The Impact of Chemotherapy on the Lymphatic System in Thoracic Oncology

Antonio Passaro, MD[1,*], Patrizia Trenta, MD[1], Davide Conte, MD, Giuseppe Campennì, MD, Angelina De Benedetto, MD, Enrico Cortesi, MD

KEYWORDS

• Non–small cell lung cancer • Adjuvant chemotherapy
• Neoadjuvant chemotherapy • Lymph node

Lung cancer is the leading cause of cancer-related mortality in the United States and Europe. The median 5-year survival rate for patients with non–small cell lung cancer (NSCLC) is about 15%. Relative survival for lung tumors is strongly dependent from stage at diagnosis: 5-years survival is 49%, 16%, and 2% for patients with early, locally advanced, and metastatic disease, respectively.[1,2]

The natural history of lung cancers is influenced by the acquired ability of cancer cells to invade lymphatic and vascular vessels resulting in nodal and distant metastases. In particular, lymphatic spreading generally follows the pulmonary artery branching system: lower lobe lymphatics generally drain to the posterior mediastinum and to the subcarinal nodes; right upper lobe drains to the superior mediastinum; and left upper lobe drains to the anterior and superior mediastinum.

The determination of stage at diagnosis is fundamental in terms of prognostic and therapeutic implications. To plan the best therapeutic strategy, the most important clinical features are the detection of distant metastases and, in nonmetastatic disease, the identification and localization of pathologic thoracic lymph nodes by station. Histologic type, tumor size and location, involvement of pleura, tumor grade, performance status, and biological features are the other cornerstones of prognosis for NSCLC.

Surgery, chemotherapy, target agents, and radiotherapy are the therapeutic options available to treat NSCLC. Surgery is the only really curative treatment choice, but its outcome is still poor, in particular for patients with mediastinal lymph node involvement. Good long-term survival is obtained in stages I and II after pulmonary resection, whereas patient survival after surgery in stage IIIA-N2 is still disappointing. Data from several clinical trials show that in completely resected early stages, the 5-year recurrence rates for patients in stage I, stage II-N0, and stage II-N1 were 16%, 39%, and 46%, respectively.[3,4] On the other side, patients with surgically treated stage IIIA-N2 NSCLC have a 5-year recurrence rate and a 5-year overall survival (OS) rate of 10% to 15%. In particular, patients with bulky mediastinal involvement have a 5-year survival rate of 2% to 5%.[4]

High frequency of distant failure after surgical resection of NSCLC with nodal metastasis suggests that nodal invasion could be considered an indicator of systemic metastasis. Multimodal treatments have been investigated to maximize the gain in survival for patients with metastasis in regional lymph nodes or locally advanced disease.

The authors have no conflict of interest.

Division of Medical Oncology, Sapienza–University of Rome, Viale Regina Elena, 324/00161–Rome, Italy
[1] Both authors contributed equally to this work.
* Corresponding author.
E-mail address: a-passaro@hotmail.it

Thorac Surg Clin 22 (2012) 243–249
doi:10.1016/j.thorsurg.2011.11.002
1547-4127/12/$ – see front matter

Presurgical staging is extremely important to select the correct therapeutic strategy in a patient with newly diagnosed NSCLC, but no single examination is sufficient alone to determine both lymph nodal status and the presence of distant metastases at the moment.

Several radiologic investigations such as computed tomography (CT), bone scan, positron emission tomography (PET) or magnetic resonance imaging of the brain are performed for initial assessment. However, these noninvasive techniques, performed for preoperative staging, seem to be still imperfect for the correct evaluation of thoracic nodal involvement. Invasive surgical procedures, such as mediastinoscopy, are the gold standard for the correct evaluation of lymph nodal status. Mediastinoscopy can help clinicians to select patients eligible for surgery from those who will receive only a palliative treatment; above all, it should be mandatory to select patients with a locally advanced disease who could benefit from a preoperative downstaging induction treatment.[5,6]

After surgery, most patients develop regional or distant metastases, in particular those with pathologic nodal involvement. Several randomized adjuvant/neoadjuvant trials, using chemotherapy and/or radiotherapy investigated the possibility to improve the outcome of patients with lung cancer by increasing their OS. Use of postoperative chemotherapy in patients with resected NSCLC has been evaluated in several randomized controlled trials and meta-analyses, and a 5-year absolute benefit of about 5% was obtained with cisplatin-based doublet regimens.[7] On the other side, postoperative radiotherapy (PORT) showed detrimental effects in patients with pathologic stage I/II and N0-N1 disease, with an 18% relative increase of the death risk for patients who received PORT compared with those who underwent surgery alone (hazard ratio [HR], 1.18, $P = .002$). In resected stage IIIA-N2 disease, this adverse effect is controversial. Although some studies suggest that PORT can improve local control for patients with node-positive lung cancer who have undergone surgical resection, it remains unclear whether PORT can really improve survival. Postoperative chemoradiotherapy for stage IIIA-N2 NSCLC has been evaluated in 5 randomized trials versus radiation following surgical resection; only 1 trial reported a disease-free survival gain by adding chemotherapy to radiotherapy, but no trial reported improvement in OS. No difference in local control or survival was observed in 3 trials evaluating platinum-based chemotherapy followed by surgery versus combined platinum-based chemoradiotherapy alone in IIIA-N2 diseases, but those studies were small and with a limited enrollment.[8] Radiation and chemoradiotherapy have also been investigated as exclusive treatments for unresectable stage IIIA-N2 NSCLC; both treatments are not curative, and they are performed for a long-term survival benefit and palliation of symptoms.

Neoadjuvant chemotherapy in resectable node-negative and node-positive lung cancers has also been investigated, with controversial results. This therapy aims to reduce tumor size, facilitate surgical resection, eradicate micrometastases, and improve tolerability. Of particular interest is the possible role that preoperative chemotherapy could play in a particularly heterogeneous group of patients, those with stage IIIA with resectable or potentially resectable N2 tumor.

It is clear that nodal thoracic involvement is the principal clinical feature that influences the prognosis of patients with nonmetastatic NSCLC. The aim of the present analysis is to evaluate if and how a medical treatment such as chemotherapy, given before or after surgery, can improve the outcome and reduce cancer-related mortality of both patients with node-negative and node-positive NSCLC.

IMPACT OF ADJUVANT TREATMENT ON THORACIC LYMPH NODE INVOLVEMENT

Adjuvant chemotherapy has been explored with the goal of eliminating occult metastases and reducing the risk of recurrence. Adjuvant trials (the first- and second-generation ones) have sometimes shown controversial results, but, in 2008, the Lung Adjuvant Cisplatin Evaluation (LACE) collaborative group published a meta-analysis based on data from the 5 largest trials of cisplatin-based adjuvant chemotherapy (Adjuvant Lung Cancer Project Italy [ALPI], Adjuvant Navelbine International Trialist Association [ANITA], International Adjuvant Lung Cancer Trial [IALT], Big Lung Trial [BLT], and JBR.10) that confirmed a 5-year absolute survival benefit of about 5.4% for postoperative chemotherapy for stage II and III disease[7] that was sufficient to recommend adjuvant cisplatin-based treatment as part of clinical routine practice.[9]

When radical surgery is performed (lobectomy or pneumonectomy and lymphadenectomy), the nodal pathologic status is of great importance to determine if patients will benefit or not from an adjuvant treatment and how much relevant is this benefit, as can be deduced from the subgroup analysis of principal adjuvant studies. Some differences can be found if the results of the principal trials are analyzed stage by stage (I, II, and IIIA) and, in particular, according to nodal pathologic status (pN0 vs pN1-2 disease).

The only 2 adjuvant cisplatin-based trials (ALPI and IALT) including stage IA NSCLC agree about the detrimental effect that chemotherapy has for these patients,[10,11] with an overall HR for OS of 1.4 (95% confidence interval [CI], 0.95–2.06).[7]

If chemotherapy should have a role in adjuvant treatment of stage IB cancer (referring to the 6th edition of TNM) is still an open question because of the controversial data derived from clinical trials. After a follow-up of 76 months, ANITA trial established lack of survival advantage from adjuvant chemotherapy for all patients with pN0 stage I disease with an HR of 1.14 (95% CI, 0.83–1.57).[12] Similar data come from long-term follow-up of JBR.10 study,[13] IALT trial,[5] and LACE meta-analyses.[7] However, CALGB [Cancer and Leukemia Group B] 9633 study expressly created to test adjuvant treatment with carboplatin and paclitaxel in high-risk node-negative disease (stage IB) gives some points of reflection. Although preliminarily finding of the study encouraged chemotherapy use, with a surprising HR for OS of 0.62 (90% CI, 0.44–0.89, $P = .14$), mature data after a longer follow-up (74 months) showed a 17% reduction of the risk of death for the chemotherapy group but without statistical significance (HR, 0.83; 90% CI, 0.64 to 1.08; $P = .125$). The small number of enrolled patients probably let the study to be underpowered to detect survival differences between the 2 arms. Despite this, an unplanned subgroup analysis of the same trial showed a 31% reduction of the risk of death for patients treated with chemotherapy whose tumors were 4 cm and larger (HR, 0.69; 90% CI, 0.48–0.99; $P = .043$), with a similar advantage for disease-free survival also. A trend toward inferior OS and disease-free survival for the chemotherapy group was observed for those patients with pT of 4 cm or less, pN0.[14] This could mean that only smaller pN0 NSCLCs do not benefit of adjuvant treatment.

Anyway, whether patients with stage IB tumors should be treated with systemic adjuvant chemotherapy is still an open question. The Union for International Cancer Control seventh TNM classification reclassifies pT2 pN0 tumors larger than 5 cm in diameter as stage IIA instead of IB; this could partially solve this controversy.

On the other side, the positive role of adjuvant chemotherapy for node-positive disease seems to be well established, but some differences between pN1 and pN2 NSCLCs can be found in terms of magnitude of the absolute benefit if clinical trial results are deeply analyzed. For example, according to the ANITA trial, patients with a greater node involvement would benefit more from chemotherapy; HR for OS for pN1 disease is 0.67 (0.47–0.94), whereas it is 0.60 (0.44–0.82) for patients with pN2 NSCLC. In particular, in patients with pathologic stage IIIA, the study showed an improvement in survival of 16%.[12]

IALT subgroup analyses show a real survival advantage only for pN2 disease,[5] whereas the principal meta-analyses of second-generation cisplatin-based adjuvant trials (LACE) did not find any difference in survival advantage between stage II and III NSCLC (both HR, 0.83 [0.73–0.95] $P = .04$).[7]

It seems clear that the impact of adjuvant treatment is strictly influenced by nodal status; for pN0 little tumors chemotherapy should be detrimental, whereas available data seem to suggest that benefit maximizes when there is a greater nodal involvement. Adjuvant radiotherapy, allowed in some of those trials, could have played an important role in influencing this survival advantage, most of all for pN2 disease.

IMPACT OF NEOADJUVANT TREATMENT ON THORACIC LYMPH NODE INVOLVEMENT

Neoadjuvant chemotherapy generally gives some important advantages in the management of nonmetastatic tumors because it allows an early control on systemic micrometastasis, giving the possibility to reduce tumor volume, facilitating surgical approach, and granting a better compliance to chemotherapy, with a generally higher dose intensity. Moreover, it is a way to test chemotherapy efficacy in vivo. On the other hand, possible toxicities and consequent delaying of surgery should sometimes be detrimental. Despite this theoretical rationale, the efficacy of neoadjuvant treatment of early-stage disease is still not so clear; the greatest part of individual trials found a trend over a survival benefit for neoadjuvant therapy that did not reach the statistical significance, probably because of the underpowering of the individual studies or the contamination of the outcome by the use of adjuvant therapy in some of them. For that reason, neoadjuvant medical treatment is still considered an experimental approach for early-stage disease.[15]

Available data demonstrate some differences in the impact of neoadjuvant chemotherapy according to nodal clinical involvement. In 2002, Depierre and colleagues[16] published a phase III clinical trial in which 355 patients with resectable (IB-IIIA) NSCLC were randomized to 2 cycles of induction chemotherapy (and 2 more cycles after surgery) or surgery alone. Despite the impressive differences in 3- and 4-year survivals observed in favor of preoperative approach, survival advantage was significant only for cN0 (not T1) to cN1 disease (HR, 0.68; 95% CI, 0.49–0.96) and not for patients

with cN2 disease (HR, 1.04; 95% CI, 0.68–1.60). Despite these impressive results, larger trials did not confirm the benefit of neoadjuvant chemotherapy for patients with cN2 disease. In the investigators' trial, there was no statistically significant gain in survival for patients affected by NSCLC stage IIIA-N2 (HR, 1.04) receiving preoperative treatment.

The SWOG (Southwest Oncology Group) 9900 trial of neoadjuvant chemotherapy excluded clinical N2 disease. The advantage in OS and progression-free survival of administering treatment based on carboplatin/paclitaxel before surgery did not join the statistical significance (probably because of the lower than expected accrual), but cN0 disease seems to benefit more from preoperative treatment with an HR of 1.43 (95% CI, 1.05–1.96; $P = .025$) in favor of lower stages.[17]

Of particular interest are the role and effective benefit of neoadjuvant chemotherapy in potentially resectable stage IIIA-N2 NSCLC.

In 1994, Rosell and colleagues[18] published the results of a phase III randomized trial examining the possible benefit of preoperative chemotherapy for 60 patients diagnosed with stage IIIA NSCLC. Patients were randomly assigned to receive either surgery alone or 3 courses of neoadjuvant chemotherapy, given intravenously at 3-week intervals, followed by surgery. All patients received mediastinal radiation after surgical resection. Median survival in the group receiving induction chemotherapy was 26 months compared with 8 months in those treated with surgery alone ($P<.001$); 5-years survival was 17% for patients treated with neoadjuvant chemotherapy versus 0% for those treated with surgical resection only.[18]

In the same year, the results of another randomized phase III trial of preoperative chemotherapy was published by Roth and colleagues[19] from MD Anderson Cancer Center. In this trial, 60 patients with potentially resectable clinical stage IIIA NSCLC were randomized to receive preoperative chemotherapy and then surgery or surgery alone. Median survival time was 21 months in patients treated with neoadjuvant chemotherapy and 14 months for other patients not receiving medical treatment ($P = .056$). The 5-year survivals for the perioperative chemotherapy group and the surgery-alone group were 36% and 15%, respectively.

Despite these impressive results, larger trials did not confirm the benefit of neoadjuvant chemotherapy for patients with cN2 disease.

In addition to these studies, 2 meta-analyses explored the role of induction chemotherapy in patients with NSCLC with or without lymph node involvements showing a better effect of treatment of more advanced stages. In the first study, Berghmans and colleagues[20] analyzed data from 6 randomized trials, published between 1990 and 2003, based on a comparison of induction chemotherapy followed by surgery versus surgery alone for a total of 590 patients. Only in 4 of these trials, patients with stage III NSCLC only were included. The results of this meta-analysis showed the greatest efficacy of induction chemotherapy in the subgroup of patients with clinical resectable stage IIIA-N2 NSCLC at initial workup with an HR of 0.65 (95% CI, 0.41–1.04; $P = .02$) for survival. The second meta-analysis published in 2006 by Burdett and colleagues,[21] based on 12 trials, including 988 patients, showed improved survival for patients treated with preoperative chemotherapy with an HR of 0.82 (95% CI, 0.69–0.97), a 5-years absolute benefit of 6% (similar to adjuvant therapy), and increasing OS across all stages of disease from 14% to 20% at 5 years. This benefit seems to increase for higher stages (and consequently for higher nodal involvement): stage IA, +4%; stage IB, +6%; and stage II-III, +7%.

Furthermore, the rate of nodal response to induction chemotherapy and the clearance of mediastinal lymph nodes in cN2 operable tumors, in particular, have been hypothesized to be also a prognostic factor. Although many studies evaluate the effect in survival of adjuvant and/or neoadjuvant chemotherapy, there are only a few trials that assessed the impact of chemotherapy on lymph node downstaging before surgery.

In 2000, Bueno and colleagues[22] published the results of their study that determined the predictive value of nodal status at resection in regard to long-term outcome of patients undergoing neoadjuvant therapy and resection for stage IIIA-N2–positive NSCLC. In this study, 103 patients were enrolled (44 woman and 59 men); of these, 55 patients had adenocarcinoma, 33 had squamous cell carcinoma, 9 had undifferentiated NSCLC, 5 had large cell cancer, and 1 patient had adenosquamous carcinoma. All the patients enrolled in this study had an involvement of lymphatic system; 57 patients had paratracheal lymph node involvement, 30 had subcarinal lymph node involvement, 29 had aortopulmonary window or subaortic lymph node involvement, and 2 had pulmonary ligament lymph node involvement. After induction chemotherapy, 2 patients showed a complete pathologic response with downstaging to T0N0. In 18 patients the disease downstaged to stage N0 and in 21 to N1, whereas 37 patients remained N2 positive at resection. Before surgery, 74 patients received an additional treatment; 58 patients received radiotherapy, 14 concomitant chemotherapy and radiation therapy, and 2 chemotherapy alone. The results showed a 5-year survival of 17.5%, with

a median survival of 17.8 months. In a subgroup of 29 patients in whom the disease downstaged to N0, the 5-year survival was 35.8%, with a median survival of 21.3 months. The freedoms from recurrence at 12 and 24 months were 71% (CI, 51%–85%) and 43% (CI, 25%–60%), respectively, for patients who were node negative at the time of resection. The freedom from recurrence at the same time intervals for patients who were node positive at the time of resection was significantly lower (43% [CI, 31%–55%] and 22% [CI 12%–33%]). The results of this interesting trial revealed that there were 2 significant and independent factors associated with improved cancer-free survival in these patients: freedom from nodal disease at resection and histology other than adenocarcinoma.[22]

A Belgian experience including 92 patients with pathology-confirmed operable cN2 NSCLC showed a downstaging (ypN0-1) of mediastinal lymph nodes in 43% of the sample treated with induction chemotherapy. A trend for better survival in those patients was observed, with a 5-years survival of 49% versus 27% in patients with persistent N2 disease ($P = .095$). Maybe, this was not significant because patients with persistent N2 disease underwent radiotherapy. Moreover, in patients with pN2 disease, a significant difference in 5-years survival was found between those with single-level versus multilevel nodal involvement (37% vs 7.1%; $P<.005$).[23] Multilevel ypN2 and ypN3 had been identified as negative prognostic factors in previous reporting,[24,25] and recent series confirm a significant difference in survival between patients with and without downstaged mediastinal lymph nodes after induction chemotherapy as if the sterilization of the mediastinum could be an important predictor of good outcome.[26]

COMMENT

The therapeutic strategy of NSCLC has undergone deep changes over the past year with the introduction of new chemotherapeutic and target agents in clinical practice. Despite considerable progress over the last decade, the prognosis of this disease remains severe with a 5-year survival rate of 16% to 49% for radically resected cases and about 2% for inoperable cases.[1]

Approximately 26% to 44% of patients with NSCLC present mediastinal lymph node involvement at diagnosis, which is the most important prognostic factor in early-stage NSCLC, and multimodal treatments show a better influence on survival than surgery alone in patients with lymph node metastatic disease. Based on currently available data, adjuvant chemotherapy is considered a standard treatment in patients with stage II-IIIA tumor radically operated who recovered after surgery in good general condition and do not have contraindications to the use of platinum with approximately a 5-years survival of 5%.[11] At present, platinum-based doublet as adjuvant chemotherapy is recommended for patients with completely resected stage II and IIIA, for no more than 4 cycles and should be initiated no later than 2 months by surgery,[27] for the high recurrence of metastatic disease (about 60%–70%).[28,29] The poor survival rates after surgery alone in cN2 disease has led to designing protocols with neoadjuvant therapy before nonsurgical treatment (radiotherapy and/or chemotherapy), especially to convert to surgery "unresectable" tumor, eradicate any micrometastases, and improve long-term survival of resectable cN2 NSCLC. Andre and colleagues[28] investigated the heterogeneity of mediastinal lymph node involvement in 702 patients treated with surgical resection of N2 NSCLC. In these patients, the 5-year survivals rate varied according to N2 characteristics: one level involvement with microscopic disease (34%), multiple level lymph nodes with microscopic disease (11%), single-level clinically apparent disease (8%), and multilevel clinically apparent disease (3%). Neoadjuvant or induction chemotherapy offers different potential advantages compared with adjuvant chemotherapy, such as improved compliance, drug delivery, early control of micrometastases, and shrink tumor volume before surgery, thus allowing for more conservative and possibly complete cancer resection.[29] At present, the role of induction chemotherapy remains ill defined, but it is emerging in technically resectable stage IIIA-N2 disease.[20,21] Patients with cN3 disease are not thought to be candidates for surgery and they are treated with concurrent chemotherapy/radiation therapy. In patients with stage IIIA - N2 NSCLC the 5-years survival is from 20% to 30% compared with 5% to 10% for surgery alone.[16] The disease in patients with documented pathologic mediastinal lymph node disease will be found at surgery to be downstaged after multimodality therapy in approximately 45% to 65% of the cases.[22,30,31] Mediastinal clearance and complete resection of tumor in these patients has been associated with a 3-year survival of 53% to 61%, compared with 11% to 18% for those without mediastinal clearance. These evidences suggest that mediastinal nodal sterilization is the strongest predictor of long-term survival, and it could be a surrogate marker for eradication of distant chemotherapy-sensitive micrometastases.[32,33] Surgical resection should be avoided in patients after induction therapy who have definite biopsy-proven residual tumor in the

mediastinal nodes, and definitive chemotherapy/radiotherapy treatment should be preferred.

Based on the contradictory results and limitations of phase 2 and 3 clinical trials, the benefit of induction chemotherapy in patients with resectable stage IB-II-IIIA selected disease remains uncertain, and additional studies are warranted to further address this issue.

SUMMARY

Pathologic lymph node involvement is an important prognostic factor for patients with NSCLC. Several trials showed that lung cancer resection combined with complete lymph node dissection is associated with a modest improvement in survival. In these cases, chemotherapy in adjuvant or neoadjuvant settings can improve the survival rate. The role of chemotherapy in patients with lymph node involvement depends from stage at diagnosis. In stage II and IIIA, different studies indicate that cisplatin-based adjuvant chemotherapy improves 5-year survival, whereas the use of adjuvant chemotherapy in stage I remains controversial. Induction chemotherapy presents different benefits over adjuvant chemotherapy, particularly for stage IIIA-N2 disease. In these patients, neoadjuvant chemotherapy should be considered the standard of care, to shrink tumor size and eradicate micrometastases, with a better tolerability than adjuvant treatment. Despite these encouraging results, further studies are needed to define the role of preoperative and postoperative chemotherapy in NSCLC early stage with lymph node involvement. Although clinical and pathologic prognostic factors drive the selection of the best treatment, in patients with lymph node involvements, a multimodal approach between surgery, chemotherapy, and radiotherapy is needed not only to improve survival but also to keep a good quality of life.

REFERENCES

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2010. CA Cancer J Clin 2010;60(5):277–300.
2. Ries L, Eisner M, Kosary C, et al. Cancer statistics review, 1975-2002. Bethesda (MD): National Cancer Institute; 2005. Available at: http://seer.cancer.gov/. Accessed August 13, 2010.
3. Martini N, Bains MS, Burt ME, et al. Incidence of local recurrence and second primary tumors in resected stage I lung cancer. J Thorac Cardiovasc Surg 1995;109(1):120–9.
4. Maeda R, Yoshida J, Ishii G, et al. Poor prognostic factors in patients with stage IB non-small cell lung cancer according to the seventh edition TNM classification. Chest 2011;139(4):855–61.
5. Webb WR, Gatsonis C, Zerhouni EA, et al. CT and MR imaging in staging non-small cell bronchogenic carcinoma: report of the Radiologic Diagnostic Oncology Group. Radiology 1991;178(3):705–13.
6. Toloza EM, Harpole L, McCrory DC. Noninvasive staging of non-small cell lung cancer: a review of the current evidence. Chest 2003;123(Suppl 1): 137S–46S.
7. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008; 26(21):3552–9.
8. PORT Meta-analysis Trialists Group. Postoperative radiotherapy for non-small cell lung cancer. Cochrane Database Syst Rev 2005;2:CD002142.
9. Crino' L, Weder W, Van Meerbeeck J, et al. Early stage and locally advanced (non-metastatic) non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21(Suppl 5):v103–15.
10. Scagliotti GV, Fossati R, Torri V, et al. Randomized study of adjuvant chemotherapy for completely resected stage I, II, or IIIA non–small-cell lung cancer. J Natl Cancer Inst 2003;95(19):1453–61.
11. The International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected nonsmall cell lung cancer. N Engl J Med 2004;350: 351–60.
12. Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB–IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol 2006;7:719–27.
13. Butts CA, Ding K, Seymour L, et al. Randomized phase III trial of vinorelbine plus cisplatin compared with observation in completely resected stage IB and II non–small-cell lung cancer: updated survival analysis of JBR-10. J Clin Oncol 2010;28(1):29–34.
14. Strauss GM, Herndon JE, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non–small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. J Clin Oncol 2008;26(31):5043–51.
15. De Marinis F, Gebbia V, De Petris L. Neoadjuvant chemotherapy for stage IIIA-N2 non-small cell lung cancer. Ann Oncol 2005;16(Suppl 4):iv116–22.
16. Depierre A, Milleron B, Moro-Sibilot D, et al. Preoperative chemotherapy followed by surgery compared with primary surgery in resectable stage I (except T1N0), II, and IIIa non-small-cell lung cancer. J Clin Oncol 2002;20(1):247.

17. Pisters K, Vallie'res E, Crowley J, et al. Surgery with or without preoperative paclitaxel and carboplatin in early-stage non–small-cell lung cancer: Southwest Oncology Group Trial S9900, an intergroup, randomized, phase III trial. J Clin Oncol 2010;28:1843–9.
18. 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(3):153–8.
19. Roth JA, Fossella F, Komaki R, et al. A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. J Natl Cancer Inst 1994;86(9):673–80.
20. Berghmans T, Paesmans M, Meert AP, et al. Survival improvement in resectable non-small cell lung cancer with (neo)adjuvant chemotherapy: results of a meta-analysis of the literature. Lung Cancer 2005;49:13–23.
21. Burdett S, Stewart L, Rydzewska L, et al. A systematic review and meta-analysis of the literature: chemotherapy and surgery versus surgery alone in non-small cell lung cancer. J Thorac Oncol 2006;1:611–21.
22. Bueno R, Richards WG, Swanson SJ, et al. Nodal stage after induction therapy for stage IIIA lung cancer determines patient survival. Ann Thorac Surg 2000;70(6):1826–31.
23. Decaluwé H, De Leyn P, Vansteenkiste J, et al. Surgical multimodality treatment for baseline resectable stage IIIA-N2 non-small cell lung cancer. Degree of mediastinal lymph node involvement and impact on survival. Eur J Cardiothorac Surg 2009;36:433–9.
24. 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(7):603–12.
25. Paul S, Mirza F, Port JL, et al. Survival of patients with clinical stage IIIA non–small cell lung cancer after induction therapy: age, mediastinal downstaging, and extent of pulmonary resection as independent predictors. J Thorac Cardiovasc Surg 2011;141(1): 48–58.
26. Scagliotti GV, Novello S. Current status of adjuvant chemotherapy in NSCLC. Ann Oncol 2006;17:62–3.
27. Betticher DC, Hsu Schmitz SF, Totsch M, et al. Prognostic factors affecting long-term outcomes in patients with resected stage IIIA pN2 non-small-cell lung cancer: 5-year follow-up of a phase II study. Br J Cancer 2006;94(8):1099.
28. 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.
29. Albain KS, Rusch VW, Crowley JJ, et al. Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB non-small-cell lung cancer: mature results of Southwest Oncology Group phase II study 8805. J Clin Oncol 1995;13:1880–92.
30. Pass HI, Pogrebniak HW, Steinberg SM, et al. Randomized trial of neoadjuvant therapy for lung cancer: interim analysis. Ann Thorac Surg 1992;53:992–8.
31. Betticher DC, Hsu Schmitz SF, Totsch M, et al. Mediastinal lymph node clearance after docetaxel-cisplatin neoadjuvant chemotherapy is prognostic of survival in patients with stage IIIA pN2 non-small-cell lung cancer: a multicenter phase II trial. J Clin Oncol 2003;21:1752–9.
32. De WM, Hendriks J, Lauwers P, et al. Nodal status at repeat mediastinoscopy determines survival in non-small-cell lung cancer with mediastinal nodal involvement, treated by induction therapy. Eur J Cardiothorac Surg 2006;29(2):240.
33. Port JL, Korst RJ, Lee PC, et al. Surgical resection for residual N2 disease after induction chemotherapy. Ann Thorac Surg 2005;79(5):1686.