Article published online: 2021-02-18

Is Adjuvant Radiochemotherapy Always Mandatory in Patients with Resected N2 Non-Small Cell Lung Cancer?

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Thorac Cardiovasc Surg 2022;70:244–250.

Abstract

Background In patients with non-small cell lung cancer (NSCLC), the pathologic union for international cancer control (UICC) stage IIIA is a heterogeneous entity, with different forms of N2-lymph node involvement representing different prognoses. Although a multimodality treatment approach, including surgery, systemic therapy, and/or radiotherapy, is almost always recommended, in this retrospective observational study, we sought to determine whether long-term survival might be possible in selected patients who are treated with complete surgical resection alone.

Methods Between 2013 and 2018, we retrospectively identified 24 patients with NSCLC (16 men and 8 women), who were found to have pathologic N2-lymph node involvement, and were treated with complete surgical lung resection and systematic mediastinal and hilar lymph node dissection but no neoadjuvant or adjuvant treatment.

Results The most frequent reason ($n = 14$) for forgoing adjuvant treatment was patient refusal. The mean overall survival (OS) was 34.5 months (interquartile range [IQR]: 15.5–53.5 months). The mean disease-free survival (DFS) was 18 months (IQR: 4.75–46.75 months). We identified five patients who survived at least 5 years without recurrence (21%). In each of these cases, the nodal metastases were restricted to a single level and no extracapsular lymph node involvement were detected. Additionally, worse DFS was associated with pT3/4 (vs. a lower T-stage), as well as microscopic lymphovascular invasion.

Conclusion Although the small sample size precludes any definitive conclusions, it was possible to demonstrate that long-term survival without neoadjuvant and adjuvant treatment is possible in some patients if complete tumor and nodal resection is performed.

Keyword
- lung cancer treatment (surgery
- medical)
- practice guidelines
- pathology

received
October 4, 2020
accepted after revision
December 21, 2020
published online
February 18, 2021

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Georg Thieme Verlag KG,
Rüdigerstraße 14,
70469 Stuttgart, Germany

DOI https://doi.org/10.1055/s-0041-1723081.
ISSN 0171-6425.

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Introduction

Patients with technically operable but locally advanced non-small cell lung cancer (NSCLC) (UICC stage IIIA) present clinicians with a particular challenge. Although these patients usually receive some combination of surgery, systemic therapy, and/or radiotherapy, establishing reliable protocols is difficult. This disease category is itself heterogeneous, and earlier studies were frequently limited by the absence of analyzing uniform groups of N2-patients. Of the large randomized multimodality treatment studies of stage-IIIA NSCLC that do exist, many were performed before the routine use of more precise diagnostic techniques such as endobronchial ultrasound (EBUS) and positron emission tomography/computed tomography scanning (FDG-PET/CT), which often assign patients a higher tumor stage than previously.[1,2] The LACE meta-analysis represents one of the most comprehensive analyses of adjuvant chemotherapy following complete tumor resection in NSCLC, and although it suggests a survival benefit for patients with locally advanced tumors who received platinum-based chemotherapy, here too, there is much heterogeneity in terms of tumor and nodal characteristics, patient population, and adjuvant treatment regime.[3]

Despite these limitations, when complete surgical resection is possible but metastases in mediastinal lymph nodes are identified (pN2), adjuvant treatment is almost always recommended.[4] Both the ASCO and the German S3 guidelines currently recommend adjuvant platinum-based chemotherapy and, depending on the circumstances, radiation of the mediastinum as well.[5,6]

Despite evidence of benefits, adjuvant (or neoadjuvant) treatment presents serious risks,[7,8] and although the reported rates of direct mortality are low, they may be significantly underestimated.[9] Moreover, current recommendations notwithstanding, there are a small number of patients with locally advanced but completely resected disease, who for various reasons (with or without the support of their clinicians) choose to forgo further treatment.

Up until now, there have been no long-term investigations of this admittedly small group of patients with stage-IIIA pN2 NSCLC who were treated with surgery alone. Although our clinic continues to recommend adjuvant treatment for most patients in this disease category, we were able to identify a small series of patients who had received only surgery. In this manuscript, we present reasons for denial of adjuvant treatment, outcomes, and patterns of clinical–pathological characteristics. Although the case number is too small to offer any decisive conclusions, we seek to identify possible constellations of what might be termed as "minimally affected" N2 disease and raise the question of whether surgery alone might be an acceptable alternative in selected patient populations.

Methods

Patients

We retrospectively scanned the database of the Lung Clinic for patients who underwent curative-intent surgery (lobectomy, pneumonectomy, or anatomic segmentectomy) for stage-IIIA pN2 NSCLC between 2013 and 2018. In all cases, systemic hilar and mediastinal lymph node dissection was performed according to standard practice. Thus, right-sided lung resections included dissection of the paratracheal, subcarinal, inferior mediastinal, interlobar, and hilar lymph nodes, and left-sided resections included dissection of aortic, infracarinal, inferior mediastinal, interlobar, and hilar lymph nodes.[10]

We excluded all patients who received some form of neoadjuvant or adjuvant treatment. In some cases, the decision to forgo adjuvant treatment was directly documented in the medical files. When no evidence of further treatment was documented but the patient had been referred by affiliated partners, we contacted the referring institution/physician to determine whether patients may have received adjuvant treatment or diagnosis of a recurrence there. Cases where it was not possible to determine whether adjuvant treatment had been performed were excluded. Patients who died within 30 days of surgery were also excluded.

The institutional review board waived the need for registration, as all data had been gathered in advance for internal quality control and patients had already given their informed consent for their data to be used for research purposes. Patients were evaluated preoperatively by physical examination, bronchoscopy (in selected cases with EBUS or mediastinoscopy), chest radiograph, and FDG-PET/CT scans. Additionally, cerebral magnetic resonance imaging (MRI) was performed in clinical stage-III patients and in cases of clinically suspected brain metastases.

Tumor and Nodal Characteristics

For the purposes of this investigation, we retrospectively established lymph node subcategories that differentiated between incidental versus nonincidental disease, single versus multiple lymph node metastases, multi- versus single-nodal stations affected, skip versus continuous lymph node metastases, bulky (short-axis diameter $\geq$20 mm) versus nonbulky nodal disease ($<$20 mm), and intact verses breached lymph node capsule (extracapsular extension). Additionally, we extracted data on gender, patient age, tumor histology, anatomic location, tumor extent (T-status), and lymphovascular invasion.

Statistical Analysis

Statistical analyses were performed with R-3.4.0 for Windows, and the demographic and clinicopathological data were summarized and reported as frequencies (percentages) or medians. Overall survival (OS) was computed from date of surgery to date of known death of any cause or last known follow-up or entry in the city's public registry of the Federal States of Berlin/Brandenburg (censored patients). Disease-free survival (DFS) was computed as date of surgery to date of confirmed recurrence either at our hospital or at a referring institution or of known death of any cause or last known follow-up or entry in the public registry (censored patients). We performed univariate analyses for significance using χ^2 tests or Fischer's exact tests (categorical variables) or Student's *t*-test or Mann–Whitney test (continuous variables).

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We considered *p*-values of less than 0.05 to be statistically significant but due to the small sample size did not perform any further multivariate analyses. We calculated probability of OS and DFS using the Kaplan–Meier method.[11] Here too the case number was too small to justify any further calculation of survival differences between subgroups.

Results

We initially identified 220 patients with pathological stage-IIIA pN2 NSCLC who received curative-intent surgery but no neoadjuvant treatment. Eight patients, out of the 220 initially operated patients, were excluded due to perioperative death within 30 days of surgery. Of these 220 patients, only 41 did not receive any adjuvant treatment. Nine patients were excluded due to incomplete follow-up, leaving 24 patients for this case series (►**Fig. 1**).

The series included 16 women (67%) and 8 men (33%). The mean patient age was 70 years (interquartile range [IQR]: 65–72). In our study sample, 3 patients had segmentectomies, 16 had lobectomies, and 5 had pneumonectomies. Broncho- and/or angioplasty was necessary in four patients. There were 15 adenocarcinomas (63%), 5 squamous cell carcinomas (21%), 3 large cell carcinomas, and 1 undefined form of NSCLC. Nine patients (38%) had tumor stages of pT3 or higher. Detailed data are summarized in ►**Table 1**.

The most frequent reason ($n = 14$) for forgoing adjuvant treatment was patient refusal. In five cases, severe postoperative complications caused patients to miss the window for initiating adjuvant treatment. In one case, a patient developed pneumonia and acute respiratory distress syndrome (ARDS), following an extended pneumonectomy with partial diaphragm resection, and spent several days on a respirator. In two additional cases, patients developed pneumonia after discharge from hospital. Although intensive care treatment was not required, the prolonged postoperative treatments, along with preexisting cardiovascular conditions, prompted decisions to forgo further oncological treatment in these cases. In another case, a patient had a bronchial stump insufficiency and consequent pleural empyema which was ultimately treated with an open window thoracostomy. Finally, one patient suffered a sigma perforation, which resulted in a series of abdominal surgeries shortly after the initial lung surgery. In three cases, no complications were reported, but adjuvant treatment was not performed due to advanced age or comorbidities (►**Table 2**).

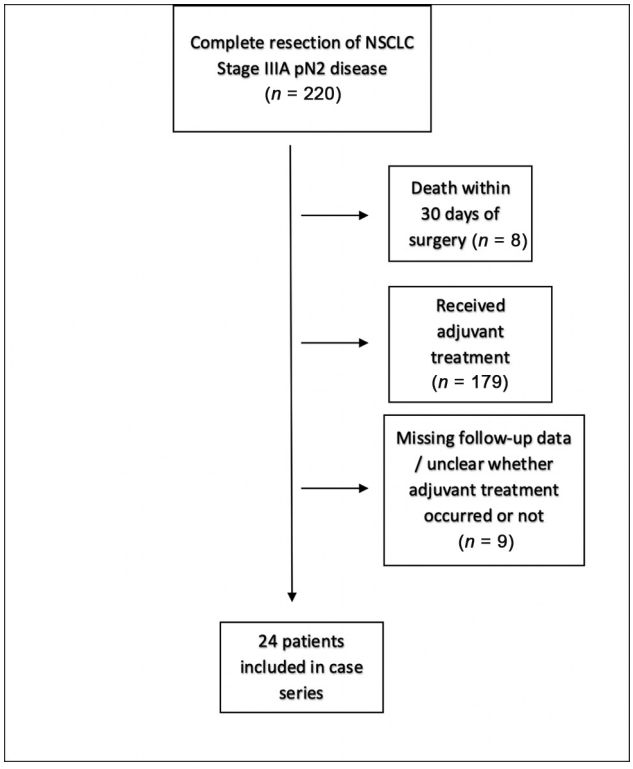

Fig. 1 Patient selection scheme. NSCLC, non-small cell lung cancer.

Table 1 Patient demographics and clinicopathological characteristics

Variable	No	IQR/%
Age at surgery (y)	70	65–72
Sex		
Female	16	67%
Male	8	33%
Histology		
Adenocarcinoma	15	63%
Squamous cell	5	21%
Large cell carcinoma	3	13%
Other NSCLC	1	4%
Tumor location		
left	10	40%
right	14	60%
OS (mo)	34.5	15.5–53.5
OS censored	10	
DFS (mo)	18	4.8–46.8
DFS censored	15	
Follow-up time	35	16–54
Lower lobe	7	29%
pT3/pT4	9	38%
5-year survival	5	21%
Lymphovascular invasion	16	67%

Abbreviations: DFS, disease-free survival; IQR, interquartile range; NSCLC, non-small cell lung cancer; OS, overall survival.

Lymph Nodes

A mean of 17 lymph nodes per patient were examined (IQR: 8–25). Fourteen patients (58%) had singular lymph node metastases. Sixteen patients had skip metastases (67%). Four patients (17%) had multilevel N2 disease and one patient (4%) had bulky disease. Five patients (21%) had incidental disease (no indication of nodal disease in preoperative staging). Ten patients (24%) had extracapsular extension. The mean percentage of affected lymph nodes

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Table 2 Reasons for no adjuvant treatment ($n = 24$)

	No.	%
Patient refusal	14	58
Postoperative complications	5	21
Advanced age, comorbidities	3	13
Unclear	2	8

Table 3 Lymph node characteristics

Variable	No.	(%) or median (IQR)
Number of Lymph nodes examined/per patient	17	8–25
Single lymph node	14	58%
Skip metastases	16	67%
Multilevel	4	17%
Incidental	5	21%
Bulky disease	1	4%
Isolated station five-sixths metastasis	1	44%
Extracapsular extension	10	42%
Proportion of lymph nodes affected	16%	7%–26%

Abbreviation: IQR, interquartile range.

(affected/total number examined) was 16% (IQR: 7.0–26%; ►**Table 3**).

Survival Data

The mean follow-up time was 35 months (IQR: 16–54). The mean OS was 34.5 months (IQR: 15.5–53.5 months). The mean DFS was 18 months (IQR: 4.75–46.75 months). Five patients (21%) survived 5 years or longer. The estimated survival curves are presented in ►**Figs. 2** and **3**. In the

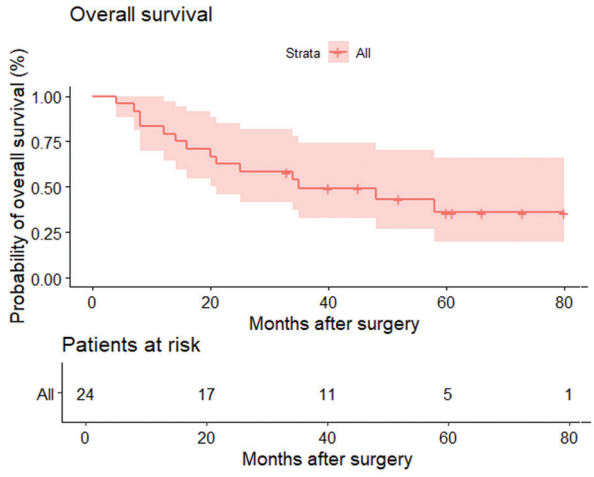

Fig. 2 Kaplan–Meier overall survival curve for patients with no neoadjuvant or adjuvant therapy.

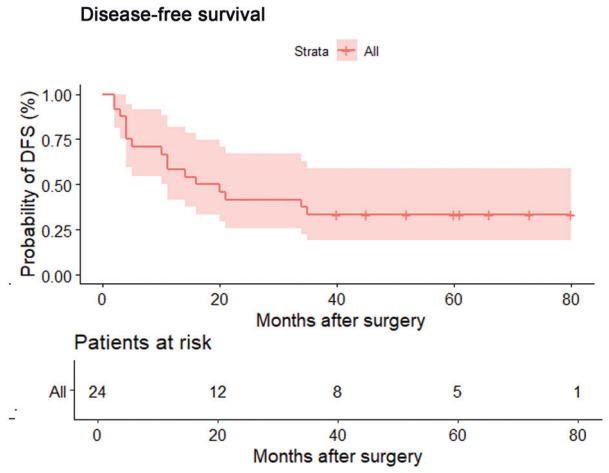

Fig. 3 Kaplan–Meier disease-free survival curve for patients with no neoadjuvant or adjuvant therapy. DFS, disease-free survival.

univariate analysis, we found that earlier recurrence was significantly associated with pT3/4 (vs. a lower T-stage), as well as microscopic lymphovascular invasion ($p = 0.03$ and 0.045, respectively). We also observed a strong trend between shorter OS and extracapsular extension of lymph node metastases ($p = 0.051$). No other factors investigated approached the level of significance.

Best Outcomes

We identified five patients who survived 5 years or longer without recurrence (21%). In each of these cases, the nodal metastases were restricted to a single level, and although they had all been identified on preoperative imaging, none represented bulky disease. In every case but one, only a single lymph node was affected (skip metastases). In the remaining case, 7 of 33 lymph nodes were affected; this was also the only case where lymphovascular invasion was present. There were no cases of extracapsular extension. In four of the five cases, the decision to forgo adjuvant treatment was due to patient preference. In one case, it was due to a complicated course involving postoperative pneumonia and multiple days of mechanical ventilation. Two tumors were adenocarcinomas, one was a squamous cell carcinoma, one was an undefined NSCLC, and one was a large cell carcinoma. Interestingly, in three of five cases, the primary tumor was either pT3 or pT4.

Worst Outcomes

Additionally, we identified seven patients who had recurrences within 6 months of surgery, five of whom also died within a year. Interestingly, despite the early recurrence, one patient survived for a total of 58 months and one for at least 48 months (last records show patient still alive). Of the five patients with early recurrence and death, two had a singular nodal metastasis and three had multiple nodal metastases. All had single level disease, but one had bulky disease. Two patients had pT3- or pT4-stage tumors. Two different patients (with pT2b or lower) had metastatic extension

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beyond the lymph node capsule. Interestingly, in three of the five cases, the lymph node metastases were occult. In all five patients in the worst performing group, lymphovascular invasion was present. In every case except one, the decision to forgo adjuvant treatment was due because of medical considerations. In one case, a patient had a bronchial stump insufficiency with consequent sepsis and mechanical ventilation. In one case, a patient suffered a sigma perforation with consecutive peritonitis and long-term intensive care treatment. In two cases, no further treatment was performed due to generally poor performance status, as well as simultaneous discovery of other malignancies. In the one case where the decision was made due to patient preference, the cancer had actually been diagnosed 2.5 years previously (cT2 N0 M0) at which time the patient had rejected all treatment including surgery (later: pT4 pN2 (3/35).

Discussion

In this retrospective observational study, we present a sample of NSCLC patients with confirmed stage-IIIA pN2 nodal disease, who against current recommendations did not receive treatment beyond surgery. The patients in our series had a 5-year OS rate of 21%. This is at least on par with the reported survival rates for patients with this disease constellation in other studies, most of whom received adjuvant or neoadjuvant treatment per standard recommendations. Mountain and colleagues reported a 5-year survival rate of 23%,[12] and in a multicenter analysis of 11,619 patients Kassis and Vaporciyan reported a 5-year survival rate of 16%.[13] The perhaps surprisingly favorable outcomes in our patient collective may indeed be due to chance alone, and the small sample size of course demands that they should be treated with extreme caution. Nevertheless, our series demonstrates that it is possible to achieve long-term survival with locally advanced disease and no treatment other than complete resection of the primary tumor and associated lymph nodes. Moreover, of the patients with the worst outcomes, all but one were denied adjuvant treatment for medical reasons. Thus, those who in retrospect might seem to have stood to gain the most from adjuvant treatment were unable to receive it anyway. Those who actively decided against further treatment did not fare particularly badly. Although our series is far too small to suggest any definitive conclusion, our hope is to inspire further investigations of whether adjuvant treatment is always necessary or even beneficial when sufficiently radical surgery has been performed.

The evidence based on hitherto, investigations continue to weigh in favor of adjuvant radiochemotherapy for patients with stage-IIIA pT2 NSCLC. And yet, we know that the calculation is a statistical one: although many patients will benefit, some will not and will be subjected to the toxic side effects unnecessarily. Although it is more difficult to quantify, prolongation of treatment with adjuvant methods over weeks and months can also mean serious compromises to quality of life and unnecessary squandering of (limited) time in medical settings.

The challenge of course is to determine which subset of patients will truly benefit from adjuvant treatment and which could do just as well or better without it. As molecular characterization of tumors becomes more refined, this will surely play a role in future stratifications, but as this data are not always readily available, we chose to focus on the simple pathological data that are always available to us as clinicians and ask how it might help guide future treatment decisions. We offer our findings not to suggest any answers but simply to raise questions.

Our only statistically significant findings were that larger tumor size/extension (pT3/4 vs. pT2 or lower) and lymphovascular invasion were both associated with shorter DFS. Moreover, lymphovascular invasion was present in every patient who had a recurrence within 6 months of surgery and in only one of the patients who survived 5 years or longer without recurrence. Although it does not inform staging directly, other authors have reported that lymphovascular invasion has a negative effect on prognosis.[14–16] The other finding of borderline statistical significance was the association between extracapsular extension and shorter OS. None of the patients with the best outcomes had extracapsular extension, while two of the five with the worst outcomes did. This is in line with the findings of two recent meta-analyses, which also report that extracapsular extension is associated with worse outcomes.[17,18] T-status of course plays a role in current decisions on adjuvant treatment but if enough compelling evidence is found, perhaps lymphovascular invasion and extracapsular infiltration could also be included in future decisions on whether to recommend adjuvant treatment.

Although the sample sizes were truly too small for any meaningful statistical analysis, when comparing the best and worst performing groups in our series, a few additional patterns emerge. Of the patients with the best outcomes, none had bulky disease and four of the five had singular, skip metastases. Within the worst performing group, three of the five patients had multiple nodal metastases and one had bulky disease. Other authors have reported that N2 skip metastases may represent a more favorable subset of N2 disease[19] and smaller number of affected lymph nodes have also been reported to associate with better prognosis.[20] Whether or not in selected cases, for example, in single (non-bulky) N2 lymph node with no lymphovascular or extracapsular spread, adjuvant treatment may not be indicated has to be further explored. Nakanishi and colleagues found that isolated metastases to stations 5 and 6 were prognostically equivalent to N1 metastases, and that adjuvant treatment did not improve survival at all in this group.[21] In our series, we did not observe any patterns related to lymph node location, but there was one patient with an isolated station five-sixths metastasis who had DFS and OS of 52 months.

Some authors have suggested that clinically apparent nodal metastases have a worse prognosis than those discovered on pathological examination.[22,23] Much of this data, however, comes from the time before PET-CTs had become a routine part of clinical staging. Moreover, even as clinical staging becomes more uniform, differences in surgical resection of lymph nodes (sampling vs. complete dissection) persist. In our series, where patients were preoperatively staged with PET-CT and underwent systematic mediastinal

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and hilar dissection, the difference between clinical and pathological lymph node stage did not seem to play any role in outcome. Nevertheless, the extent of required lymph node dissection remains controversial. Some investigators have found a survival benefit for more extensive lymph node dissection, particularly with increasing tumor stage,[3,24] and the number of removed lymph nodes seems to associate with better outcome in several other solid tumor diseases too. It is unclear, however, whether this is due to the potentially greater sensitivity (and subsequent decisions to deliver adjuvant treatment) or whether complete lymph node removal is inherently therapeutic,[25] and many thoracic surgeons continue to perform lymph node sampling only. Future decisions to potentially forgo adjuvant treatment of course would also depend on the extent of surgical lymph node dissection.

Limitations and Conclusion

One limitation of this investigation is the small sample size. The limited number of patients in our dataset with locally advanced NSCLC, who did not receive adjuvant treatment, cannot offer definitive conclusions or recommendations. It was possible, however, to demonstrate that long-term survival without adjuvant treatment is indeed possible if complete tumor and nodal resection is performed. We also investigated the clinicopathological characteristics that might allow patients to survive long-term without adjuvant treatment, and although no statistically meaningful analysis was possible, we were able to recognize certain patterns, minimal lymph node involvement and no lymphovascular invasion, which seemed to associate with equivalent or even better long-term outcomes compared with stage-IIIA pN2 patients in other investigations, treated according to standard recommendations. We hope that future, larger investigations might determine whether there is any statistical significance to these observed patterns, so that adjuvant treatment can be delivered in a more targeted manner and so that patients who do not stand to benefit can be spared.

Funding
None.

Conflict of Interest
None declared.

Acknowledgments
The authors thank for her assistance in the data management.

References

1 Rosell R, Gómez-Codina J, Camps C, et al. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. N Engl J Med 1994;330(03):153–158
2 van Meerbeeck JP, Kramer GWPM, Van Schil PEY, et al; European Organisation for Research and Treatment of Cancer-Lung Cancer Group. 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(06):442–450
3 Pignon J-P, Tribodet H, Scagliotti GV, et al; LACE Collaborative Group. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008;26(21): 3552–3559
4 Bezjak A, Temin S, Franklin G, et al. Definitive and adjuvant radiotherapy in locally advanced non-small-cell lung cancer: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the American Society for Radiation Oncology Evidence-Based Clinical Practice Guideline. J Clin Oncol 2015;33 (18):2100–2105
5 Kris MG, Gaspar LE, Chaft JE, et al. Adjuvant systemic therapy and adjuvant radiation therapy for stage I to IIIA completely resected non-small-cell lung cancers: American Society of Clinical Oncology/Cancer Care Ontario Clinical Practice guideline update. J Clin Oncol 2017;35(25):2960–2974
6 S3-Leitlinie Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms. Accessed December 4, 2020 at: https://www.awmf.org/uploads/tx_szleitlinien/020-007OL_l_S3_Lungenkarzinom_2018-03.pdf
7 Verstappen CCP, Heimans JJ, Hoekman K, Postma TJ. Neurotoxic complications of chemotherapy in patients with cancer: clinical signs and optimal management. Drugs 2003;63(15):1549–1563
8 Morishima Y, Ogura M, Yoneda S, et al; Japan Erythropoietin Study Group. Once-weekly epoetin-beta improves hemoglobin levels in cancer patients with chemotherapy-induced anemia: a randomized, double-blind, dose-finding study. Jpn J Clin Oncol 2006;36(10):655–661
9 Anders JC, Grigsby PW, Singh AK. Cisplatin chemotherapy (without erythropoietin) and risk of life-threatening thromboembolic events in carcinoma of the uterine cervix: the tip of the iceberg? A review of the literature. Radiat Oncol 2006;1:14
10 Dienemann H, Hoffmann H, Koebe H-G. Technik und Rationale der Lymphknotendissektion bei Bronchialcarcinom. Chirurg 1998;69(04):412–417
11 Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–481
12 Mountain CF. Revisions in the international system for staging lung cancer. Chest 1997;111(06):1710–1717
13 Kassis ES, Vaporciyan AA. Defining N2 disease in non-small cell lung cancer. Thorac Surg Clin 2008;18(04):333–337
14 Wang J, Chen J, Chen X, Wang B, Li K, Bi J. Blood vessel invasion as a strong independent prognostic indicator in non-small cell lung cancer: a systematic review and meta-analysis. PLoS One 2011;6 (12):e28844
15 Okiror L, Harling L, Toufektzian L, et al. Prognostic factors including lymphovascular invasion on survival for resected non-small cell lung cancer. J Thorac Cardiovasc Surg 2018;156(02):785–793
16 Gabor S, Renner H, Popper H, et al. Invasion of blood vessels as significant prognostic factor in radically resected T1-3N0M0 non-small-cell lung cancer. Eur J Cardiothorac Surg 2004;25(03): 439–442
17 Tabatabaei SV, Nitche C, Michel M, Rasche K, Hekmat K. Prognostic impact of extracapsular lymph node invasion on survival in non-small-cell lung cancer: a systematic review and meta-analysis. Adv Exp Med Biol 2018;1116:27–36
18 Luchini C, Veronese N, Nottegar A, et al. Extranodal extension of nodal metastases is a poor prognostic moderator in non-small cell lung cancer: a meta-analysis. Virchows Arch 2018;472(06): 939–947
19 Riquet M, Assouad J, Bagan P, et al. Skip mediastinal lymph node metastasis and lung cancer: a particular N2 subgroup with a better prognosis. Ann Thorac Surg 2005;79(01):225–233
20 Saji H, Tsuboi M, Shimada Y, et al. A proposal for combination of total number and anatomical location of involved lymph nodes for nodal classification in non-small cell lung cancer. Chest 2013;143 (06):1618–1625

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21 Nakanishi R, Osaki T, Nakanishi K, et al. Treatment strategy for patients with surgically discovered N2 stage IIIA non-small cell lung cancer. Ann Thorac Surg 1997;64(02):342–348
22 Andre F, Grunenwald D, Pignon JP, et al. Survival of patients with resected N2 non-small-cell lung cancer: evidence for a subclassification and implications. J Clin Oncol 2000;18(16):2981–2989
23 Vansteenkiste JF, De Leyn PR, Deneffe GJ, et al; Leuven Lung Cancer Group. Survival and prognostic factors in resected N2 non-small cell lung cancer: a study of 140 cases. Ann Thorac Surg 1997;63 (05):1441–1450
24 David EA, Cooke DT, Chen Y, Nijar K, Canter RJ, Cress RD. Does lymph node count influence survival in surgically resected non-small cell lung cancer? Ann Thorac Surg 2017;103(01): 226–235
25 Sigurdson ER. Lymph node dissection: is it diagnostic or therapeutic? J Clin Oncol 2003;21(06):965–967

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