BRIEF REPORT

Resectable Clinical N2 Non–Small Cell Lung Cancer; What Is the Optimal Treatment Strategy? An Update by the British Thoracic Society Lung Cancer Specialist Advisory Group

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ABSTRACT

Patients and clinicians are faced with uncertainty as to the optimal treatment strategy for potentially resectable NSCLC in which there is clinical evidence of involvement of the ipsilateral mediastinum. Randomized controlled trials and meta-analyses have failed to demonstrate superiority of one bimodality strategy over another (chemotherapy plus surgery versus chemotherapy plus radiotherapy). One trial of trimodality treatment with chemotherapy, radiotherapy, and surgery demonstrated an improvement in progression-free, but not overall, survival versus chemotherapy and radiotherapy. There are a number of limitations to the data in this complex and heterogenous patient group. No randomized controlled trial has specifically studied patients with single-station N2 disease versus multistation N2 disease. When discussing treatment for fit patients with potentially resectable cN2 NSCLC, lung cancer teams should consider trimodality treatment with chemotherapy, radiotherapy, and surgery or bimodality treatment with chemotherapy and either surgery or radiotherapy. We advocate that all patients see both a thoracic surgeon and the oncology team to discuss these different approaches.

Keywords: Non–small cell lung cancer; Thoracic surgery; Radiotherapy; N2 NSCLC

Introduction

NSCLC with metastases to the ipsilateral mediastinum (N2) is a heterogeneous disease group.[1] At one end of the spectrum lies occult N2 disease, which is detected only after pathological examination of lymph nodes sampled during surgical resection. At the opposite is conglomerate and bulky N2 disease, which is easily identified on index computed tomography (CT) imaging. In this scenario the disease is considered unresectable and concurrent chemoradiotherapy is recommended in the international guidelines.[2–4] Between these two ends

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of the spectrum sit those patients with discrete and potentially resectable N2 disease identified during preoperative investigations (Fig. 1). This subgroup of clinical N2 (cN2) patients are those with enlarged and/or metabolically active lymph nodes on CT and positron emission tomography imaging that has been pathologically confirmed to be nodal metastases but deemed potentially resectable at the point of treatment decision (referred to as *resectable cN2* within this update). It is widely accepted that in the presence of appropriate physiological reserve, a bimodality approach of systemic treatment for distant control (chemotherapy) and a local therapy for local control (either surgery or radiotherapy) is appropriate for resectable cN2. However, there remain unanswered questions about the optimal treatment strategy. This brief report provides clinicians with a concise summary based on the highest-quality evidence on resectable cN2 to facilitate discussions with patients and with colleagues within multidisciplinary teams and tumor boards.

What Bimodality Treatment Is Superior in Resectable cN2: Chemotherapy plus Surgery or Chemotherapy plus Radiotherapy?

The key trial that has addressed this question is the European Organisation for Research and Treatment of Cancer (EORTC) 08941 trial (Table 1).[5] It compared surgical resection with radiotherapy after induction chemotherapy in patients with cN2 NSCLC. Inclusion criteria were any N2 disease for the nonsquamous

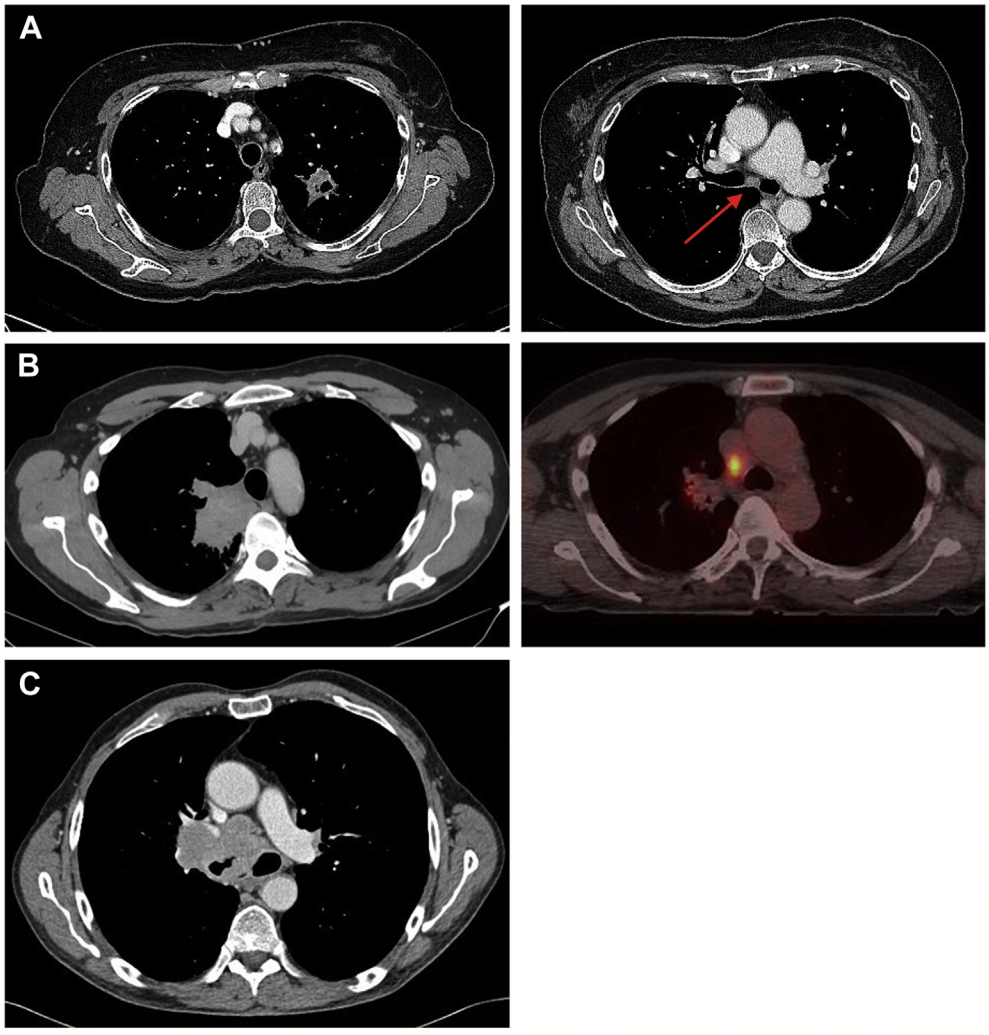

Figure 1. The spectrum of N2 disease. (*A*) Left upper lobe tumor with normal mediastinum on computed tomography and positron emission tomography. Subcarinal station 7 lymph node (*red arrow*) positive for squamous cell carcinoma from intraoperative lymph node sampling: occult N2. (*B*) Right upper lobe tumor with a 14-mm and positron emission tomography–positive right paratracheal lymph node confirmed as adenocarcinoma by endobronchial ultrasound: clinical N2. It is this group of patients that is the focus of this review. (*C*) Right lower lobe tumor and bulky, unresectable N2 disease invading central airways.

histological subtype and N2 disease exceeding the right paratracheal station for right-sided tumors and exceeding the prevascular stations for left-sided tumors of the squamous histological subtype. A total of 582 patients with IIIA-N2 NSCLC were enrolled (target of 640). This was before the era of positron emission tomography scanning, when staging was performed with CT of the thorax and ultrasound of the abdomen. All patients received three cycles of platinum-based induction chemotherapy, and those with radiological response were randomized to either a surgical procedure (167 patients) or radiotherapy (165 patients). Surgical mortality was 4% within 30 days for all resections and 7% for patients undergoing pneumonectomy (47% of patients required pneumonectomy). The respective median and 5-year survival rates for the surgical group were 16.4 months and 15.7% versus 17.5 months and 14% after chemoradiation treatment (hazard ratio [HR] =1.06, 95% confidence interval [CI]: 0.84–1.35, $p = 0.596$).

Johnstone et al.[6] conducted a randomized phase III trial (RTOG 89-01) in patients with histologically proven cN2 disease that compared the same two bimodality strategies. There was no significant difference in survival; however, the study was significantly underpowered, with only 73 patients recruited against a target of 224 to detect a 40% difference in median survival.

One meta-analysis has been undertaken to compare survival after chemotherapy plus surgery with that after chemotherapy plus radiotherapy.[7] Data were combined from the EORTC 08943 trial, the RTOG 89-01 trial, and two trials comparing bimodality treatment with induction chemotherapy followed by surgery versus unimodality treatment with radical radiotherapy.[8,9] There was no difference in overall survival between patients treated with chemotherapy plus surgery and those treated with chemotherapy plus radiotherapy (HR = 1.01, 95% CI: 0.82–1.23, $p = 0.954$, [Table 1]).[5,6,8-15]

Is Trimodality Therapy Superior to Bimodality Treatment in Resectable cN2 NSCLC? Chemotherapy, Radiotherapy, and Surgery versus Chemotherapy and Radiotherapy (with or without Surgery)

Trimodality therapy with induction chemoradiotherapy followed by surgical resection was compared with definitive chemoradiotherapy in patients with T1 to T3 cN2 NSCLC in the landmark Intergroup Trial 0139 by Albain et al.[13] The study closed at 429 patients against a target of 602 patients to detect a 10% difference in 5-year survival. A total of 396 patients received induction chemoradiation with cisplatin and etoposide and 45-Gy radiotherapy. In the absence of radiological progression, 202 patients were randomized to surgical resection and 194 patients to continued radiotherapy uninterrupted up to 61 Gy. All patients were deemed *resectable* at the outset, and 76% had single-station N2 disease. There was no significant difference in median survival between trimodality and bimodality treatment (23.6 versus 22.2 months). The secondary end points of progression-free survival and the percentage of patients without disease progression at 5 years were both significantly higher in the trimodality treatment group (12.8 versus 10.5 months and 22% versus 11% [$p = 0.017$]). An unusually high mortality rate (26%) was noted in the 54 patients (35% of resections) who underwent pneumonectomy, which is reflected in the higher percentage of treatment-related deaths in the surgical arm (8% versus 2%). A post hoc subgroup analysis of 90 patients who had a lobectomy demonstrated higher overall survival (33.6 versus 21.7 months [$p < 0.002$]) compared with matched patients who received chemoradiotherapy.

One meta-analysis has considered this question by using the data from the Intergroup trial and data from a published conference abstract from the 2005 American Society of Clinical Oncology Conference. The abstract described the Scandinavian phase III trial of neoadjuvant chemotherapy and surgery versus surgery alone in stage IB to IIIA in NSCLC.[16] Only T3N1 tumors from the stage group IIIA were included, and a negative mediastinoscopy for N2 disease was an entry criteria; therefore, the trial specifically targeted early-stage NSCLC. Postoperative radiotherapy was delivered in cases of incomplete resection. Therefore, these patients may not be truly representative of the resectable cN2 population that this review is considering. That being said, the meta-analysis suggested a trend toward improved survival for patients undergoing trimodality treatment with surgery compared with that for those undergoing bimodality treatment with surgery and radiotherapy (HR = 0.87, 95% CI 0.75–1.01, $p = 0.068$).[7]

The more recent phase III ESPATUE trial[10] randomized patients with potentially resectable stage III NSCLC after induction chemoradiotherapy to either surgical resection or completion of definitive chemoradiation. Thirty-two percent of patients entered into this trial were clinically staged as T4N1 and 37% were clinically staged as IIIB on the basis of T4N2 staging or N3 disease in the contralateral mediastinum. A total of 246 patients were enrolled against a target of 300 to detect an improvement in 5-year survival of 15% with trimodality therapy. After induction chemotherapy 161 of 246 patients (65.4%) continued to have resectable disease and were randomized to either surgical resection or completion of definitive chemoradiotherapy. There was

no statistically significant difference in the 5-year overall survival rate between the two groups (44% with trimodality treatment versus 40% with chemoradiotherapy [$p = 0.34$]). Given the significant heterogeneity of the patients enrolled in the ESPATUE trial, the data cannot be used within a meta-analysis specifically evaluating N2 disease.

Is Trimodality Therapy Superior to Bimodality Treatment in Resectable cN2 NSCLC? Chemotherapy, Radiotherapy, and Surgery versus Chemotherapy and Surgery (with or without Radiotherapy)

The Swiss Group for Clinical Cancer Research phase III trial compared trimodality treatment with bimodality treatment (with or without radiotherapy).[11] After induction chemotherapy with cisplatin and docetaxel, patients were randomized to proceed with radiotherapy followed by surgery or surgery alone. A total of 232 patients were enrolled against a target of 240 to detect a 6-month improvement in event-free survival. The study targeted low-volume N2 disease, with less than 10% of patients having a total mediastinal bulk of disease larger than 5 cm. There was no significant difference in event-free survival between trimodality and bimodality treatment (12.8 versus 11.6 months [$p = 0.67$]) or overall survival (37 versus 26 months [p value not provided]) across the two arms.

A further phase III trial (Katakami et al.[12]) comparing induction chemotherapy with induction chemoradiotherapy before surgical resection did not demonstrate a survival difference between the two arms but was significantly underpowered after enrolling only 60 patients against a target of 180.

A meta-analysis examined trimodality versus bimodality treatment (with or without radiotherapy)[17] by using data from the following trials: EORTC 08941, Intergroup 0139, RTOG 89-01, Katakami et al. (2012), Thomas et al. (2008), and Shepherd et al. (1998).[5,8,12–14] No difference in overall survival was reported (HR = 0.79, 95% CI: 0.57–1.09, $p = 0.15$).[17] A number of meta-analyses looking at all different permeations of trimodality versus bimodality treatment have also failed to show a survival benefit from any one treatment regimen.[7,17–19] The data are summarized in Table 2 and are restricted to only meta-analyses using randomized controlled trial data.

Discussion

The available evidence suggests that one bimodality treatment (e.g., chemotherapy and radiotherapy) has not been shown to be superior to another (e.g., chemotherapy and surgery) in resectable cN2 NSCLC. A significant improvement in progression-free survival has been shown in the Intergroup 0139 trial,[13] as has a trend toward improved overall survival in meta-analysis[7] from trimodality therapy consisting of chemotherapy, radiotherapy, and surgery versus chemotherapy and radiotherapy. Furthermore, a subgroup analysis in the Intergroup 0139 trial demonstrated high mortality after trimodality treatment that included pneumonectomy but improved mortality in cases of lobectomy. An approach of offering chemotherapy plus radiotherapy in cases requiring pneumonectomy might be favored, although consideration must be given to the experience and volume of the surgical center involved when making individual patient decisions. No survival benefit has been shown with trimodality treatment consisting of chemotherapy, radiotherapy, and surgery over chemotherapy and surgery.

There are a number of limitations to consider in interpreting the published data. The first is the difficulty the trials encountered in recruiting sufficient numbers of patients to meet the predefined power calculations. This highlights the challenges of recruiting patients to trial when the treatment arms are very different (i.e., radiotherapy versus surgery). Furthermore, slow accrual to trials of multimodality treatment is compounded by potential changes to the standard of care for each treatment (e.g., new systemic therapies, advanced image-guided radiotherapy, and minimally invasive surgical techniques). The second limitation is the heterogeneity within this disease group. Specifically, there are no evidence-based definitions of what constitutes "resectable" cN2 disease. Such conclusions are often made by the surgical team present in the multidisciplinary team or tumor board. Consensus opinion from the European Society of Thoracic Surgeons states that discrete lymph nodes measuring less than 25 mm in diameter in the short axis are potentially resectable assuming that there is no evidence of nodal invasion into adjacent structures.[20] The final notable deficiency to this literature is the lack of quality of life data associated with different treatment modalities. When survival outcomes are similar, the impact of treatment on quality of life becomes a critical factor in decision making. Such data could help patients, families, and clinicians in the decision-making process in this challenging scenario.

The distinction between single-station N2 and multistation N2 has been advocated as a selection criterion for a surgical approach to stage IIIA N2 disease,[4] but the data do not support this. The International Association for the Study of Lung Cancer (IASLC) staging data sets demonstrate a similar survival between patients with multistation N1 disease and those with single-station N2 disease.[21] These results have been interpreted by some to define single-station N2 disease as a primary surgical entity.

Table 1. Summary of Journal-Published Multicenter Phase III Randomized Controlled Trials Comparing Different Treatment Strategies in Clinical N2 NSCLC from the MEDLINE and EMBASE Search for 1980–2017 Performed as the Basis of This Review

Study	Eligibility and Staging	Study Arms	Recruitment	Primary End Point	Results
Eberhardt et al.[10] (2015) ESPATUE trial	Discrete and measurable clinical N2 Selected N3: contralateral mediastinum Selected T4: resectable N2 pathologically proven pretreatment PS 0-1 CT, PET-CT, brain imaging, EBUS, and mediastinoscopy	3 cycles induction chemotherapy Induction chemoradiotherapy (45 Gy + 1 cycle chemotherapy). If NSCLC remains resectable, randomize: surgical resection vs. chemoradiotherapy boost	2004-2013 Target 300 patients, 246 recruited	5-y OS	5-y OS = 44% vs. 40%, $p = 0.34$
Pless et al. (2015)[11] SAKK trial	Discrete and measurable clinical N2 (T1-3) N2 pathologically proven pretreatment PS 0-1 CT, PET-CT, brain MRI, EBUS, and mediastinoscopy	3 cycles induction chemotherapy vs. 3 cycles induction chemotherapy + 44 Gy radiotherapy. All patients for surgical resection after induction treatment	2001-2012 Target 240 patients, 232 recruited. Stopped at third analysis	EFS	EFS = 11.6 vs. 12.8 mo, HR = 1.1, 95% CI: 0.8-1.4, $p = 0.67$
Katakami et al.[12] (2012) WJTOG9903	Discrete and measurable clinical N2 (T1-3) N2 pathologically proven pretreatment PS 0-1 Staging CT, bone scan, brain imaging, and mediastinoscopy. No PET-CT	2 cycles induction chemotherapy vs. 2 cycles induction chemotherapy + 40 Gy radiotherapy. All patients for surgical resection after induction treatment	2000-2005 Target 180 patients, 60 recruited. Closed early	5-y OS	3-y OS = 39.3% vs. 51.7%, HR = 0.77, 95% CI: 0.42-1.41, $p = 0.397$
Albain et al. (2009)[13] Intergroup 0139	Discrete and measurable clinical N2 (T1-3) N2 pathologically proven pretreatment Staging CT, brain imaging, bone scan and mediastinoscopy. No PET-CT	2 cycles induction chemotherapy Induction radiotherapy (45 Gy). If stable disease, randomize: surgical resection vs. complete radiotherapy to 61 Gy	1994-2001 Target 612 patients, 429 recruited	5-y OS	5-y OS = 27% vs. 20%, HR = 0.87, 95% CI: 0.7-1.1, $p = 0.24$
Thomas et al.[14] (2008) GLCCG	N2 disease up to borderline resectable Selected N3: contralateral mediastinum Selected T4: resectable N2 pathologically proven pretreatment PS 0-1, age <70 y Staging CT, bone scan, brain imaging and mediastinoscopy	3 cycles induction chemotherapy. If stable disease, randomize: surgical resection and PORT 54 Gy vs. chemoradiotherapy (45 Gy), then surgical resection	1995-2003 Target 500 patients, 558 recruited	PFS	PFS = 10 mo vs. 9.5 mo, HR = 0.99, 95% CI: 0.81-1.19, $p = 0.87$

(continued)

Table 1. Continued

Study	Eligibility and Staging	Study Arms	Recruitment	Primary End Point	Results
van Meerbeeck et al. (2007)[5] EORTC 08941	Discrete and measurable clinical N2 N2 pathologically proven pretreatment Any N2 disease in nonsquamous NSCLC N2 exceeding 4R/5 and 6 in SqCC PS 0-2 Staging CT. No PET-CT	3 cycles induction chemotherapy. If response, randomize: surgical resection vs. 60-62.5 Gy in 30-32 fractions	1994-2002 Target 358 patients, 332 randomized	5-y OS	5-y OS = 15.7% vs. 14%, HR = 1.06, 95% CI: 0.84-1.35, $p = 0.596$
Stephens et al.[9] (2005)	Clinical stage IIIA/N2 (T3N1, T1-3N2) Deemed unresectable but potential for downstaging PS 0-1 Staging CT and mediastinoscopy. No PET-CT	4 cycles induction chemotherapy ± surgical resection if response vs. definitive radiotherapy (50-60 Gy)	1995-1998 Target 350 patients, 48 recruited. Closed early	OS	2-y OS = 15% vs. 16%, HR = 0.91, 95% CI: 0.49-1.72, $p = 0.78$; 4 patients had an operation
Johnstone et al. (2002)[6] RTOG 89-01	Discrete and measurable clinical N2 N2 pathologically proven pretreatment PS 0-1 Staging CT and mediastinoscopy. No PET-CT	2 cycles induction chemotherapy. If stable disease, randomize: surgical resection vs. sensitive radiotherapy (64 Gy)	1990-1994 Target 224 patients, 73 recruited. Closed early	OS	4-y OS = 22% vs. 22%, $p = 0.46$
Rosell et al.[15] (1999)	Clinical stage IIIA/N2 (T3N1, T1-3 N2) N2 pathologically proven pretreatment Staging CT, bronchoscopy, and mediastinoscopy. No PET-CT	Surgery alone vs. 3 cycles induction chemotherapy and surgical resection	1989-not reported. 60 patients. No power calculation	5-y OS	5-y OS = 0% vs. 17%, $p = 0.005$
Shepherd et al. (1998)[8]	Clinical stage IIIA (N2 only) N2 pathologically proven pretreatment PS 0-2 Staging pathway not provided	2 cycles induction chemotherapy and surgical resection vs. definitive radiotherapy (60 Gy)	Date not provided. 31 patients. No power calculation	OS	OS = 18.7 mo vs. 16.2 mo. No HR or p value given

CT, computed tomography; PS, performance status; PET, positron emission tomography; EBUS, endobronchial ultrasound; OS, overall survival; EFS, event-free survival, PORT, postoperative radiotherapy; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; SqCC, squamous cell carcinoma.

Table 2. Summary of Meta-analyses in N2 NSCLC Management (Using Published Phase 3 Randomized Controlled Trial Data Only)

Author	Comparison	Search Strategy	Studies	Results
Xu XL et al.[18] (2016)	CS/CRS vs. CR	Up to 2015 PubMed, Medline, and Embase	Shepherd et al.[8] (1998) Johnstone et al.[6] (2002) Stephens et al.[9] (2005) van Meerbeck et al.[5] (2007) Albain et al.[13] (2009)	HR = 0.94, 95% CI: 0.81-1.09, $p = 0.44$
McElnay et al.[7] (2015)	CS vs. CR CRS vs. CR CRS vs. CS/CR	1980-2013 Medline and Embase Patients with N2 only	Shepherd et al.[8] (1998) Johnstone et al.[6] (2002) Stephens et al.[9] (2005) Van Meerbeck et al.[5] (2007) Albain et al.[13] (2009)	CS vs. CR: HR = 1.01, 95% CI: 0.82-1.23, $p = 0.954$ CRS vs. CR: HR = 0.87, 95% CI: 0.75-1.01, $p = 0.068$ CR or CS vs. CRS: HR = 0.92, 95% CI: 0.81-1.03, $p = 0.157$
Ren et al.[19] (2015)	CS/CRS vs. CR	1980-2015 PubMed, Embase, and Cochrane	Johnstone et al.[6] (2002) Van Meerbeck et al.[5] (2007) Albain et al.[13] (2009)	2-y OS HR = 1.0, 95% CI: 0.85-1.17, $p = 0.98$ 4-y OS HR = 1.13, 95% CI: 0.85-1.51, $p = 0.39$
Xu YP[17] (2015)	CS/CRS vs. CR CRS vs. CS	Dates not given PubMed, Embase, Medline, and Cochrane	Shepherd et al[8] (1998) Johnstone et al.[6] (2002) Van Meerbeck et al.[5] (2007) Thomas et al.[14] (2008) Albain et al.[13] (2009) Katakami et al.[12] (2012)	CS/CRS vs. CR: HR = 0.95, 95% CI: 0.81-1.10, $p = 0.49$ CS vs. CRS: HR = 0.79, 95% CI: 0.57-1.09, $p = 0.15$

CS, chemotherapy plus surgical resection; CR, chemotherapy plus radiotherapy; CRS, chemotherapy plus radiotherapy plus surgical resection; HR, hazard ratio; CI, confidence interval; OS, overall survival.

However, the IASLC results apply strictly to pathologically staged single-station N2 confirmed by extensive intraoperative nodal sampling and do not relate to cN2 detected preoperatively. Furthermore, the IASLC results simply imply the same survival outcomes from surgical intervention for multistation N1 and single-station N2. These are not randomized controlled data, and it is unclear what the outcomes would have been for these patients with N2 disease had they undergone alternative treatment regimens.

Conclusion

When faced with a patient with potentially resectable cN2 NSCLC (regardless of single-station versus multistation status) lung cancer teams should consider trimodality treatment consisting of chemotherapy, radiotherapy, and surgery or a bimodality approach that includes chemotherapy with either radiotherapy or surgery for patients who are fit enough for treatment. Patient preference, comorbidities, and individual factors such as the likelihood of pneumonectomy will all contribute to the decision-making process, as will the expertise and experience of local treatment centers. In our view, patients should be offered an appointment with and opinion from the oncology team and thoracic surgeon before making a final decision. The lung cancer community must continue to seek new approaches given that the current outcomes in N2 disease remain overall disappointing.

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References

1. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. *J Thorac Oncol*. 2007;2:706-714.
2. Ramnath N, Dilling TJ, Harris LJ, et al. 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. *Chest*. 2013;143(suppl 5):e314S-e340S.
3. Eberhardt WE, De Ruysscher D, Weder W, et al. 2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer. *Ann Oncol*. 2015;26:1573-1588.
4. Lim E, Baldwin D, Beckles M, Duffy J, Entwisle J, Faivre-Finn C, et al. Guidelines on the radical management of patients with lung cancer. *Thorax*. 2010;65(Suppl 3):iii1-iii27.
5. van Meerbeeck JP, Kramer GW, Van Schil PE, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. *J Natl Cancer Inst*. 2007;99:442-450.
6. Johnstone DW, Byhardt RW, Ettinger D, Scott CB. Phase III study comparing chemotherapy and radiotherapy with preoperative chemotherapy and surgical resection

in patients with non-small-cell lung cancer with spread to mediastinal lymph nodes (N2); final report of RTOG 89-01. Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys*. 2002;54(2):365–369.
7. McElnay PJ, Choong A, Jordan E, Song F, Lim E. Outcome of surgery versus radiotherapy after induction treatment in patients with N2 disease: systematic review and meta-analysis of randomised trials. *Thorax*. 2015;70(8):764–768.
8. Shepherd FA, Johnston MR, Payne D, et al. Randomized study of chemotherapy and surgery versus radiotherapy for stage IIIA non-small-cell lung cancer: a National Cancer Institute of Canada Clinical Trials Group Study. *Br J Cancer*. 1998;78(5):683–685.
9. Stephens RJ, Girling DJ, Hopwood P, Thatcher N. Medical Research Council Lung Cancer Working P. A randomised controlled trial of pre-operative chemotherapy followed, if feasible, by resection versus radiotherapy in patients with inoperable stage T3, N1, M0 or T1-3, N2, M0 non-small cell lung cancer. *Lung Cancer*. 2005;49: 395–400.
10. Eberhardt WE, Pottgen C, Gauler TC, et al. Phase III study of surgery versus definitive concurrent chemoradiotherapy boost in patients with resectable stage IIIA(N2) and selected IIIB non-small-cell lung cancer after induction chemotherapy and concurrent chemoradiotherapy (ESPATUE). *J Clin Oncol*. 2015;33(35): 4194–4201.
11. Pless M, Stupp R, Ris HB, et al. Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial. *Lancet*. 2015;386:1049–1056.
12. Katakami N, Tada H, Mitsudomi T, et al. A phase 3 study of induction treatment with concurrent chemoradiotherapy versus chemotherapy before surgery in patients with pathologically confirmed N2 stage IIIA nonsmall cell lung cancer (WJTOG9903). *Cancer*. 2012;118:6126–6135.
13. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet*. 2009;374:379–386.
14. Thomas M, Rube C, Hoffknecht P, et al. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer. *Lancet Oncol*. 2008;9:636–648.
15. Rosell et al. 1999.
16. Sorensen JB, Riska H, Ravn J, et al. Scandinavian phase III trial of neoadjuvant chemotherapy in NSCLC stages IB-IIIA/T3 [abstract]. *J Clin Oncol*. 2005;23:7146.
17. Xu YP LB, Xu XL, Mao WM. Is there a survival benefit in patients with stage IIIA (N2) non-small cell lung cancer receiving neoadjuvant chemotherapy and/or radiotherapy prior to surgical resection: a systematic review and meta-analysis. *Medicine*. 2015;94:e879.
18. Xu XL, Dan L, Chen W, Zhu SM, Mao WM. Neoadjuvant chemoradiotherapy or chemotherapy followed by surgery is superior to that followed by definitive chemoradiation or radiotherapy in stage 111A (N2) nonsmall-cell lung cancer: a meta-analysis and system review. *Onco Targets Ther*. 2016;9:845–853.
19. Ren Z, Zhou S, Liu Z, Xu S. Randomized controlled trials of induction treatment and surgery versus combined chemotherapy and radiotherapy in stages IIIA-N2 NSCLC: a systematic review and meta-analysis. *J Thorac Dis*. 2015;7:1414–1422.
20. De Leyn P, Dooms C, Kuzdzal J, et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. *Eur J Cardiothorac Surg*. 2014;45:787–798.
21. Rusch VW, Crowley J, Giroux DJ, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the N descriptors in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2007;2:603–612.