with disease presentation ranging from apparently resectable tumors with occult microscopic nodal metastases to unresectable, bulky nodal disease. This review updates the published clinical trials since the last American College of Chest Physicians guidelines to make treatment recommendations for this controversial subset of patients.**

Methods: **Systematic searches were conducted through MEDLINE, Embase, and the Cochrane Database for Systematic Review up to December 2011, focusing primarily on randomized trials, selected meta-analyses, practice guidelines, and reviews.**

Results: **For individuals with stage IIIA or IIIB disease, good performance scores, and minimal weight loss, treatment with combined chemoradiotherapy results in better survival than radiotherapy alone. Consolidation chemotherapy or targeted therapy following definitive chemoradiation for stage IIIA is not supported. Neoadjuvant therapy followed by surgery is neither clearly better nor clearly worse than definitive chemoradiation. Most of the arguments made regarding patient selection for neoadjuvant therapy and surgical resection provide evidence for better prognosis but not for a beneficial impact of this treatment strategy; however, weak comparative data suggest a possible role if only lobectomy is needed in a center with a low perioperative mortality rate. The evidence supports routine platinum-based adjuvant chemotherapy following complete resection of stage IIIA lung cancer encountered unexpectedly at surgery. Postoperative radiotherapy improves local control without improving survival.**

Conclusions: **Multimodality therapy is preferable in most subsets of patients with stage III lung cancer. Variability in the patients included in randomized trials limits the ability to combine results across studies and thus limits the strength of recommendations in many scenarios. Future trials are needed to investigate the roles of individualized chemotherapy, surgery in particular cohorts or settings, prophylactic cranial radiation, and adaptive radiation.**

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Abbreviations: ACCP = American College of Chest Physicians; EORTC = European Organisation for Research and Treatment of Cancer; HR = hazard ratio; IASLC = International Association for the Study of Lung Cancer; IMRT = intensity-modulated radiotherapy; MLND = mediastinal lymph node dissection; NSCLC = non-small cell lung cancer; PCI = prophylactic cranial irradiation; PORT = postoperative radiotherapy; RCT = randomized controlled trial; SWOG = Southwestern Oncology Group

Infiltrative Stage III (N2,3) Non-small Cell Lung Cancer

2.3.1. In patients with infiltrative stage III (N2,3) non-small cell lung cancer (NSCLC) and performance status 0-1 being considered for curative-intent treatment, radiotherapy alone is not recommended (Grade 1A)**.**

2.3.2. In patients with infiltrative stage III (N2,3) NSCLC and performance status 0-1 being considered for curative-intent treatment, combination platinum-based chemotherapy and radiotherapy (60-66 Gy) are recommended (Grade 1A)**.**

Remark: Dose escalation of radiotherapy is not recommended (except in a clinical trial).

Remark: For patients with stage IIIB NSCLC, once daily thoracic radiotherapy plus platinum-based doublet chemotherapy is recommended.

2.3.3. In patients with infiltrative stage III (N2,3) NSCLC, performance status 0-1, and minimal weight loss being considered for curative-intent treatment, concurrent chemoradiotherapy is recommended over sequential chemoradiotherapy (Grade 1A)**.**

Remark: We cannot currently recommend for or against induction chemotherapy (ie, before) concurrent chemoradiotherapy, and patients should be referred for clinical trials to answer this question.

Remark: We cannot currently recommend for or against consolidation chemotherapy (ie, after) concurrent chemoradiotherapy, and patients should be referred to clinical trials to answer this question.

2.3.4. In patients with infiltrative stage III (N2,3) NSCLC with a complete response after treatment with concurrent chemoradiotherapy, we suggest that prophylactic cranial irradiation should not be given (outside of a clinical trial) (Grade 2C)**.**

2.3.5. In patients with infiltrative stage III (N2,3) NSCLC and performance status 0-1 being considered for curative-intent treatment, treatment with neoadjuvant (induction) chemotherapy or chemoradiotherapy followed by surgery is not recommended (Grade 1C)**.**

2.3.6. In patients with infiltrative stage III (N2,3) NSCLC and performance status 2 or those with substantial weight loss (> 10%), concurrent chemoradiotherapy is suggested but with careful consideration of the potential risks and benefits (Grade 2C)**.**

Remark: Patient-related and tumor-related factors can influence the balance of risks vs benefits; patient preferences should also play a significant role.

2.3.7. In patients with infiltrative stage III (N2,3) NSCLC, performance status 0-1, and minimal weight loss being considered for curative-intent treatment, a platinum-based doublet chemotherapy is suggested (Grade 2C)**.**

Remark: An optimal agent to be combined with platinum cannot be defined; one should choose a regimen with an acceptable toxicity profile for the individual patient among several combinations that have demonstrated activity when used concurrently with radiation in stage III NSCLC.

2.3.8. In patients with symptomatic infiltrative stage III (N2,3) NSCLC and either performance status 3-4, comorbidities, or disease too extensive to treat with curative intent, palliative radiotherapy is recommended. The fractionation pattern should be chosen based on the physician's judgment and patient's needs (Grade 1C)**.**

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Discrete Mediastinal Node Involvement

3.5.1. In patients with discrete N2 involvement by NSCLC identified preoperatively (IIIA), we recommend the treatment plan should be made with the input from a multidisciplinary team (Grade 1C)**.**

Remark: The multidisciplinary team should include at a minimum a thoracic surgeon, medical oncologist, and radiation oncologist.

Remark: The decision should be made collaboratively by the entire team so as to reflect collective judgment.

Remark: The plan should include the entire proposed treatment, including plans contingent on the results of reevaluations (ie, initial treatment response or nonresponse), not simply a first step.

3.5.2. In patients with discrete N2 involvement by NSCLC identified preoperatively (IIIA), either definitive chemoradiation therapy or induction therapy followed by surgery is recommended over either surgery or radiation alone (Grade 1A)**.**

Remark: As the data do not permit the selection of one option or the other as superior, patient values and preferences should factor significantly in the decision.

Remark: All multimodality therapy should be performed in centers with experienced multidisciplinary teams that track their relevant clinical outcomes and are capable of minimizing and managing the toxicity and complications involved.

Remark: Further identification of patients more likely to benefit from surgical resection after induction therapy is not possible based upon pretreatment characteristics. Decisions to pursue surgical resection after induction therapy should be made prior to initiation of any therapy.

3.5.3. In patients with discrete N2 involvement by NSCLC identified preoperatively (IIIA), primary surgical resection followed by adjuvant therapy is not recommended (except as part of a clinical trial) (Grade 1C)**.**

Occult N2 Involvement Discovered at Resection Despite Thorough Preoperative Staging (Stage IIIA)

Surgical Considerations

4.5.1. In patients with NSCLC undergoing surgical resection, systematic mediastinal lymph node sampling or complete mediastinal lymph node dissection is recommended (Grade 1B)**.**

Remark: At least a systematic sampling is needed to accurately assess the pathologic stage; this is critical to direct adjuvant therapy.

Remark: It is unclear whether lymphadenectomy offers a survival benefit over systematic sampling, but in general, lymphadenectomy is suggested if there is evidence of N2 node involvement.

4.5.2. In patients with NSCLC who have incidental (occult) N2 disease (IIIA) found at surgical resection despite thorough preoperative staging and in whom complete resection of the lymph nodes and primary tumor is technically possible, completion of the planned lung resection and mediastinal lymphadenectomy is suggested (Grade 2C)**.**

Remark: This recommendation assumes that staging for distant disease and invasive preoperative mediastinal staging according to guidelines have been carried out.

Remark: In a patient who has not received preoperative staging despite clinical suspicion of N2 node involvement (ie, enlarged on CT, uptake on PET, or negative CT and PET but with a central tumor or N1 involvement), the operation should be aborted and staging completed if N2 disease is identified intraoperatively.

Adjuvant Therapy

4.5.3. In patients with resected NSCLC (R0) who were found to have incidental (occult) N2 disease (IIIA) despite thorough preoperative staging and who have good performance status, adjuvant platinum-based chemotherapy is recommended (Grade 1A)**.**

Remark: We suggest this should typically involve a doublet regimen for 3 to 4 cycles initiated within 12 weeks.

4.5.4. In patients with R0 resected NSCLC who were found to have incidental (occult) N2 disease (IIIA) despite thorough preoperative staging, sequential adjuvant radiotherapy is suggested when concern for a local recurrence is high (Grade 2C)**.**

Remark: Adjuvant postoperative radiotherapy reduces the incidence of local recurrence, but it is unclear whether it improves survival.

Remark: Adjuvant chemotherapy should be used initially followed by radiotherapy; concurrent chemoradiotherapy is not recommended (except in a clinical trial).

4.5.5. In patients with NSCLC who were found to have incidental (occult) N2 disease (IIIA) despite thorough preoperative staging and were incompletely resected (R1,2), combined postoperative concurrent chemotherapy and radiotherapy is suggested (Grade 2C)**.**

Remark: Incomplete resection (R1,2) does not appear to confer a survival benefit over no resection.

The evidence-based guidelines that follow provide a synthesis of the medical literature and specific treatment guidelines as a resource for the clinician who deals directly with stage IIIA/B non-small cell lung cancer (NSCLC). Exhaustive detail about published trials is avoided to provide a more readable and useable guide. These guidelines are built on a systematic, thorough literature review through December 2011, including meta-analyses, systematic reviews, and primary articles from clinical trials.

Historically, stage III lung cancer was defined as locoregionally advanced disease attributed to primary tumor extension into extrapulmonary structures (T3 or T4) or mediastinal lymph node involvement (N2 or N3) without evidence of distant metastases (M0). With the 2009 revisions to the TNM staging system, stage III lung cancers now include T3 tumors when associated with hilar (N1) nodal involvement.[2-4] $T3_{>7}$ N1 M0 and $T3_{Satell}$ N1 M0 tumors are discussed by Kozower et al,[131] "Special Treatment Issues in Non-small Cell Lung Cancer," in the American College of Chest Physicians (ACCP) Lung Cancer Guidelines as well as $T4_{Inv}$ N0,1 M0 and $T4_{IpsiNod}$ N0.1 M0 tumors. $T3_{Inv}$ N1 M0 tumors with chest wall invasion are also covered by Kozower et al[131] in the ACCP Lung Cancer Guidelines. This article specifically addresses stage IIIA with N2 node involvement and stage IIIB with N3 node involvement. In the International Association for the Study of Lung Cancer (IASLC) database, about 20% of the patients had stage cIIIa (N2) disease, with a 5-year survival of 16%.[5] Wisnivesky et al[6] reported that 17.6% of >80,000 NSCLC cases were stage IIIB in the 2005 Surveillance, Epidemiology, and End Results registry. The anticipated 5-year survival for patients presenting with clinical stage IIIB NSCLC is 3% to 7%[5]; however, these data include patients with malignant pleural effusions, a disease now reclassified as stage IV. The IASLC database included 3% stage cIIIB (N3) cases with a 5-year survival of 7%.[2]

Of all the patients with lung cancer, those with stage IIIA N2 disease are perhaps the most therapeutically challenging subset. These patients have been the subject of multiple clinical trials, yet controversy and confusion characterize discussion about the optimal therapeutic approach. Stage IIIA (N2) represents a heterogeneous population. Unfortunately, a clear and widely accepted characterization of subgroups has not yet emerged. It is difficult to compare results across clinical trials because characterization of the patients included is generally limited, yet there is a general sense that the populations included have not been the same. Description of the patients is complex because of all the variables, including whether trial eligibility is based on clinical vs pathologic staging, whether clinical stage is based on imaging (acceptable with extensive infiltration) or invasive staging, and the thoroughness of staging for mediastinal and distant metastases (ie, PET scanning).

These caveats in interpretation of the evidence make reliance on phase 2 and cohort series particularly hazardous and underscore the need for randomized studies. Furthermore, it emphasizes the need to analyze the treatment results on an intention-to-treat basis and on characteristics that can be identified before treatment begins. Although data based on subgroups that have met certain treatment milestones or have completed treatment may provide useful prognostic information for such patients, they are of limited value in defining a treatment strategy.

Definition of Subgroups

We have approached the difficulties inherent in interpretation of data for stage III by separating the discussion into three readily identifiable groups: (1) patients with infiltrative stage III (N2/N3) tumors, (2) patients with occult N2 node involvement despite thorough preoperative staging, and (3) patients with discrete clinically evident (by CT or CT-PET scan) N2 involvement. Of course, one can subdivide these groups further and in many other ways, but our evidence review suggested that this was a practical way to structure the discussion about how to approach treating patients with stage III lung cancer. This division specifically excludes patients in whom there is reasonable suspicion of N2 involvement (by CT or CT-PET scan) but who undergo resection without thorough preoperative staging and then found to have malignant N2 nodes. Such patient management is inappropriate, and we discuss this briefly at the end of the section 4.0.

Patients with infiltrative N2/N3 involvement have N2 or N3 disease where discrete nodes can no longer be clearly distinguished and measured; this corresponds to the radiographic group A in the stage evaluation

article of these guidelines.[7] These patients have fairly extensive mediastinal involvement, with tumor infiltration in the mediastinum partially surrounding the major structures (ie, great vessels, trachea). The panel recognizes that the term "infiltrative N2/N3 involvement"has not been in widespread use and that the available data do not define patients included in such a way. Nevertheless, from a practical, clinical standpoint, this way seems to distinguish a recognizable subgroup of patients with stage III disease. Furthermore, in such patients, invasive proof of mediastinal involvement is not usually believed to be necessary; thus, separation of this group from others allows for better characterization of the patients by preoperative invasive staging (ie, appropriate reliance on image-defined staging vs invasive staging). However it is especially important to carefully rule out distant disease in patients with infiltrative N2/N3 involvement.

Discrete N2/N3 involvement denotes patients in whom individual mediastinal nodes can be distinguished. These nodes may be enlarged or normal sized and may be suspected by PET uptake or by other clinical characteristics (eg, size, a central tumor). Thus, these patients correspond to the radiographic groups B and C in the stage evaluation article.[7] The mediastinal stage suggested by imaging in these patients must be confirmed through thorough invasive staging.[7] We would include patients with malignant involvement of discrete N3 nodes in this group. We recognize that the category of discrete N2/N3 involvement can be further subdivided (eg, exclusion of N3 involvement, enlarged vs normal-sized nodes, multistation vs single-station involvement), and these issues are discussed. However, the frequent lack of distinction between such further subdivision in published trials makes grouping these patients together a reasonable way to structure the discussion as it relates to published evidence. Furthermore, if one considers mediastinal downstaging to be a crucial factor, such further subdivision may be of less importance.

We avoid the terms "potentially resectable" or "unresectable." An exact definition of these terms is not available and not possible. Such terms are subjective, depend on the individual surgeon's judgment, and may even vary from day to day. Furthermore, data show that a substantial proportion of patients with stage IIIA (N2) tumors judged to be resectable (25%-35%) end up undergoing an R1,2 resection,[8] further calling into question the accuracy of this term. Although the concept of patients potentially suitable or unsuitable for surgery as part of multimodality treatment is implied by the categorization of infiltrative and discrete N2/N3 involvement, we believe that the objective definition of patients according to radiographic characteristics more readily facilitates the discussion.

Patients with occult N2 disease despite thorough preoperative staging are found intraoperatively or postoperatively to have positive N2 nodes. The thoroughness of the preoperative staging and intraoperative mediastinal assessment is critical.[8] Nevertheless, this group of patients with N2 involvement is distinct and identifiable.

The importance of appropriate stage evaluation must be emphasized. Particularly for patients with stage III, the introduction of PET imaging has created a significant stage shift through finding asymptomatic occult distant metastases, resulting in better survival of both patients with stage III and patients with stage IV disease.[8-10] The importance of thorough preoperative and intraoperative mediastinal staging cannot be overstated. Of course, other factors such as performance status, comorbidities, and patient preferences also are important to consider in planning the best treatment approach for patients with stage III lung cancer.

1.0 Methods

To update previously published guidelines for the treatment of stage III NSCLC, the writing committee repeated prior searches of Medline for studies of therapy for stage III NSCLC as well as performed new systematic searches of MEDLINE, Embase, and the Cochrane Database of Systematic Reviews up to December 2011, including primarily randomized trials, selected meta-analyses, practice guidelines, and reviews. In addition, we identified additional articles by searching personal files and reviewing reference lists of included studies. The multidisciplinary writing committee comprised three pulmonologists, three thoracic surgeons, one radiation oncologist, one medical oncologist, and one ACCP staff methodologist. The committee formulated key population, intervention, comparison, and outcome (PICO) questions (Table S1), synthesized and reviewed available evidence, rated the quality of evidence, proposed recommendations, and proposed the grading of the strength of the recommendations by using a standardized approach, as described in the methodology article of these guidelines.[1] The writing committee reviewed all recommendations and reached consensus by iterative discussion and debate. The article was extensively revised, reflecting input from the writing committee as well as the entire ACCP Lung Cancer Guidelines panel. The guideline was reviewed and approved by the Lung Cancer Guidelines panel prior to approval by the Thoracic Oncology NetWork, the Guidelines Oversight Committee, and the Board of Regents of the ACCP.

2.0 Infiltrative Stage III (N2/N3) Disease

2.1 Combined Chemotherapy With Radiotherapy

Despite varying doses and delivery schedules, the use of radiotherapy alone as a curative mode of therapy for stage IIIA or IIIB disease yields poor survival at 5 years (5%-10%) with traditional dose and fractionation schedules (1.8-2.0 Gy per fraction per day to 60-70 Gy in 6-7 weeks).[11] Although patients with unresectable, bulky, locally advanced stage IIIA disease

gain symptomatic benefit with radiotherapy, their outcome has generally been poor, often as a result of distant, extrathoracic metastasis.

With the development of more-effective platinum-based chemotherapy, investigators have attempted to improve survival by decreasing relapse from distant disease by combining systemic chemotherapy with radiotherapy. Chemotherapy has been combined with radiotherapy in different ways (chemotherapy followed sequentially by radiotherapy, concurrent chemoradiation, induction chemotherapy followed by concurrent chemoradiation, or concurrent chemoradiation followed by consolidation chemotherapy) in multiple phase 2 trials involving heterogeneous and often poorly staged groups of patients with locally advanced disease. In general, trials that used platinum-containing regimens in combination with radiotherapy have shown good tumor response rates and an improvement in survival.[12] Looking at collective data from multiple phase 2 trials, acute and late toxicities associated with combined chemotherapy and radiotherapy have included mild to severe esophagitis, pneumonitis, and treatment-related death. Overall, however, these trials showed the feasibility of combined modality therapy and suggested that chemotherapy plus radiotherapy would yield improved outcomes compared with radiotherapy alone.

Multiple phase 3 trials using platinum-based chemotherapy have confirmed improved survival for patients treated with chemotherapy plus radiotherapy compared with radiotherapy alone (Fig 1).[13-17] Of note, the earliest trials showed no survival benefit with the addition of chemotherapy to radiotherapy but used either low-dose cisplatin or nonplatinum-based chemotherapy. Later trials using more-appropriate doses of platinum-based chemotherapy showed evidence of improved survival using combination therapy over radiotherapy alone. Trials were heterogeneous in their stage inclusion, performance status, and chemotherapy regimens, with many using regimens that would not be considered standard today (eg, three or four drug regimens). Toxicity in the form of esophagitis and pneumonitis was higher after combined therapy but at acceptable levels. With combined chemotherapy and

FIGURE 1. [Section 2.1] Addition of cisplatin-based chemotherapy to radiotherapy improves survival in stage III NSCLC.

First Author	Year	No.	% good PS [a]	Chemo	RT (both arms)	Survival						p
						MST (mo)		2 y (%)		5 y (%)		
						ChRT	RT	ChRT	RT	ChRT	RT	
Sequential												
Le Chevallier[15]	1991	353	80	CVdPL	65	12	19	21	14	(12)[b]	(4)[b]	0.08
Cullen[13]	1999	446	86	MIP	40-64	12	10	20	16	-	-	.NS
Sause[16, c]	2000	303	(100)[d]	VbP	69.6 HF	14	12	32	24	8	6	0.04
Sause[16, c]	2000	300	(100)[d]	VbP	60	14	11	32	19	8	5	0.04
Mattson[18]	1988	238	69	CAP	55	11	10	19	17	-	-	(NS)[e]
Miller[19]	1998	229	89	FVMCAP	58	9	9	13	18	4	3	NS
Dillman[14]	1996	155	100	VbP	60	14	10	26	13	17	6	0.01
Average [f]						**12**	**10**	**23**	**18**	**9**	**5**	
Concurrent												
Schaake-Koenig[17, c]	1992	210	94	P qd	55 SC	12	12	26	13	10[g]	2[g]	0.003
Trovo[20]	1992	146	(79)[d]	P qd	45	10	10	14	14	-	-	NS
Jeremic[21]	1996	135	49	CbE qd	69.6 HF	22	14	43	26	23[g]	9[g]	0.02
Schaake-Koenig[17, c]	1992	206	94	P q wk	55 SC	13	12	19	13	10[g]	2[g]	NS
Jeremic[22, c]	1995	113	80	CbE q wk	64.8 HF	18	8	35	25	21	5	0.003
Jeremic[22, c]	1995	117	80	CbE q 2wk	64.8 HF	13	8	27	25	16	5	NS
Blanke[23]	1995	215	80	P q 3wk	60-65	11	10	18	13	5	2	NS
Average						**14**	**11**	**26**	**18**	**14**	**4**	

Inclusion criteria: randomized controlled trial of cisplatin-based chemotherapy and RT vs RT alone in > 100 patients with stage III NSCLC.

CAP = cyclophosphamide, doxorubicin, cisplatin; CbE = carboplatin, etoposide; Ch = chemotherapy; ChRT = chemoradiotherapy; CVdPL = cyclophosphamide, vindesine, cisplatin, lomustine; ECOG = Eastern Cooperative Oncology Group; FVMCAP = 5-fluorouracil, vincristine, mitomycin c, cyclophosphamide, doxorubicin, cisplatin; HF = hyperfractionated 1.2 Gy per fraction twice daily to 69.6 Gy; MIP = mitomycin C, ifosfamide, cisplatin; MST = median survival time; NS = not significant; NSCLC = non-small lung cancer; P = cisplatin; PS = performance status; RT = radiotherapy; SC = split course; VbP = vinblastine, cisplatin, y=years.

[a]Defined as ECOG 0-1 or Karnofsky 80-100.

[b]Three-year survival.

[c]Three-arm trial.

[d]PS > 70.

[e]$P < .05$ if analysis is restricted to only patients with stage III NSCLC.

[f]Excluding values in parentheses.

[g]4-y survival.

radiotherapy demonstrating improved survival over radiotherapy alone in locally advanced, unresectable stage III NSCLC, this combination became the standard of care. Two meta-analyses reviewing > 50 trials confirmed the survival benefit of combined platinum-based chemotherapy with radiotherapy over radiotherapy alone in locally advanced, unresectable NSCLC.[24,25]

The paramount goal in treating the patient with stage III lung cancer seems simple: to eradicate both visible, intrathoracic disease and to reduce the incidence of subsequent systemic, extrathoracic metastases. Local control can be achieved through radiotherapy, with higher doses generally resulting in higher rates of disease control and higher and eventually unacceptable rates of toxicity that limit the dose that can be delivered. Systemic chemotherapy is used to achieve two aims. As a radiosensitizing agent, the aim is to increase the therapeutic index of radiation therapy, and as a cytotoxic agent, the aim is to eradicate unsuspected or prevent de novo development of systemic metastasis, which is made more complex by the fact that the optimum drugs, doses, and schedules of chemotherapy to achieve these two goals are unknown and may not be the same. Hence, the various trials described here represent attempts to elucidate the most effective means of combining chemotherapy and radiotherapy to treat local disease and prevent the emergence of systemic disease in patients with stage III lung cancer.

2.2 Concurrent Chemoradiotherapy

The definitive chemotherapy and radiotherapy trials included patients with infiltrative disease as well as discrete nodal involvement (Fig 2). Therefore, the results of the studies reviewed are applicable to the patients under discussion in this section (infiltrative disease) as well as to the patients in the next section (discrete nodal involvement). In most of these studies, the presence of mediastinal nodal involvement was not confirmed by biopsy specimen, but the mediastinal tumor burden was extensive enough that there was no substantial doubt (ie, radiographic type A, bulky discrete nodes). The definitive chemotherapy and radiotherapy studies included patients with both N2 and N3 disease and did not distinguish between these, which is consistent with a tumor burden that makes identification of discrete nodes difficult in many patients. On the other hand, the mediastinal tumor volume was limited enough to allow definitive radiotherapy to be administered. The median age of the patients was about 60 to 65 years, and the studies involved primarily patients with a performance status of 1, with a smaller proportion with a performance status of 0; exceptions are mentioned specifically.[26,27]

FIGURE 2. [Section 2.2, 3.3] A depiction of the heterogeneous patient characteristics of stage III lung cancer and the inclusion of various patient subtypes into clinical studies evaluating treatment options for patients with stage III disease. PS = performance status; RT = radiotherapy.

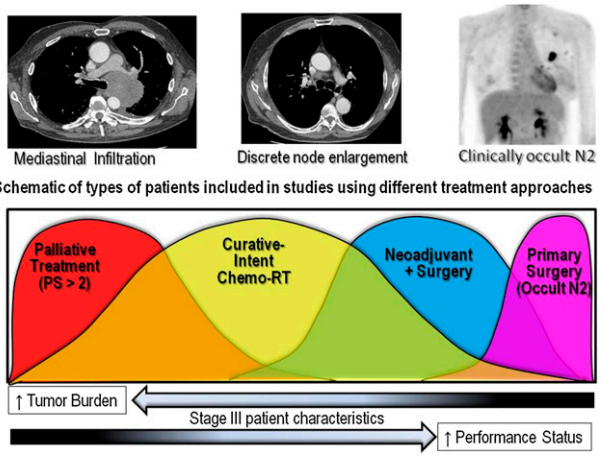


Figure 3 lists the major trials comparing chemotherapy given concurrently with thoracic radiotherapy vs sequentially.[28-32] These trials differ in their dose of cisplatin, the drugs combined with platinum, and the exact timing and dose schedule of concurrent radiotherapy. Each trial shows a benefit for the patients randomized to receive concurrent chemoradiotherapy over sequential treatment. A Cochrane meta-analysis of concurrent vs sequential chemotherapy and radiation had a hazard ratio (HR) of 0.74 (95% CI, 0.62-0.89) and a 10% absolute survival benefit at 2 years.[26] An analysis by the Non-Small Cell Lung Cancer Collaborative Group, revealed that concurrent chemoradiation had a significant absolute survival benefit of 5.7% at 3 years and 4.5% at 5 years (HR, 0.84; 95% CI, 0.74-0.95; $P = .004$).[35] Some of the difference may be explained by the longer median follow-up (6 years) and the inclusion of three trials with single-agent cisplatin or carboplatin and two trials with split-course radiation in the latter analysis. Locoregional control is improved with concomitant chemoradiation, but there is no difference in the rates of distant progression with concomitant vs sequential treatment.

The improved survival associated with concurrent chemoradiation comes at a cost of increased acute esophageal toxicity (grade 3-4) from 4% to 18% (relative risk, 4.9; 95% CI, 3.1-7.8; $P < .001$) but no difference in acute pulmonary toxicity. In patients with poorer performance status, weekly low-dose concurrent carboplatin and paclitaxel have been given with concurrent thoracic radiation to 63 Gy followed by two cycles of consolidation with standard-dose carboplatin and paclitaxel,[33] but this has never been compared with full-dose chemoradiotherapy in a randomized trial. Sequential chemotherapy followed by radiation or radiation alone can still be used for patients with

FIGURE 3. [Section 2.2] Concurrent vs sequential chemoradiotherapy treatment details.

First Author	Year	No.	Chemo	Additional treatment?	RT (Gy) (both arms)	Survival						p
						MST (mo)		2 y (%)		5 y (%)		
						Conc	Seq	Conc	Seq	Conc	Seq	
Curran[28, a]	2011	~400	VbP		60	17	15	-	-	16	10	0.05
Curran[28, a]	2011	~400	E(oral) P		60	16	15	-	-	13	10	-
Belani[33, a]	2005	163	Cb Pac	Induction	63	13	13	25	30	-	-	NS
Belani[33, a]	2005	183	Cb Pac	Consolidation	63	16	13	31	30	-	-	NS
Fournel[30]	2005	105	EP→PV		66	16	15	39	26	21	14	NS
Zatloukal[34]	2004	102	VP		60	17	13	34	14	18	10	.02
Furuse[31]	1999	320	MVP		56 SC	17	13	35	27	16	9	0.04
Average[c]						**16**	**14**	**33**	**25**	**17**	**10**	

Inclusion criteria: randomized controlled trial of concurrent vs sequential chemotherapy and RT in stage III NSCLC.

AUC = area under the curve; Cb Pac = carboplatinum, paclitaxel; EP = etoposide, cisplatin; MVP = mitomycin C, vindesine, cisplatin; VP = vinorelbine, cisplatin. See Figure 1 legend for expansion of other abbreviations.

[a]Three-arm trial.

[b]Four-year survival.

[c]Excluding data in parentheses because they are not entirely comparable for reasons cited.

very large radiation ports or significantly decreased performance status, each of which puts patients at higher risk for severe toxicity.

The optimal chemotherapy combinations and sequencing have not been determined, and other agents, including pemetrexed, newer taxanes, and epidermal growth factor receptor inhibitors, are being examined. All the trials from the Cochrane database analysis used cisplatin-based doublets and continuous radiation.

The optimal radiation dose for concurrently treated patients typically is 60 to 70 Gy, but limited evidence suggests that 74 Gy may be given safely.[36] Newer, three- and four-dimensional conformal techniques and respiratory gating have decreased the off-target delivery to the lungs, spinal cord, and esophagus.[37] Various experimental protocols have also examined the use of hyperfractionated radiation or intensity-modulated radiotherapy (IMRT) to optimize radiation dosing. IMRT involves modulating the radiation beam to allow for a larger radiation dose to the primary tumor and to decrease the dose to normal tissues, and early results are promising.[37,38] Although there is a lack of data from randomized controlled trials (RCTs) to support any recommendation for the standard use of IMRT, this mode of radiotherapy is being used increasingly in some centers treating stage III NSCLC.

Even with the increased survival and improved local disease control that comes with combining chemotherapy and radiotherapy concurrently, the rate of systemic metastasis remains high. To reduce the incidence of extrathoracic disease, investigators have conducted trials giving full-dose systemic chemotherapy either before (induction) or after (consolidation) concurrent chemoradiotherapy. Both induction and consolidation chemotherapy have been examined in phase 2 studies when added to concomitant chemoradiation, but in a randomized phase 3 study[39] comparing the addition of two cycles of induction therapy to standard concurrent chemoradiotherapy in 366 patients with unresectable stage III lung cancer, the difference in median survival was not statistically significant (14 months vs 12 months for induction vs control groups). Some experts point out that this study used carboplatin rather than cisplatin, the former potentially having less efficacy. Two other major randomized trials compared induction therapy added to concurrent chemoradiotherapy (CALGB/ECOG [Cancer and Acute Leukemia Group B/Eastern Cooperative Oncology Group][40] and the French Lung Cancer Study Group[41]) but did not show any survival benefit for adding induction chemotherapy over concurrent chemoradiation alone. Therefore, at this time, induction with definitive chemoradiation is not recommended outside a clinical trial.

The value of consolidation chemotherapy is unclear at this time. Initial phase 2 studies involving either docetaxel or cisplatin and etoposide consolidation after definitive chemoradiation were encouraging.[42] With regard to consolidation therapy, initial phase 2 data from the Southwestern Oncology Group (SWOG) were promising for docetaxel consolidation after definitive chemoradiation. SWOG enrolled 50 patients with stage IIIA NSCLC who received cisplatin and etoposide with concurrent radiotherapy (61 Gy) followed by two additional cycles of cisplatin and etoposide.[42] The 5-year survival of 15% was encouraging and led to the SWOG 9504 phase 2 trial of 83 patients receiving concurrent chemotherapy and radiotherapy, but the follow-up consolidation was accomplished by docetaxel.[43,44] The follow-up phase 3 study was stopped early because of increased toxicity in the consolidation

docetaxel arm, with no difference in median overall survival found between the two arms.[45] The overall 5-year survival rate was 29% with docetaxel consolidation, which was much improved over the 15% rate with cisplatin and etoposide consolidation in the prior study. These encouraging results prompted the two ongoing phase 3 randomized trials: SWOG 0023, which has accrued >500 patients, and the Hoosier Oncology Group LUN 01-24, which is currently enrolling. These trials feature different designs intended to uncover, to varying degrees of confidence, the role of consolidation chemotherapy after definitive concurrent chemoradiation.

Concurrent chemoradiotherapy has several drawbacks, including difficulty in maintaining full-dose chemotherapy sufficient to treat systemic disease, especially with some of the newer agents such as gemcitabine, docetaxel, and paclitaxel of which all require dose reductions when given concurrently with radiotherapy. Concurrent chemoradiotherapy also has increased local adverse effects (esophagitis and pneumonitis). Finally, although concurrent is superior to sequential therapy, the long-term survival for patients with stage III NSCLC remains low. Whether adding consolidation chemotherapy provides an effective means to address this issue awaits validation with larger randomized trials. The newer targeted therapies are theoretically attractive either in combination with concurrent therapy (perhaps functioning as radiosensitizers) or in the consolidation setting. Again, further clinical trials are needed to define the optimal role of these novel agents in treatment strategies for unresectable stage III disease.

Given the high incidence of CNS metastasis in NSCLC and the proven benefit of prophylactic cranial irradiation (PCI) in patients with small cell lung cancer with a complete response to treatment,[35] studies have tested the idea that PCI may benefit patients with stage III NSCLC after treatment with curative-intent chemoradiation therapy. Trials addressing this have generally found that PCI indeed delays or prevents the onset of symptomatic CNS metastases, but none have demonstrated a clear survival benefit[46-48]; therefore, this is not currently considered an effective addition to the management of patients with stage III NSCLC.

The optimal treatment recommendations in the various clinical presentations of stage IIIA and IIIB disease are still evolving. Hopefully, as the current and future phase 3 trials accrue and mature and subsequent randomized trials with newer chemotherapy agents and radiotherapy schemata are started and completed, more definitive treatment guidelines will emerge. Novel agents, including small peptides, as well as molecular-directed chemotherapy and immunostimulating techniques may significantly change the future recommendations in stage IIIA and IIIB disease. Until that time, it is important that whenever possible, the clinician who manages locally advanced NSCLC enroll their patients in every available clinical trial.

2.3 Recommendations

2.3.1. In patients with infiltrative stage III (N2,3) NSCLC and performance status 0-1 being considered for curative-intent treatment, radiotherapy alone is not recommended (Grade 1A)**.**

2.3.2. In patients with infiltrative stage III (N2,3) NSCLC and performance status 0-1 being considered for curative-intent treatment, combination platinum-based chemotherapy and radiotherapy (60-66 Gy) are recommended (Grade 1A)**.**

Remark: Dose escalation of radiotherapy is not recommended (except in a clinical trial).

Remark: For patients with stage III NSCLC, once daily thoracic radiotherapy plus platinum-based doublet chemotherapy is recommended.

2.3.3. In patients with infiltrative stage III (N2,3) NSCLC, performance status 0-1, and minimal weight loss being considered for curative-intent treatment, concurrent chemoradiotherapy is recommended over sequential chemoradiotherapy (Grade 1A)**.**

Remark: We cannot currently recommend for or against induction chemotherapy (ie, before) concurrent chemoradiotherapy, and patients should be referred for clinical trials to answer this question.

Remark: We cannot currently recommend for or against consolidation chemotherapy (ie, after) concurrent chemoradiotherapy, and patients should be referred for clinical trials to answer this question.

2.3.4. In patients with infiltrative stage III (N2,3) NSCLC with a complete response after treatment with concurrent chemoradiotherapy, it is suggested that PCI should not be given (outside of a clinical trial) (Grade 2C)**.**

2.3.5. In patients with infiltrative stage III (N2,3) NSCLC and performance status 0-1 being considered for curative-intent treatment, treatment with neoadjuvant (induction) chemotherapy or chemoradiotherapy followed by surgery is not recommended (Grade 1C)**.**

2.3.6. In patients with infiltrative stage III (N2,3) NSCLC and performance status 2 or those with substantial weight loss (> 10%), concurrent chemoradiotherapy is suggested but with careful

consideration of the potential risks and benefits (Grade 2C)**.**

Remark: Patient-related and tumor-related factors can influence the balance of risks vs benefits; patient preferences should also play a significant role.

2.3.7. In patients with infiltrative stage III (N2,3) NSCLC, performance status 0-1, and minimal weight loss being considered for curative-intent treatment, a platinum-based doublet chemotherapy is suggested (Grade 2C)**.**

Remark: An optimal agent to be combined with platinum cannot be defined; one should choose a regimen with an acceptable toxicity profile for the individual patient among several combinations that have demonstrated activity when used concurrently with radiation in stage III NSCLC.

2.3.8. In patients with symptomatic infiltrative stage III (N2,3) NSCLC and either performance status 3-4, comorbidities, or disease too extensive to treat with curative intent, palliative radiotherapy is recommended. The fractionation pattern should be chosen based on the physician's judgment and patient's needs (Grade 1C)**.**

3.0 Discrete Mediastinal Node Involvement

3.1 The Role of Primary Surgery

Patients in whom the possibility of N2 involvement is suspected must undergo a careful staging evaluation, as outlined in the stage evaluation article of these guidelines.[7] This evaluation should include both a careful search for unsuspected distant metastases and a thorough invasive evaluation of the mediastinum. The discussion that follows assumes adherence to these principles. In other settings, it cannot be assumed that the data provided, arguments presented, and recommendations made are applicable or appropriate.

Several RCTs compared the outcomes of primary surgery vs preoperative (induction or neoadjuvant) therapy followed by surgery (Fig 4). These trials demonstrated a fairly consistent trend to better 2- and 5-year survival after preoperative therapy vs primary surgery. However, most of these studies had small numbers of patients, and the difference was not statistically significant. The patients included in these studies have been carefully selected and represent those with preoperatively identified N2 tumors that were believed to have such a good prognosis that primary resection was justified. No information was reported with regard to whether the nodes were enlarged, but given that the patients were believed to have a good

Figure 4. [Section 3.1] Randomized phase 3 trials of preoperative therapy followed by surgery vs surgery alone for stage III NSCLC.

First Author	No.	% with N2 confirmed	% T4, N3	Induction-therapy, # of cycles	Adjuvant Therapy	Survival						p
						MST (mo)		2 yr (%)		5 yr (%)		
						Ind→S	S	Ind→S	S	Ind→S	S	
Depierre[49, a]	167	Few [b]	0	MIP x2	MIP x2[c,d]	14	12	41	37	30	22	-
Nagai[50]	62	100	- [k]	PVd x3		17	16	32	35	23	22	NS
Roth[51]	60	85	0	CEP x6	CEP x3[e]	84	11	50	34	36	15	0.05
Rosell[52]	60	73	0	MIP x3	RT[f]	26	8	37	10	17	9	0.005
Wagner[53]	57	95	14	MVbP x2	-	12	12	-	-	27 [g]	27 [g]	NS
Elias[54, j]	57	100	0	EP x2/RT	EP; RT[f]	19	23	-	-	-	-	NS
Pass[55]	27	100	-	EP x2/RT	EP	29	16	-	-	(42) [h]	(12) [h]	NS
Average [i]								40	29	24	17	

Inclusion criteria: randomized controlled trials of primary surgical resection vs neoadjuvant therapy and resection in patients with stage III (N2) tumors from 1980-2011.
CEP = cyclophosphamide, etoposide, cisplatin; MVbP = mitomycin C, vinblastine, cisplatin; PVd = cisplatin, vindesine. See Figure 1 and 3 legends for expansion of other abbreviations.
[a]Only patients with stage IIIa disease are included here (trial included a majority of patients who had stage I and II disease).
[b]But about 75% of cases were clinically N2 positive.
[c]RT for patients with R1,2 resections, both arms.
[d]RT for patients with T4 and N3 disease in both arms.
[e]cN2 mostly by chest radiograph but also by CT scan.
[f]In both arms.
[d]P = .056 by log-rank, P = .048 by Breslow-Gehan-Wilcoxon test.
[g]Four-year survival.
[h]Reported as abstract.
[i]Three-year survival.
[j]Excluding values in parentheses.
[k]Only 49% of those randomized to surgery underwent thoracotomy (as well as 55% of patients in the induction arm).

prognosis, it is likely that they had a relatively small burden of disease (ie, probably cN0/N1 with single-station involvement).

A 2007 Cochrane meta-analysis (for stages I-III) revealed a benefit of platinum-based neoadjuvant chemotherapy over surgery alone (HR, 0.82; 95% CI, 0.69-0.97; $P = .022$), corresponding to an absolute benefit of 6% to 7% in stages IB to IIIA and 3% to 5% in IIIb.[56] When data from a European intergroup trial was added to this meta-analysis, the statistical significance was no longer present (HR, 0.88; 95% CI, 0.76-1.01; $P = .07$).[57] When this meta-analysis was restricted to only patients with stage III disease, an HR of 0.73 (95% CI, 0.51-1.07; $P = .1$) was found.[56] Taken together, these data demonstrate that surgery as the primary therapy for preoperatively identified (or suspected) N2 involvement is inferior to approaches involving neoadjuvant treatment.

3.2 Specific Subgroups

The interest in pursuing primary surgery for preoperatively identified N2 involvement has generally been low, as reflected in the lack of ongoing trials to address this issue further. However, the question remains whether specific subgroups of patients with N2 disease can be identified for whom primary resection is indicated. This strategy has been more widely accepted in Asia and Europe than in North America. No RCT has been done to address specific subgroups, and without data from well-characterized patients in such trials, favorable outcomes resulting from selection of the most favorable patients can easily be confused as demonstrating efficacy of the treatment. Nevertheless, it is reasonable to ask whether a subgroup of patients with N2 disease can be identified to have a good prognosis with primary surgery with or without other postoperative therapies.

Outcomes in patients with N2 disease identified preoperatively for whom primary surgery was performed are shown in Figure 5. For these data to be applicable to preoperative patients, one has to look at the results for all patients. For a significant proportion of patients (20%-40%), complete resection was not feasible. Assessment of outcomes with primary surgery requires consideration of all operated patients, without exclusion of those identified postoperatively as having undergone an incomplete resection. In general, the data show that the outcomes are poor even among highly selected patients in centers that believed they were able to select the patients with good prognosis (5-year survival of 10%-15%).

Because the practice of mediastinal staging has generally improved, it is necessary to ask whether the prognosis of a single micrometastasis (0.2-2 mm) identified through a video-assisted mediastinal lymphadenectomy is the same as what has been traditionally reported in the literature as N2. Furthermore, there is marked variation in the prognosis of patients with N2 disease by continent in the IASLC database (see Detterbeck et al,[132] "The Stage Classification of Lung Cancer" in the ACCP Lung Cancer Guidelines); thus, regional differences might affect a role for primary surgery. However, this explanation is speculative, and until data are available to the contrary, one must conclude that survival of patients with preoperatively identified N2 disease is poor with primary surgery and that RCTs suggest that if surgery is to play a role, it should be done after neoadjuvant therapy.

3.3 The Role of Surgery After Preoperative Therapy

Our systematic review identified several RCTs that evaluated the role of surgery after preoperative therapy compared with a nonsurgical curative-intent treatment strategy (Fig 6). The patients included in the RCTs were treated with varying combinations and doses of platinum-based chemotherapy regimens as well as varied doses and delivery methods of radiotherapy.

Patients were confirmed to have N2 disease in the majority of cases. Detailed information is not provided in these reports, but it appears that the patients in the RCTs had a substantial burden of mediastinal disease. It is likely that around one-half had what some would call bulky nodal disease (ie, primarily radiographic group B as outlined in stage evaluation article[7]), and probably a similar number had multistation involvement (Fig 2). The European Organisation for Research

FIGURE 5. [Section 3.2] Outcomes of preoperatively identified N2 involvement with primary surgery.

First Author	No.	cStage by CT	N2/N3 biopsy done?	Mediastinoscopy result	% R1/R2	% 5 y Survival		Adjuvant Therapy
						R0	All	
Pearson[58]	79	?	All	Positive	40	15	9	RT
Coughlin[59]	36	?	All	Positive	22	18	14	?
Vansteenkiste[60]	19	?	All	Positive	36	?	15	±RT
Average					**33**	**17**	**13**	

Inclusion criteria: studies reporting on ≥ 15 operated patients with pN2 and preoperatively identified N2 involvement from January 1980-December 2011.
See Figure 1 legend for expansion of abbreviation.

FIGURE 6. [Section 3.3] Randomized phase 3 trials of preoperative therapy followed by surgery vs chemoradiotherapy for stage III NSCLC.

First Author	Year	No.	% with N2 confirmed	Mediastinal tumor burden	Induction Chemotherapy	Control arm	Survival (%)				p
							2-year		5-year		
							Ind→S	ChRT	Ind→S	ChRT	
Albain[61]	2009	396	100	24% multistation[a]	EP	ChRT	49	45	27	20	NS
Van Meerbeck[62]	2007	342	100	All "unresectable"	P based	Ch→RT	35	41	16	14	NS
Stephens[63]	2005	48	?	All "unresectable"	MIC/MVP	RT	15	16	-	-	NS
Johnstone[64]	2002	45	100	54% bulky	MVP	Ch→RT	48	34	22[b]	22[b]	NS
Average							**37**	**34**	**22**	**19**	

Inclusion criteria: randomized controlled trials comparing neoadjuvant therapy and surgery to an alternative definitive treatment from January 1980-December 2011.
Ch→RT = sequential chemotherapy; Ind→S = induction therapy then surgery; MVbP = mitomycin, vinblastine, cisplatin. See Figure 1 and 3 legends for expansion of other abbreviations.
[a]Documentation of the status of a single node station was sufficient for enrollment; the true number with multistation involvement is likely higher.
[b]Four-year survival.

and Treatment of Cancer (EORTC) study[62] specifically targeted patients believed to be unresectable and randomized those patients in whom a response to induction therapy was achieved (including complete, partial, or minor responses). The presumably more advanced disease in this study compared with other studies is corroborated by the poor survival of patients in this study (in both arms). All patients in these RCTs were considered physically fit to undergo potential surgical resection, and the median age in these studies was about 60 years.

Overall, the results are fairly consistent that preoperative therapy, and surgical resection offers long-term outcomes that are similar to chemoradiotherapy alone. In most studies, the survival curves appear to be quite similar; however, the North American Intergroup 0139 study[65] suggested better progression-free survival and flatter survival curves in the induction therapy and surgery arm, which were offset by the operative mortality, thus resulting in equivalent overall survival (Fig 7). There was a statistically significant better rate of local control in the surgery arm in the Intergroup and EORTC studies but with little difference in the number of distant recurrences. Thus, benefits and harms are fairly closely matched; a treatment strategy with induction therapy and surgery is neither clearly better nor clearly worse than chemoradiotherapy alone.

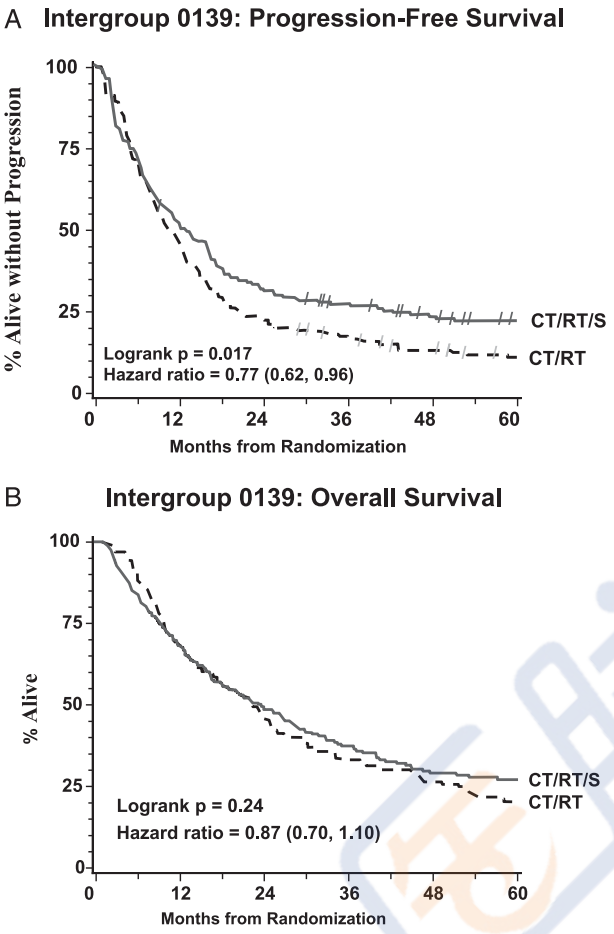
This apparent equivalence between neoadjuvant therapy followed by surgery, and definitive chemoradiation has several implications. First, patient preferences and characteristics should be considered. Second, the studies highlight the importance of minimizing harms. The data demonstrate that operative mortality can easily negate achieving any benefit. If surgery is to be undertaken, it should be done in a center with experience, that tracks its results, and that can demonstrate a low operative mortality rate for resection after neoadjuvant therapy. Third, if there are reasons to be concerned about the ability of radiotherapy to achieve local control (ie, large treatment field, reduced dose), surgery may have a benefit provided that a complete R0 resection is likely to be achieved.

Another issue to consider is that the studies of preoperative therapy and resection have had as a comparator arm fairly standard sequential or concurrent chemoradiotherapy. However, more-aggressive chemoradiotherapy approaches are also being explored. Whether these are better than standard chemoradiotherapy and how they compare with neoadjuvant therapy followed by surgery approach cannot be assessed. Both the survival outcomes and the toxicity must be carefully evaluated with these more-aggressive chemoradiation treatment strategies.

3.3.1 Specific Favorable Subgroups: Despite the results of RCTs, the question remains whether certain subgroups of patients exist for whom surgical resection after preoperative therapy is superior to definitive chemoradiotherapy. Many such subgroups have been suggested, including patients with nonenlarged N2 nodes, nonbulky nodes (How is this defined?), and single-node-station involvement; patients with nodal downstaging or other signs of good response to neoadjuvant therapy (eg, tumor shrinkage, decrease in intensity of uptake on fluorodeoxyglucose PET scan); and patients in whom a pneumonectomy is not necessary. Data from formal prospective studies are needed to answer the question of whether such subgroups benefit from the addition of surgery to a multimodality treatment approach. Because such data are not available, clinicians and investigators have looked to cohort and retrospective data. However, this approach is burdened with potential biases that must be understood and taken into account before drawing any conclusions.

The argument for surgery in particular subgroups is primarily based on prognosis. Major issues are the impact of patient selection and the attribution of cause

FIGURE 7. [Section 3.3] Survival of patients with stage IIIA (N2) lung cancer treated with CT/RT or CT/RT/S from the North American Intergroup Study 0139.[65] A, Progression-free survival. B, Overall survival. The initial steeper slope of the trimodality arm demonstrates the importance of the perioperative mortality rate on the overall results of trimodality therapy. CT/RT = chemotherapy and radiotherapy; CT/RT/S = chemotherapy and radiotherapy followed by surgery.



and effect. Typically, patients are selected for surgery because they have characteristics that predict a good prognosis, but this good prognosis often is incorrectly attributed to the fact that they underwent surgery. Another issue is out-of-context application of data. Often, retrospectively derived results from one subgroup are applied directly to a different group (eg, outcomes of incidentally discovered N2 involvement do not appear to apply to patients with preoperatively identified N2 disease) and involves landmark data (ie, analysis of only patients who have achieved a particular landmark); for example, treatment response or mediastinal downstaging of patients completing all steps of therapy are outcomes that cannot be used to predict results for all patients embarking on a multimodality treatment plan. Furthermore, to be a useful guide to treatment planning, potential factors to identify subgroups as candidates for surgery must be identifiable at the time the treatment decision is made (eg, postresection final pathology results are of no use to select patients for surgery).

Another source of confusion is that arguments for or against surgery are not always reciprocal. For example, high operative mortality may be a reasonable argument against surgery, but low operative mortality is not an argument that surgery is beneficial. It is merely the lack of a contraindication.

So what characteristics identify subgroups that may benefit from multimodality treatment that includes surgery? A qualitative summary is provided in Figure 8. Postresection data from patients who have undergone primary surgical resection show that a lower burden of mediastinal disease portends a better prognosis.[66] This lower burden has been defined as clinical cN0/N1, single-station N2 involvement or as intracapsular node involvement in older literature. Whether these data from primary surgical resection apply in the context of multimodality therapy and preoperative identification has not been studied. In the context of multimodality treatment, a low mediastinal burden often is referred to loosely as nonbulky or minimal N2 disease, but there is no consensus about how these concepts should be defined. No actual data show that these concepts have prognostic value, although it is logical that they probably do given the data on cN0-1 and single-station involvement. However, no data define whether the prognosis in these patients is further improved by the inclusion of surgery in the treatment strategy. Thus, the role of surgery as part of the treatment plan for these subgroups is unclear at best.

An indirect argument against selection of only patients with a minimal mediastinal burden of disease comes from multiple phase 2 studies of neoadjuvant therapy. Many of these studies have included patients with fairly extensive disease yet reported good survival. A recent review of studies that involved a majority of patients with T4, N3, or both T4 and N3 disease found a 5-year survival of 25% for all patients (although only about two-thirds underwent surgery and one-half received an R0 resection).[67] Further analysis of these 15 prospective studies did not suggest any difference in outcome relative to the proportion of T4 or N3 involvement (or other factors). Thus, many prospective neoadjuvant studies have included patients with a substantial mediastinal burden; comparison across studies does not suggest that outcomes in these patients are poor with induction therapy and surgery. In other words, a comparison across prospective studies does not support the concept that surgery for stage III NSCLC can only be justified in patients with a minimal burden of mediastinal disease.

Response to preoperative treatment is often cited as a potential criterion for the selection of patients for surgery. Ample consistent data from multiple tumor

FIGURE 8. [Section 3.3.1] Selection criteria for trimodality therapy with surgery in patients with stage III (N2) lung cancer.

Selection Criteria	Assessment of commonly cited arguments				**Summary: Justification for Surgery**
	Pre-operatively identifiable?	Prognostic value?	Potential Flaw	Defines treatment value?	
"Minimal" N2	Moderate	Probably	Out-of-context	Unclear	Unclear
Single station	Moderate	Yes	Out-of-context	Unclear	Unclear
cN0,1	Yes	Yes	Out-of-context	Unclear	Unclear
Non-bulky nodes	Yes	Probably	Out-of-context	Unclear	Unclear
Good surgical risk	Yes	-	-	No	Not applicable
Downstaged	Limited	Yes	Landmark	Unclear	Unclear
Shrinkage	Yes	Yes	Subjective	Unclear	Unclear
Lobectomy	Yes	Probably	-	Probably	Probably

A qualitative assessment of arguments commonly cited in support of various selection criteria for trimodality therapy, including surgery, in patients with stage III (N2) lung cancer. Landmark = data only applicable to patients achieving a particular landmark; out of context = data taken from one group of patients and applied to a different group; subjective = no definition available; assessment is personal, variable, and not objective.

types demonstrate that the prognosis of responders is better than that of nonresponders; therefore, this can be accepted as a clear general prognostic factor. Whether prognosis is further affected by the inclusion of surgery is unclear. A retrospective analysis has never been undertaken of patients whose tumors responded to a similar degree between those who underwent surgery and those who did not (eg, in the North American Intergroup 0139 study[65]). Furthermore, in the EORTC study,[62] only responding patients were randomized (mostly partial and some minor responses), but no benefit to surgical resection was demonstrated (no subgroup analysis according to the degree of response was performed).

Furthermore, defining response to neoadjuvant treatment is not straightforward. Mediastinal downstaging has been suggested as a marker of response. Data from patients who underwent resection clearly identify mediastinal downstaging as a prognostic factor, but this is not clinically useful unless it can be identified preoperatively. Noninvasive means of restaging (by PET or CT scan) have not been found to have sufficient negative predictive value after neoadjuvant therapy.[69] A review of the correlation between methods of mediastinal restaging and postoperative results revealed poor correlation of both noninvasive and invasive methods of restaging other than a thorough first-time mediastinoscopy done at the time of restaging.[68] (The argument for mediastinal downstaging as the key to patient selection for multimodality surgical treatment actually undermines the argument for selection of patients with less mediastinal tumor burden; if downstaging has been achieved, the amount of disease initially present in the mediastinum is irrelevant.)

Tumor shrinkage is also a commonly used criterion to select patients for surgery. Very few data correlate tumor shrinkage to outcomes other than as the measure of response to chemotherapy. No consensus definition has evolved with regard to how much shrinkage is an acceptable marker for selection, much less a correlation of degree of shrinkage with surgical outcomes. Thus, this criterion suffers from variability and is likely affected not only by features of the tumor that can be objectively defined but also by nonquantifiable factors, such as surgical ease of resection, willingness to be aggressive, and so forth. Furthermore, whether the tissues resected should be altered on the basis of shrinkage is unclear. How sure can we be that tissues that were previously believed to harbor cancer cells can now be left behind because the neoadjuvant therapy has eradicated all such cells? Does the tumor shrink like a balloon with chemotherapy, or do several orders of magnitude of malignant cells die throughout the area initially involved? Because there are no answers to these questions, no data defining the value of tumor shrinkage, and inherent variability of this criterion, it is probably not a good method for selection of patients for resection, at least at the present time. Therefore, it is better to make the decision about whether to include surgery in the treatment strategy at the initiation of treatment rather than later and to base it on an assessment of which tissues are believed to be involved rather than on an undefined degree of shrinkage.

Another proposed criterion to judge response to induction therapy is the degree of reduction of fludeoxyglucose uptake by PET imaging following neoadjuvant therapy. Mediastinal PET uptake correlates poorly with mediastinal downstaging, but the real outcome of interest is long-term survival. Although some studies suggest that a decrease in PET activity is prognostic, this requires further validation. Most studies suffer from first looking at the data to establish the

best point at which to dichotomize the data and then to assessing statistical significance. This approach (known as double dipping) has a high risk of identifying a false-positive prognostic factor unless it is validated in an independent data set. However, the major issue is still that although PET response is likely to have prognostic value, it is unclear whether this identifies a group of patients whose prognosis is further improved by surgical resection.

Some studies have suggested that patients with stage IIIA disease whose tumors would require a lobectomy (as opposed to pneumonectomy) might benefit from neoadjuvant therapy and surgery. In favor of this criterion is the fact that data from a large randomized study show both better overall and progression-free survival with the addition of surgery to a multimodality treatment strategy.[65] However, this is based on an unplanned subgroup analysis of retrospectively matched patients; therefore, these data cannot be viewed as conclusive.

3.3.2 Specific Unfavorable Subgroups: A relevant question is whether certain subgroups can be defined in which outcomes are so poor that carrying out a surgical resection is unjustified. Proposed subgroups include those who need a pneumonectomy, lack of mediastinal downstaging, lack of response on PET or CT imaging. If a patient experiences disease progression with distant metastases or an inability to achieve an R0 resection, surgery is unjustified, which is also true if comorbidities that significantly increase operative mortality develop in the patient. This proportion is substantial. In an analysis of prospectively collected data, Cerfolio et al[69] demonstrated that of patients with nonbulky N2 involvement planned for preoperative therapy and resection, only 37% eventually underwent thoracotomy, and 28% achieved complete resection (8% died, 10% did not complete neoadjuvant therapy, 24% progressed, 11% had insufficient response to be considered for surgery, and 10% were lost to follow-up). Similar results were reported in another prospective cohort with a somewhat greater mediastinal tumor burden.[62]

It is often stated that resection after neoadjuvant therapy is contraindicated if a pneumonectomy is required. This idea stems primarily from the results of the randomized North American Intergroup 0139 study.[65] However, several points should be highlighted. The lack of benefit for the neoadjuvant approach in the Intergroup 0139 study was the result of a high perioperative mortality in an unplanned subgroup analysis in patients undergoing pneumonectomy compared with those not undergoing surgery but matched by tumor extent. In fact, the slope of the survival curve after the first 90 days was more favorable (less steep) in the patients undergoing pneumonectomy than in the matched patients not undergoing surgery. A review of published data on pneumonectomy following neoadjuvant therapy shows that the Intergroup 0139 study had one of the highest perioperative mortality rates, and a meta-analysis identified this study as a statistical outlier.[70] Many single-institution reports from centers with substantial experience demonstrated lower perioperative mortality rates, especially for left-sided pneumonectomy, with an average perioperative mortality rate of about 8%. The question has been raised about whether the high mortality rate in the Intergroup 0139 study was the result of it being a multiinstitutional study in which the majority of centers only enrolled a small number of patients. Thus, although the perioperative mortality after pneumonectomy is a significant concern, this may be a less important issue in high-volume centers with documented low mortality rates. In summary, pneumonectomy after neoadjuvant therapy probably should not be performed unless it is done in a center that has a demonstrated low mortality rate for this procedure (and the same argument holds true for lobectomy).

Data regarding outcomes of patients in whom mediastinal downstaging was not achieved are shown in Figure 9. On average, the 5-year survival is about 15%. It is interesting that this number is similar to the results for primary surgery for preoperatively identified N2 disease. However, in the case of patients having persistent N2 disease after preoperative therapy, alternatives to surgery are of questionable value (but undefined). The data for patients with pyN2 disease also suffer from being defined after resection. In other studies that used repeat mediastinoscopy to define persistent N2 disease, practically none of the patients underwent resection, with survival of $< 5\%$. In summary, for patients with persistent N2 disease after neoadjuvant therapy, the available data do not clearly demonstrate that resection is futile, especially given that there is little alternative.

PET reimaging after neoadjuvant therapy has been proposed to define patients in whom surgery is futile. PET imaging can show progression of disease, although this should be proven by biopsy specimen given a high incidence of false-positive metastases.[75] Excluding progressive disease, those patients who show poor response nevertheless have reasonable 5-year survival after resection (average, 14%) (Fig 10). A comparison across studies suggests that the survival was better in those studies in which patients underwent resection despite the lack of PET response vs those studies in which the patients generally did not undergo resection. A lack of response by CT scan was less studied but seems to show little value as a criterion for avoiding resection. Thus, from the limited data available, it does not appear that a cohort has been defined in which the outcome is so poor that one can clearly recommend against resection.

FIGURE 9. [Section 3.3.2] Outcomes of patients with persistent N2 after induction therapy (ypN2) who underwent resection.

First Author	# patients having Surgery	Induction Treatment	5-year Survival (%)			
			All pts operated	All R0	R0 ypN2	No surgery
Cerfolio[106]	216	ChRT	34	42	9	-
Depierre[93]	167	Ch	44	50[a]	29	-
Albain [103]	164	ChRT	27	41	24	8
Thomas[107]	154	Ch	18	42	13	3
van Meerbeck [48]	154	Ch	17	23[b]	15	-
Thomas[107]	142	ChRT	21	45	13	3
Martini [108]	136	Ch	17	28	-	5
Lorent [109]	75	Ch	24	37	16	-
Average			**29**	**37**	**16**	**5**

Inclusion criteria: Studies reporting outcomes of patients with persistent pN2 disease after induction therapy. See Figure 1 for expansion of other abbreviations.
[a]Approximated from survival graph.[93]
[b]Includes pathologic N0 and N1.

3.4 Summary

Data from RCTs demonstrate that surgery as the primary therapy for preoperatively identified (or suspected) N2 involvement is inferior to approaches involving neoadjuvant treatment. Subgroups of patients with preoperatively identified N2 disease who might have good survival with primary surgery have been proposed, but the data from retrospective studies do not support this. RCTs comparing multimodality treatment with or without surgery have shown equivalent results. Considerations that influence the choice of therapeutic approach are patient preferences and values, a demonstrated ability to accomplish surgery with low operative mortality, and factors influencing the ability to achieve local control (ie, radiotherapy dose and volume vs R0 resection). These studies involved primarily patients with histologically confirmed discrete nodal enlargement.

Many subgroups of patients have been proposed as potentially benefiting from an approach that includes surgery, but these arguments generally are either weak, potentially flawed, or based on characteristics that cannot be identified prior to making a treatment decision. The ability to achieve a complete resection through lobectomy is the only area for which there is any evidence suggesting a possible benefit to multimodality treatment that includes surgery, but this is based on an unplanned subgroup analysis. Subgroups have also been proposed for which survival is so poor that surgery might be unjustified. However, the available data do not support that this is the case (except for patients with disease progression or significant treatment-related toxicity).

The decision regarding treatment of patients with discrete nodal enlargement should be made collectively by members of a multidisciplinary team, including specialists from thoracic surgery, medical oncology, and radiation therapy with a focus on thoracic oncology. The entire plan should be made at the outset, including contingent strategies that are based on defined landmarks if necessary, to ensure an efficient and coordinated process. If surgery is to be included, it should be carried out at a center with experience and demonstrated low rates of treatment-related mortality and morbidity.

3.5 Recommendations

3.5.1. In patients with discrete N2 involvement by NSCLC identified preoperatively (IIIA), it is recommended that the treatment plan should be made with the input from a multidisciplinary team (Grade 1C)**.**

Remark: The multidisciplinary team should include at a minimum a thoracic surgeon, medical oncologist, and radiation oncologist.

Remark: The decision should be made collaboratively by the entire team so as to reflect collective judgment.

Remark: The plan should include the entire proposed treatment, including plans contingent on the results of reevaluations (ie, initial treatment response or nonresponse), not simply a first step.

3.5.2. In patients with discrete N2 involvement by NSCLC identified preoperatively (IIIA), either definitive chemoradiation therapy or induction therapy followed by surgery is recommended over either surgery or radiation alone (Grade 1A)**.**

FIGURE 10. [Section 3.3.2] Survival of patients having surgery after poor response to induction therapy.

Study	No.	ChRT	Ch	Technique	Measure	Details	Interval (weeks)	Threshhold	Surgery	Survival		
										MST	2-y	5-y
Taylor[76]	15	0	100	CT			3-4	SD/PD	**100**	18	37	**16**
Hoeckstra[77]	26	0	100	CT		N2,3	3-4	cN2,3	**few** [a]	(18)[b]	(34)[b]	(28)[b, c]
Eschman[78]	26	100	0	PET	Visual	T+N	2	SD	**few**	(26)[b]	(50)[b]	(13)[b]
Hoeckstra[77]	22	0	100	PET	Visual	N2,3	3-4	cN2,3	**few**[a]	(15)[b]	(25)[b]	(26)[b, c]
Hellwig[79]	(37)[d]	70[d]	28[d]	PET	SUV		4	≥4	**100**	19	34	**23**
Dooms[80]	(30)[d]	0	100	PET	SUV_{max}		3-4	>median	**100**	16	-	**7**
Eschman[78]	18	100	0	PET	ΔSUV_{mean}		2	0%↓	**few**	(13)[b]	(18)[b]	(<4)[b]
Hoeckstra[77]	17	0	100	PET	MR_{Gluc}	cycle 3	3-4	>.13	**few**[a]	(14)[b]	(0)[b]	(0)[b]
Dooms[80]	15	0	100	PET	ΔSUV		3-4	<60%↓	**100**	18	33	**13**
Hoeckstra[77]	21	0	100	PET	MR_{Gluc}	cycle 1	3-4	>.13	**few**[a]	(16)[b]	(25)[b]	-
Escheman[81]	45	0	100	PET	ΔSUV_{mean}	cycle 1	2	<60%↓	**51**	16[e]	38[e]	**17**[e]
Escheman[81]	16	0	100	PET	ΔSUV_{mean}	cycle 1	2	<25%↓	**50**	13[e]	31[e]	**7**[e]
DeWaele[82]	40	24[d]	76[d]	ReMed			~4-6	positive	**0**	(14)[b]	(7)[b]	(7)[b]
DeWaele[83]	12	19[d]	81[d]	ReMed			-	positive	**0**	(7)[b]	(8)[b]	(8)[b]
Stamatis[84]	19	100	0	ReMed			~4	positive	**0**	(18)[b]	-	(5)[b]
Cerfolio[85]	45	100	0	EUS+			~4-6[a]	positive	**0**	-	-	(17)[b]
Stigt[86]	12	79[d]	21[d]	EUS			2	positive	**0**	(9)[b]	(13)[b]	-
Average[f]									**100**	18	35	**15**
Average[f]									**50**	15	35	**12**
Average									**few**			**12**
Average									**0**	12	9	**9**
Average all[f]									**all**	**17**	**35**	**14**

Inclusion criteria: studies of > 20 patients (total) that reported survival results relative to restaging assessment after neoadjuvant therapy. Patients were proven to have N2,3 disease prior to neoadjuvant therapy, unless otherwise noted.

EUS = esophageal ultrasound; interval = interval between last dose of chemotherapy (or RT) and restaging; MR = metabolic rate of glucose consumption; PD = progressive disease; ReMed = remediastinoscopy; SD = stable disease; SUV = standardized uptake value; T + N = both at the primary tumor and nodal sites. See Figure 1 legend for expansion of other abbreviations.

[a]Estimated from description; explicit data not provided.

[b]Most patients did not undergo surgery.

[c]Four-year survival.

[d]For all patients in study.

[e]Approximately 50% of patients underwent surgery.

[f]Excluding values in parentheses.

Remark: As the data do not permit the selection of one option or the other as superior, patient values and preferences should factor significantly in the decision.

Remark: All multimodality therapy should be performed in centers with experienced multidisciplinary teams that track their relevant clinical outcomes and are capable of minimizing and managing the toxicity and complications involved.

Remark: Further identification of patients more likely to benefit from surgical resection after induction therapy is not possible based upon pretreatment characteristics. Decisions to pursue surgical resection after induction therapy should be made prior to initiation of any therapy.

3.5.3. In patients with discrete N2 involvement by NSCLC identified preoperatively (IIIA), primary surgical resection followed by adjuvant therapy is not recommended (except as part of a clinical trial) (Grade 1C)**.**

4.0 Occult N2 Involvement Despite Thorough Preoperative Staging (Stage IIIA)

4.1 Surgery

Use of the term "unexpected" or "incidental" implies mediastinal nodal involvement discovered intraoperatively in the course of lung resection surgery and specifically excludes patients whose nodal disease was clinically evident by CT or CT-PET scan prior to surgery. Furthermore, about 25% of patients with negative involvement of the mediastinum by CT or PET scan but with a central tumor or with N1 disease are found to have N2 involvement.[87,88] Therefore, thorough invasive staging is necessary as outlined in the stage evaluation article.[7] One must differentiate between ignored N2 (enlarged or PET scan positive but no biopsy specimen), underappreciated N2 (known high risk of false-negative CT or PET findings but no biopsy specimen), and true unsuspected N2 (discovered at surgery despite thorough preoperative invasive staging).[8] The positive N2 nodes may be identified intraoperatively on frozen section or postoperatively by the final pathologic assessment. This section primarily addresses

patients with true unsuspected N2 disease who have undergone invasive staging. Modern reports of patients with thorough staging indicate that true unsuspected N2 disease occurs in about 10% of surgical patients (5%-16%).[89-91]

Multiple studies suggested prognostic factors that can differentiate patients who have a better or worse outcome. A review of published data suggests that cN0/N1, single-station involvement, and T1/T2 are markers of a better prognosis (average 5-year survival, 25%-30%).[8] Conversely, multistation involvement, cN2 by CT scan, multilevel N2, T3 tumors, or subcarinal node involvement all predict worse survival (5-year survival, about 15%). Factors that appear to have little prognostic value are histology, extent of resection (lobectomy vs pneumonectomy), tumor location (upper vs lower lobe), and the presence of involved N1 nodes (ie, skip metastases). However, although these findings have prognostic value, they are of limited use in the selection of patients for surgery unless factors can be identified that predict the futility of surgical treatment. From the data, this does not seem to be the case except for incomplete resection. Therefore, if N2 nodal involvement is found at the time of surgical resection and all the involved lymph nodes and the primary tumor are technically resectable, then the surgeon should proceed with the planned lung resection along with a mediastinal lymphadenectomy. If a complete resection is not possible, the planned lung resection should be aborted because the average 5-year survival is $< 5\%$.[8] In all other situations, it is probably better to proceed with the planned resection. Data comparing exploratory thoracotomy and resection suggest that the morbidity, mortality, and quality-of-life impact of surgery has largely already been incurred, and survival is reasonable enough to justify resection in all subgroups (except R1-2 resection).[8]

Intraoperative handling of the mediastinum can involve a complete mediastinal lymph node dissection (MLND), systematic node sampling, or selective sampling. A formal MLND involves removal of all the node-bearing tissues, leaving only the skeletonized trachea, phrenic nerves, aorta, and superior vena cava. A systematic mediastinal node sampling means that the pleura overlying each ipsilateral node station is opened and explored and representative biopsy specimens of nodes obtained. A selective sampling, on the other hand, involves biopsy of only selected mediastinal nodes that are believed to be abnormal. Some authors advocate a lobe-specific systematic node dissection, which consists of a complete dissection of those nodal regions most commonly involved by tumors in a particular lobe.[92]

Existing guidelines consistently recommend either systematic lymph node sampling, complete MLND, or lobe-specific MLND at the time of resection[92-94] because data show that the accuracy of staging is better with either MLND or systematic sampling vs only selective sampling[90,95,96] but with little difference between MLND and systematic sampling.[97-100] RCTs assessing a therapeutic role for MLND have not demonstrated a survival benefit (Fig 11).[96,99,100] Most of these studies involved patients with clinical stage I disease and do not provide relevant guidance on what is best for patients with stage cIII disease. In the case of intraoperatively identified N2 involvement, it seems reasonable to suggest that a complete MLND be performed, even though survival data are not available (given that the morbidity of MLND has been consistently found to be minimal).[90,95-97,99,100]

It is important to emphasize that outcomes data for occult N2 involvement (including that of subgroups) are primarily in patients who were thoroughly staged preoperatively. The overall outcome of patients is significantly affected if this is not the case. For well-staged patients, the 5-year survival is 20% to 40%, whereas it is only 15% for cN2 or preoperatively identified (by biopsy specimen) N2 involvement.[8] It is also important to note that the data reported in this section are for all patients. Many studies also reported data for only the subset of patients whose tumors had been

FIGURE 11. [Section 4.1] MLND: survival and recurrence data.

First Author	N	Eligibility	Sampling method	% 5-year Survival			% local recurrence		
				LND	Sampling	p	LND	Sampling	p
Allen[90]	1023	cN0,1	Selective	65	63	NS	6	5	NS
Wu[96]	471	cI-IIIa	Selective	48	37	<0.0001	3	5	
Izbicki[101]	182	cI-IIIa	Systematic	(71)[a]	(60)[a]	NS	41	79	<0.04
Sugi[100]	115	cT1N0	Systematic	81	84	NS	-	-	-

Inclusion Criteria: Randomized studies of mediastinal lymph node dissection vs sampling in patients with NSCLC undergoing surgical resection.

Selective sampling (only abnormal appearing nodes); Systematic sampling (exploration of each ipsilateral node station with representative biopsy)

See Figure 1 for expansion of other abbreviations.

[a]Three-year survival.

completely resected. Overall 5-year survival of patients with R0 resection has been about 10% higher for those with cN0/N1 disease and 5% higher for those with cN2 disease and surgically discovered N2 involvement than for all patients. However, although this may have prognostic value, definition of the therapeutic approach cannot be based on a subset that can only be identified after the therapy has been carried out. It is important to note that the proportion of patients in whom an R0 resection is not achieved is substantial (about 20%-25% for cN0/N1 and 35% for cN2).[8]

4.2 Adjuvant Chemotherapy

Many RCTs of adjuvant chemotherapy have been conducted. We do not discuss trials involving first-generation (noncisplatin) regimens because these are only of historical interest and were generally shown to be harmful. Furthermore, these studies often did not focus purely on patients with stage III disease or reported results in a stage-specific way. We limited our data analysis to studies in patients with stage III lung cancer treated with second- or third-generation chemotherapy (platinum-based) regimens.

Figure 12 shows the results of studies evaluating the efficacy of postoperative cisplatin-based chemotherapy that included patients with stage III disease. In general, a trend to better survival with adjuvant chemotherapy has been seen, but this often was not statistically significant, particularly in earlier, smaller studies. Another issue has been that compliance with adjuvant chemotherapy has been poor; only about 60% received the planned number of cycles of chemotherapy.

Several meta-analyses of adjuvant chemotherapy have been conducted. Figure 12 also shows the results of two meta-analyses selected on the basis of the inclusiveness[113] and the criterion that it included only large, cisplatin-based clinical trials.[114] These meta-analyses showed a benefit to adjuvant chemotherapy. A stage-specific subgroup analysis in the LACE (Lung Adjuvant Cisplatinum Evaluation) meta-analysis found a survival benefit for patients with completely resected stage III NSCLC receiving adjuvant cisplatin-based chemotherapy (HR for stage III, 0.83; 95% CI, 0.72-0.94). It is not surprising that adjuvant therapy, which is designed to prevent the occurrence of distant metastases, appears to have the greatest effect in stage III compared with stage II and stage I NSCLC. Taken

FIGURE 12. [Section 4.2] NSCLC adjuvant studies that included patients with stage III disease: survival with adjuvant chemotherapy.

Author	Year	N	% stage III	Chemo-therapy	RT (both arms)	Survival						p
						MST (mo)		2 yr (%)		5 yr (%)		
						Adj	Cintrol	Adj	Control	Adj	Control	
Randomized trials												
IALT[102]	2004	1,867	39	PE or PV		54	45	70	67	45	40	0.03
ALPI[103]	2003	1,209	29	MVP		55	48	-	-	-	-	NS
ANITA[104]	2006	840	39	PN	+/- [x]	42*	26*	-	-	40*	19*	0.01
BLT[105]	2004	381	34	P-based		34	33	58	60	-	-	NS
Keller[106]	2000	358	59	EP	RT	38	39	60	60	39	41	NS
Dautzenberg[107]	1995	267	71	COPAC	RT	15	15	41	33	18	19	NS
Ohta[108]	1993	181	100	PVd	-	31	37	63	59	35	42	NS
Lad[109]	1988	164	92	CAP	RT	20	13	40	32	(26)	(13)	0.002
Holmes[110]	1993	130	-	CAP	-	-	-	41	30	(29)	(18)	0.03
Pisters[111]	1994	72	-	PVd	RT	16	19	31	44	17	30	NS
Kimura [132]	1996	69	78	MVdP/LAK	-	25	26	82	51	58	32	0.01
Average[y]						**33**	**30**	**54**	**48**	**36**	**32**	
Meta-analyses												
NSCLCG[113]	1995	1,394	I-III	P-based		Overall 5 year survival benefit of 5.0%						0.08
LACE[114]	2008	4,584	27	P-based	RT [z]	Overall 5 year survival benefit of 5.4%						0.005

Inclusion criteria: randomized controlled trials involving >50 patients with stage III disease comparing surgery alone to surgery and adjuvant P-based chemotherapy from 1980-December 2011.

COPAC = doxorubicin, vincristine, cisplatin, lomustine; LAK = lymphokine-activated killer; PV = vinca alkaloids. See Figure 1, 3, 4 legends for expansion of other abbreviations.

[a]RT could be given or not to patients in both arms, depending on each center's policy. Approximately one-third received RT. Multivariate subgroup analysis indicated that this had no effect on survival.

[b]Survival for stage IIIa group only.

[c]Disease-free survival.

[d]Excluding values in parentheses.

[e]RT given according to individual trials; ~75% of patients with pN2 disease received RT.

together, the studies and meta-analyses showed an about 5% absolute 5-year survival benefit.

In these studies, the risk of a chemotherapy-related death has been < 1%. These patients generally have been relatively fit, with an average age of about 60 years, and the majority had a performance status of 0 or 1.[114] In a meta-analysis of the larger trials, the amount of benefit appears to be similar regardless of decades of age (from < 50 to > 70 years). However, although there was a similar benefit for performance status 0 and 1, there appears to be a survival detriment with adjuvant chemotherapy for patients with performance status 2 in this meta-analysis.[114]

No RCTs have addressed which chemotherapy regimen is optimal, how many cycles should be given, or when this should start. Modern studies used cisplatin-based chemotherapy, generally with two agents delivered in three to four cycles. Typically, the RCTs have required that chemotherapy be started within 8 to 12 weeks of surgery. Taking into consideration the activity and the number of recommended cycles of chemotherapy for stage IV NSCLC, it appears reasonable to suggest that adjuvant chemotherapy involve cisplatin-based doublets for three to four cycles started within 12 weeks of surgery.

Some of the trials have involved adjuvant chemotherapy alone, whereas others have included adjuvant radiotherapy in both arms (usually sequentially with chemotherapy). A review of Figure 12 does not suggest a clear difference in results whether radiotherapy was given. A meta-analysis of the larger trials suggested that the benefit of chemotherapy is similar whether it is given with or without adjuvant radiotherapy.[114]

Therefore, taken together, the results of the RCTs indicate a survival benefit to the addition of chemotherapy in fit patients with stage III disease after surgical resection. Thus, we recommend adjuvant chemotherapy for patients with completely resected NSCLC with incidentally detected stage III disease unless there is reason to believe the risk of chemotherapy-related complications is unusually high on the basis of performance status or comorbidities. Age by itself probably should not factor heavily into the decision.

4.3 Adjuvant Radiotherapy

Meta-analyses of postoperative radiotherapy (PORT) in resected NSCLC indicated a survival detriment[115]; however, many of the patients treated had stage I disease. One meta-analysis suggested neither benefit nor harm for patients with N2 involvement.[116] Subsequent studies using meta-analyses or population-based databases showed varied results in patients found postoperatively to have N2 involvement.[117-119] A single study from a review of the Surveillance, Epidemiology, and End Results database in 7,465 subjects suggested a survival benefit for PORT given to patients with N2 disease.[118]

Few data have addressed whether adding adjuvant radiotherapy to adjuvant chemotherapy improves survival in patients with fully resected stage IIIA lung cancer. A small RCT that addressed this question was closed prematurely after enrolling only 40 patients.[120] No trend toward a survival difference was seen in this study. There are limited, but conflicting data about the role of adjuvant radiotherapy in resected stage III (N2) NSCLC. Although it appears that PORT might benefit some patients with N2 disease, presently, it cannot be recommended for unselected patients. It should be considered in selected patients at risk for local recurrence, especially as assessed by the surgeon performing the resection. Therefore, the emphasis should be placed on administering adjuvant chemotherapy, which does have a proven survival benefit. Given the relatively poor compliance with adjuvant chemotherapy and toxicity of concurrent chemoradiotherapy, if radiotherapy is to be used, it should be given sequentially. The addition of radiotherapy should perhaps be reserved for patients in whom there is a particular concern about local recurrence.

4.4 Incomplete Resection

The frequency of R1 and R2 resection in patients with pN2 stage III NSCLC is, unfortunately, substantial (ranging from about 25% with thorough preoperative staging to 35% with poor preoperative staging). The amount of data to guide the definition of optimal treatment for such patients are limited. One RCT conducted from 1979 to 1985 involved 164 patients with NSCLC (92% stage III) who underwent an R1 (84%) or R2 (16%) resection.[109,121] All patients received adjuvant radiotherapy (40-Gy split course) and were randomized to nothing else vs chemotherapy (cisplatin, doxorubicin, and cyclophosphamide started concurrently for six monthly cycles). There was an increase in the recurrence-free survival favoring the chemotherapy arm ($P = .004$), but overall survival was not improved. The findings of this study provide a weak argument for adjuvant chemotherapy for R1 and R2 resection, but taken together with the data for adjuvant chemotherapy in general, such treatment appears beneficial in patients in whom toxicity can be expected to be low.

There is no benefit to a debulking procedure for locally advanced lung cancer.[122] Older studies suggested that an R2 resection be viewed simply as a large biopsy rather than as a resection with therapeutic benefit.[123-125] Therefore, we suggest that patients with stage III lung disease who have undergone an R2 resection be treated with concurrent chemoradiotherapy, as outlined in section 2.0 of this article.

No studies directly examined whether adjuvant radiotherapy is beneficial. Indirect data show that after an R1 resection (mostly of the bronchial margin), about 75% of patients are reported to experience a recurrence, but of these, only about one-third are local (intrathoracic) recurrences.[121,126-128] The proportion of recurrences that are distant is higher in patients with N1 or, especially, N2 involvement.[126]

A multivariate analysis found no correlation of recurrence to the presence of a positive microscopic margin.[128] Others also suggested that it is lymphatic involvement that is associated with recurrence.[129]

A systematic review of R1 resection in 2005 found 13 retrospective cohort studies of which four recommended re-resection.[130] The authors concluded that re-resection is a reasonable option, but there was no clear evidence that this resulted in improved survival. The authors also concluded that there was no clear evidence that adjuvant radiotherapy resulted in a survival benefit.[130]

Taken together, these data weakly suggest that emphasis should be placed on giving adjuvant chemotherapy on the basis of randomized data and the pattern of recurrence. In individual cases, if reoperation is likely to lead to an R0 resection, this may be reasonable. If the risk of local recurrence is believed to be particularly high given the evidence that radiotherapy may reduce local recurrence, the use of adjuvant radiotherapy is reasonable. It may also be reasonable to consider concurrent chemoradiotherapy, although increased toxicity in a postoperative setting and a resulting need for dose reductions are a concern.

4.5 Recommendations

4.5.1. In patients with NSCLC undergoing surgical resection, systematic mediastinal lymph node sampling or complete MLND is recommended (Grade 1B)**.**

Remark: At least a systematic sampling is needed to accurately assess the pathologic stage; this is critical to direct adjuvant therapy.

Remark: It is unclear whether lymphadenectomy offers a survival benefit over systematic sampling, but in general, lymphadenectomy is suggested if there is evidence of N2 node involvement.

4.5.2. In patients with NSCLC who have incidental (occult) N2 disease (IIIA) found at surgical resection despite thorough preoperative staging and in whom complete resection of the lymph nodes and primary tumor is technically possible, completion of the planned lung resection and mediastinal lymphadenectomy is suggested (Grade 2C)**.**

Remark: This recommendation assumes that staging for distant disease and invasive preoperative mediastinal staging according to guidelines have been carried out.

Remark: In a patient who has not received preoperative staging despite clinical suspicion of N2 node involvement (ie, enlarged on CT, uptake on PET, or negative CT and PET but with a central tumor or N1 involvement), the operation should be aborted and staging completed if N2 disease is identified intraoperatively.

4.5.3. In patients with resected NSCLC (R0) who were found to have incidental (occult) N2 disease (IIIA) despite thorough preoperative staging and who have good performance status, adjuvant platinum-based chemotherapy is recommended (Grade 1A)**.**

Remark: We suggest this should typically involve a doublet regimen for 3 to 4 cycles initiated within 12 weeks.

4.5.4. In patients with R0 resected NSCLC who were found to have incidental (occult) N2 disease (IIIA) despite thorough preoperative staging, sequential adjuvant radiotherapy is suggested when concern for a local recurrence is high (Grade 2C)**.**

Remark: Adjuvant PORT reduces the incidence of local recurrence, but it is unclear whether it improves survival.

Remark: Adjuvant chemotherapy should be used initially followed by radiotherapy; concurrent chemoradiotherapy is not recommended (except in a clinical trial).

4.5.5. In patients with NSCLC who were found to have incidental (occult) N2 disease (IIIA) despite thorough preoperative staging and were incompletely resected (R1,2), combined postoperative concurrent chemotherapy and radiotherapy is suggested (Grade 2C)**.**

Remark: Incomplete resection (R1,2) does not appear to confer a survival benefit over no resection.

5.0 Summary

In patients with infiltrative mediastinal involvement and performance status 0 to 1, a curative-intent strategy should involve concurrent chemotherapy and radiation, with a cisplatin-based doublet therapy and once-daily radiotherapy at a dose of 60 to 66 Gy. Other radiotherapy doses, non-cisplatin chemotherapy regimens, the addition of induction (before) or consolidation

(after) chemotherapy, administration of PCI, or more-aggressive chemoradiotherapy approaches should be done in the context of clinical trials. Sequential chemoradiotherapy can also be considered in patients with comorbid conditions or a poor performance status (2), but the chance of toxicity must be considered carefully. Palliative therapy (including thoracic radiotherapy) is appropriate for patients with an ECOG performance status of ≥2 in whom combination therapy would be prohibitively toxic.

In patients with discrete nodal enlargement, the same approach of concurrent chemoradiotherapy is applicable. Similar results can be obtained with multimodality treatment that includes surgery. Although many specific groups of patients have been suggested for an approach that includes surgery (eg, minimal N2 burden, radiographic response) or in whom this should be avoided (eg, pneumonectomy, lack of downstaging), the arguments are based on flawed or out-of-context data. The only subgroup for which there are suggestive data comprises patients in whom complete resection can be achieved with a lobectomy. The choice of a multimodality treatment approach with or without surgery should be made according to patient preferences, a demonstrated institutional low perioperative mortality rate, and factors influencing the ability to achieve local control. Surgery as the primary or only treatment should not be undertaken.

In patients who are thoroughly staged preoperatively but in whom N2 involvement is discovered intraoperatively or postoperatively, resection should be carried out unless an R0 resection is not possible. Adjuvant chemotherapy should be given, but the role of adjuvant radiotherapy is unclear.

6.0 Future Research

In our systematic review of the evidence, we formulated several questions that either had too little evidence upon which to formulate recommendations or evidence that was burdened by limitations in one or more areas (eg, generalizablity, conclusions drawn from post hoc analyses). These can be separated into studies or interventions that can:

1. Improve on the efficacy of chemotherapy at preventing systemic metastasis. These would include interventions to reduce toxicity and improve the efficacy of systemic chemotherapy. Studies that led to biomarker-based selection of optimum chemotherapeutic agents would also fall under this category.
2. Define the role, if any, of consolidation therapy after combined chemoradiation, including a role for so-called targeted agents, with or without biomarker-based selection, in reducing the incidence of metastasis and prolonging overall survival.
3. Define the role, if any, of induction therapy prior to chemoradiation, including a role for so-called targeted agents, with or without biomarker-based selection, in reducing the incidence of metastasis and prolonging overall survival.
4. Define patient and tumor-specific characteristics that support the use of surgery for local control and that lead to improved outcomes compared with regimens that use radiotherapy as the means of local control.
5. Define the role of IMRT or alternative fractionation schedules in improving the therapeutic index of thoracic radiotherapy in combination with chemotherapy.

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Ms Diekemper: contributed to the literature search, evidence table, and methodology expertise.
Dr Detterbeck: contributed to the literature search, evidence table, writing, guideline formulation and revision, guideline expertise, methodology expertise, and editing and synthesis of separately authored sections.
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Additional information: The supplement table can be found in the "Supplemental Materials" area of the online article.

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