JJCO Japanese Journal of Clinical Oncology

*Japanese Journal of Clinical Oncology*, 2017, 47(12) 1112–1118
doi: 10.1093/jjco/hyx147
Advance Access Publication Date: 9 November 2017
Review Article

OXFORD

Review Article

# Neoadjuvant and adjuvant therapy for Stage III non-small cell lung cancer

**Shun-ichi Watanabe[1,*], Kazuo Nakagawa[1], Kenji Suzuki[2], Kazuya Takamochi[2], Hiroyuki Ito[3], Jiro Okami[4], Keiju Aokage[5], Hisashi Saji[6], Hiroshige Yoshioka[7], Yoshitaka Zenke[8], Tadashi Aoki[9], Yasuhiro Tsutani[10], and Morihito Okada[10], on behalf of the Lung Cancer Surgical Study Group (LCSSG) of the Japan Clinical Oncology Group (JCOG)**

[1]Department of Thoracic Surgery, National Cancer Center Hospital, [2]Division of General Thoracic Surgery, Juntendo University Hospital, Tokyo, [3]Department of Thoracic Surgery, Kanagawa Cancer Center, Kanagawa, [4]Department of Thoracic Surgery, Osaka International Cancer Institute, Osaka, [5]Division of Thoracic Surgery, National Cancer Center Hospital East, Chiba, [6]Department of Chest Surgery, St. Marianna University School of Medicine, Kanagawa, [7]Department of Respiratory Medicine, Kurashiki Central Hospital, [8]Department of Thoracic Oncology and Respiratory Medicine, Tokyo Metropolitan Komagome Hospital, [9]Department of Thoracic Surgery, Niigata Cancer Center, Niigata, and [10]Department of Surgical Oncology, Hiroshima University, Hiroshima, Japan

*For reprints and all correspondence: Shun-ichi Watanabe, Department of Thoracic Surgery, National Cancer Center Hospital, Tsukiji 5-1-1, Chuo-ku, Tokyo 104-0045, Japan. E-mail: syuwatan@ncc.go.jp

Received 15 May 2017; Editorial Decision 15 June 2017; Accepted 23 September 2017

## Abstract

The treatments for advanced non-small cell lung cancer (NSCLC) should control both local and microscopic systemic disease, because the 5-year survival of patients with Stage III NSCLC who underwent surgical resection alone has been dismal. One way to improve surgical outcome is the administration of chemotherapy before or after the surgical procedure. During the last two decades, many clinical studies have focused on developing optimal adjuvant or neoadjuvant chemotherapy regimens that can be combined with surgical treatment and/or radiotherapy. Based on the results of those clinical studies, multimodality therapy is considered to be an appropriate treatment approach for Stage IIIA NSCLC patients; although, optimal treatment strategies are still evolving. When N2 nodal involvement is discovered postoperatively, adjuvant cisplatin-based chemotherapy confers an overall survival benefit. The addition of postoperative radiotherapy might be considered for patients with nodal metastases. Although definitive chemoradiation remains a standard of care for cN2 NSCLC, alternative approaches such as induction chemotherapy or chemoradiotherapy and surgery can be considered for a selective group of patients. When surgical resection can be performed after induction therapy with low risk and a good chance of complete resection, the outcome may be optimal. The decision to proceed with resection after induction therapy must include a detailed preoperative pulmonary function evaluation as well as a critical intraoperative assessment of the feasibility of complete resection.

**Key words:** non-small cell lung cancer, neoadjuvant therapy, adjuvant therapy, induction therapy

## Introduction

Lung cancer remains the leading cause of cancer-related death in many countries, as many patients are diagnosed at an advanced stage (III or IV). Surgery alone results in poor overall survival in patients with Stage III non-small cell lung cancer (NSCLC) because most of them have microscopic distant metastases. Since the 5-year survival of patients with Stage IIIA-N2 NSCLC who underwent surgical resection alone has been dismal (1), the treatments for advanced NSCLC should control both local and microscopic systemic disease. One way to improve surgical outcome is the administration of chemotherapy before or after the surgical procedure. During the last two decades, many clinical studies have focused on developing optimal adjuvant or neoadjuvant chemotherapy regimens for advanced lung cancer that can be combined with surgical treatment and/or radiotherapy.

## Neoadjuvant therapy

Preoperative therapy offers several benefits compared with adjuvant therapy: (1) an increased percentage of patients completing the planned dose of chemotherapy, (2) the ability to treat micrometastatic tumor cell dissemination preoperatively, (3) the ability to evaluate the response to the chemotherapy as a prognostic indicator and (4) increased resectability due to tumor regression.

### Induction chemotherapy

There have been many Phase II trials using induction chemotherapy. Martini et al. (2) published their experience with the administration of two or three cycles of cisplatin, vindesine or vinblastine, and mitomycin followed by surgical resection for 136 patients with 'bulky' N2 disease, which is visible on chest X-ray films. The median survival for all patients was 19 months, and the 3-year survival was 41%, which was significantly better than the historical surgery-only control of 8% ($P = 0.001$). There were significant differences in survival between patients who had a major response to chemotherapy (78% of all patients) compared with those with less than a major response (3-year survival, 34% versus 7%, respectively), as well as between patients who underwent complete resection versus incomplete or no resection (3-year survival, 41% versus 5%, respectively). Survival was greatest in patients with a tumor showing complete pathologic response, with a 71% 3-year survival and 61% 5-year survival. The Phase III neoadjuvant trial results, including Stage IIIA disease, are summarized in Table 1 (3–11). Phase III trials evaluating neoadjuvant chemotherapy followed by surgery versus surgery alone date back to the early 1990s. Two studies reported by Roth (4) and Rosell (5) suggested that induction therapy followed by surgery could lead to improved surgical outcomes; however, recent large-scale multi-institutional studies did not show improved survival in Stage IIIA patients who received neoadjuvant chemotherapy. In 2006, Burdett et al. (12) conducted a systematic review and meta-analysis of the literature describing the results of randomized controlled trials (RCTs) comparing chemotherapy and surgery versus surgery alone, and suggested that there was small benefit of neoadjuvant chemotherapy, but it was based on a small number of trials and patients. NSCLC Meta-analysis Collaborative Group (13) also conducted a systematic review and individual participant data meta-analysis to establish the effect of preoperative chemotherapy for patients with resectable NSCLC. Although it included Stage IB–IIIA patients, the analyses of 15 randomized controlled trials (2385 patients) showed a significant benefit of preoperative chemotherapy on survival (hazard ratio [HR] 0.87, 95% CI 0.78–0.96, $P = 0.007$), an absolute survival improvement of 5% at 5 years, from 40% to 45%.

### Induction chemotherapy with third-generation agents

The results of previous Phase II studies evaluating the efficacy of induction chemotherapy with third-generation agents are shown in Table 2 (14–20). These trials showed the feasibility and potential benefit of induction chemotherapy using a combination of cisplatin and third-generation agents for Stage III patients. Many studies showed promising results with more than a 60% response rate. Since data from Phase III trials with large sample sizes are lacking, an adequate induction chemotherapy regimen is not yet defined.

### Induction chemotherapy or induction chemoradiotherapy (CRT)?

It is unclear whether induction radiotherapy adds benefit when surgery is planned and this is an important clinical question because the addition of each modality increases the possibility of morbidity and mortality related to the treatment. Pless et al. (21) reported the results of Phase III randomized trial investigating whether the addition of neoadjuvant radiotherapy improves outcomes. In this trial, 232 patients were enrolled, of whom 117 were allocated to the chemoradiotherapy group and 115 to the chemotherapy group. Median event-free survival was similar in the two groups at 12.8 months (95% CI 9.7–22.9) in the chemoradiotherapy group and 11.6 months (8.4–15.2) in the chemotherapy group ($P = 0.67$). They

**Table 1.** Phase III trial results including IIIA disease which compared induction chemotherapy and surgery alone

| Primary author | Year | Stage | No of patients | Regimen | Evaluation | Results (%) Induction chemo vs. Surgery alone | *P* value |
|---|---|---|---|---|---|---|---|
| Pass et al. (3) | 1992 | IIIA | 27 | CDDP + ETP | OS at 18 months | 46 vs. 21 | 0.095 |
| Roth (4) | 1994 | IIIA | 60 | CDDP + ETP + CPA | OS at 36 months | 56 vs. 15 | 0.018 |
| Rosell (5) | 1994 | IIIA | 60 | CDDP + IFO + MMC | OS at 60 months | 17 vs. 0 | 0.005 |
| Depierre (6) | 2002 | IB–IIIA | 355 | CDDP + IFO + MMC | OS at 48 months | 44 vs. 35 | 0.15 |
| Nagai/JCOG (7) | 2003 | IIIA | 62 | CDDP + VDS | OS at 36 months | 23 vs. 26 | 0.53 |
| Gilligan (8) | 2007 | IB–IIIA | 519 | Platinum contained | OS at 36 months | 44 vs. 45 | 0.86 |
| Pisters (9) | 2010 | IB–IIIA | 354 | CBDCA + PAC | OS at 60 months | 42 vs. 33 | 0.11 |
| Felip (10) | 2010 | IB–IIIA | 413 | CBDCA + PAC | DFS at 60 months | 38 vs. 34 | 0.176 |
| Scagliotti (11) | 2011 | IB–IIIA | 270 | CDDP + GEM | PFS at 36 months | 53 vs. 48 | 0.03 |

CDDP, cisplatin; CBDCA, carboplatin; MMC, mitomycin; IFO, ifosfamide; CPA, cyclophosphamide; VDS, vindesin; PAC, paclitaxel; OS, overall survival; DFS, disease-free survival; PFS, progression-free survival.

suggested that Radiotherapy did not add any benefit to induction chemotherapy followed by surgery.

To statistically investigate the benefit of neoadjuvant radiation therapy, Shah et al. (22) conducted a systematic review and meta-analysis. They hypothesized that the addition of radiotherapy to induction chemotherapy prior to surgical resection would not improve survival compared with induction chemotherapy alone. They analyzed seven studies (23–29) that met the criteria for analysis, including one randomized control trial, one Phase II study, three retrospective reviews, and two published abstracts of randomized controlled trials. None of the studies demonstrated a survival benefit to adding induction radiotherapy to induction chemotherapy versus induction chemotherapy alone. The meta-analysis of randomized studies demonstrated no survival benefit from adding radiation (hazard ratio [HR]: 0.93; $P = 0.81$), and this was consistent with the results from a meta-analysis performed on retrospective studies (HR: 0.77; $P = 0.24$).

The most promising use of induction CRT is to treat superior sulcus tumors (SST), where preoperative local tumor regression is the key to achieving complete resection. Traditional treatment for SST, radiation plus surgery, yields a 50% rate of complete resection and a 5-year survival rate of 30%. Rush et al. (30) reported the results from the South West Oncology Group (SWOG) 9416 (Intergroup 0160) Phase II trial, which tested the feasibility of induction CRT for SST, on the basis of improved outcomes in other subsets of Stage III NSCLC. From April 1995 to November 1999, 110 eligible patients (76 men, 34 women) with T3-4N0-1 NSCLC-SST were registered (78 T3, 32 T4 tumors). Patients received two cycles of cisplatin and etoposide concurrently with 45 Gy radiation. Patients with stable or responding disease underwent thoracotomy. All patients received two more cycles of chemotherapy. Of the 95 patients eligible for surgery, 88 (80%) underwent thoracotomy, two (1.8%) died postoperatively, and 83 (76%) had a complete resection. Pathologic complete response (CR) or minimal microscopic disease was seen in 61 (56%) resection specimens. The 5-year survival was 44% for all patients and 54% after complete resection, with no difference between T3 and T4 tumors. They concluded that the combined-modality approach was feasible and was associated with high rates of complete resection and pathologic CR in both T3 and T4 tumors. Local control and overall survival seem markedly improved relative to previous studies of radiation plus resection.

Kunitoh et al. (31) also reported similar results from the Japan Clinical Oncology Group (JCOG) Phase II trial (JCOG 9806), which tested the feasibility of induction CRT for NSCLC-SST patients. From May 1999 to November 2002, 76 patients were enrolled, 20 of whom had T4 disease, and 75 patients were fully assessable. Patients received two cycles of chemotherapy every 4 weeks with mitomycin on Day 1, vindesine on Days 1 and 8, and cisplatin 80 on Day 1. Radiotherapy directed at the tumor and the ipsilateral supraclavicular nodes was started on Day 2 of each course, at a total dose of 45 Gy in 25 fractions, with a 1-week split. Thoracotomy was undertaken 2–4 weeks after completion of the CRT. Pathologic complete resection was achieved in 51 patients (68%). There were 12 patients with a pathologic complete response (CR). The disease-free and overall survival rates at 3 years were 49% and 61%, respectively; at 5 years, they were 45% and 56%, respectively. They concluded that the trimodality approach was safe and effective for the treatment of patients with SST.

Some large-scale multi-institutional clinical trials comparing definitive CRT versus induction CRT followed by surgery for Stage III patients are shown in Table 3 (32–36). In 2009, Albain et al. (35) reported results from a multi-institutional Phase III trial (INT0139) comparing CRT with or without surgery for Stage III NSCLC. Although the surgery group showed significantly better progression-free survival than the no surgery group, there was no significant difference in overall survival between the two groups. In this study, the patients underwent pneumonectomy showed higher surgical mortality (26%) and poorer prognosis than those underwent lobectomy.

**Table 2.** Phase II trial results of induction chemotherapy with third-generation agents for Stage III patients

| Primary author | Year reported | Stage | No. of patients | Regimen | Response rate | Median survival | Trial |
|---|---|---|---|---|---|---|---|
| Van Zandwijk (14) | 2000 | IIIA | 47 | CG | 70% | 18.9 months | EORTC08955 |
| Betticher (15) | 2003 | IIIA | 90 | CT | 66% | 33 months | |
| De Marinis (16) | 2003 | IIIA | 49 | CGP | 74% | 23 months | |
| O'Brien (17) | 2003 | IIIA | 52 | CaP | 64% | 20.5 months | EORTC08958 |
| Cappuzzo (18) | 2003 | IIIA–IIIB | 129 | CG | 62% | 19.4 months | |
| Biesma (19) | 2006 | IIIA | 46 | CT | 39% | 16.7 months | EORTC08984 |
| Garrido (20) | 2007 | IIIA–IIIB | 136 | CGT | 56% | 15.9 months | Spanish Lung Cancer Group Trial 9901 |

C, cisplatin; Ca, carboplatin; G, gemcitabine; P, paclitaxel; T, docetaxel.

**Table 3.** Results of induction chemoradiotherapy followed by surgery

| Primary author | Phase | Stage | No. of patients | Regimen | Survival | *P* value | TRD |
|---|---|---|---|---|---|---|---|
| Albain (SWOG8805) (32) | II | IIIA–IIIB | 126 | CRT (45 Gy) + S | IIIA 27%, IIIB 24% (3-year survival) | 0.81 | 10% |
| Albain (Intergroup 0139) (35) | III | IIIA | 429 | CRT (61 Gy) vs. CRT (45 Gy) + S | 20.3% vs. 27.2% (5-year progression-free survival) | 0.10 | 2.1% vs. 7.9% |
| Katayama (33) | II | IIIA–IIIB | 22 | CRT (40-60 Gy) + S | 66% (3-year survival) | — | — |
| Eberhardt (33) | II | IIIA–IIIB | 62 | CRT (45 Gy) + S | 31% (4-year survival) | — | — |
| Eberhardt (ESPATUE) (36) | III | IIIA–IIIB | 161 | CRT (65–71 Gy) vs. CRT (45 Gy) + S | 40% vs. 44% (5-year overall survival) | 0.34 | 2.5% vs. 6.2% |

CRT, chemoradiothrapy; S, surgery; SWOG, South West Oncology Group; TRD, treatment-related death.

However, Weder et al. (37) reported that 176 patients who underwent neoadjuvant therapy followed by pneumonectomy showed only 3% of 90 postoperative day mortality rate in their retrospective evaluation of medical records in two specialized thoracic centers. The significance of adding surgical treatment to CRT for Stage III patients requires further evaluation.

## Adjuvant therapy

### Adjuvant chemotherapy

The NSCLC Collaborative Group (38) reported a meta-analysis of 14 clinical trials addressing the role of adjuvant chemotherapy for resected NSCLC. There was no statistically significant survival benefit in the group of patients who received adjuvant chemotherapy, but a trend toward better survival prompted further studies. Since the 1995 NSCLC Collaborative Group meta-analysis (38) showed a 5% increase in 5-year survival with adjuvant cisplatin-based chemotherapy (HR, 0.87; $P = 0.08$), some multi-institutional randomized controlled trials have reported a significant overall survival benefit all using cisplatin-based doublets except one Japanese UFT study, as shown in Table 4 (39–45).

In 2005, Berghmans et al. (46) performed a meta-analysis of 25 recent randomized trials testing either induction or adjuvant chemotherapy in resectable NSCLC. Twenty-five studies eligible for this analysis were published between 1986 and 2004. They assessed the role of chemotherapy given before ($n = 6$) or after surgery ($n = 19$). A total of 8234 eligible patients, 590 in the induction trials and 7644 in the adjuvant trials, were enrolled. Individually, 11 studies demonstrated a statistically significant survival advantage in favor of the addition of chemotherapy to surgery. The chemotherapy used in these trials included platinum-based regimens that were more effective and better tolerated than those evaluated in the 1995 meta-analysis (38). A HR of 0.84 (95% CI, 0.78–0.89) favoring the use of adjuvant chemotherapy was found. Full planned chemotherapy could be administered in more than 80% of the patients for the majority of the induction trials (range 71–100%); although for adjuvant studies, chemotherapy was administered to more than 80% of the patients (range 24–85%) in only one trial.

Subsequently, the Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis (47) was conducted using individual patient data collected from the five largest trials (4 584 patients) of cisplatin-based adjuvant chemotherapy in completely resected patients with NSCLC (39–41,44,45), performed after the 1995 NSCLC Collaborative Group meta-analysis. This analysis also showed a significant survival benefit with adjuvant chemotherapy, with an overall HR of 0.89, translating into a 5-year absolute survival benefit of 5.4%. The value of chemotherapy was shown to vary with tumor stage. It was suggested that adjuvant chemotherapy was detrimental for Stage IA disease, had an unclear benefit for Stage IB tumors, but was clearly beneficial for patients with resected Stage II/III disease (HR for death for Stage IA, 1.40; 95% CI, 0.95–2.06; Stage IB, 0.93; 95% CI, 0.78–1.10; Stage II, 0.83; 95% CI, 0.73–0.95; Stage III, 0.83; 95% CI, 0.72–0.94).

The LACE meta-analysis (47) also showed that the benefit of adjuvant chemotherapy was not without cost, citing a 66% incidence of Grade 3 or 4 adverse events. A significant interaction was seen between the chemotherapy effect and the World Health Organization performance status (PS) (test for trend, $P = 0.009$ for overall survival and $P = 0.01$ for disease-free survival), with a significantly increased chemotherapy effect with a better PS and possible disadvantage when the PS was 2. As a result of these studies, the standard care for patients who underwent resection of Stage II or III NSCLC now includes adjuvant platinum-based chemotherapy.

In 2010, the NSCLC Meta-analyses Collaborative Group (48) reported on a meta-analysis of 34 clinical trials, with 8447 patients (3 323 deaths), addressing the benefit of adjuvant chemotherapy for resected NSCLC. Among those trials, the overall HR for survival in patients who received cisplatin-based adjuvant chemotherapy suggested absolute improvements in 5-year survival of 3% for Stage IA (from 70% to 73%), 5% for Stage IB (from 55% to 60%), 5% for Stage II (from 40% to 45%), and 5% (3–8) for Stage III disease (from 30% to 35%).

### Adjuvant radiotherapy

The role of postoperative radiotherapy (PORT) in the treatment of patients with completely resected NSCLC is not as clear as that of chemotherapy. In 1988, the PORT Meta-analysis Trialists Group (49) collected individual data on 2128 patients from nine available randomized trials of PORT versus surgery alone. They reported a 21% relative increase in the risk of death, which was equivalent to an absolute detriment of 7% at 2 years, with PORT reducing overall survival from 55% to 48% after resection. Subgroup analysis suggested that the adverse effect on overall survival was most notable for patients with Stage I/II (N0–N1) tumors; whereas, there was no clear evidence of either adverse effects or benefits for Stage III disease. The results of the PORT meta-analysis, however, are probably not applicable to current therapy because of recent major improvements in radiation treatment planning and delivery. In a retrospective analysis, Lally et al. (50) reported on a large database of patients with resected NSCLC who received PORT between 1988 and 2002 ($n = 7465$) using the Surveillance, Epidemiology, and End Results Program (SEER) database. This retrospective study revealed no adverse impact on overall survival. Subset analyses showed a significant decrease in survival for patients with N0 (HR, 1.1176; $P = 0.0435$)

**Table 4.** Phase III trials of adjuvant chemotherapy including Stage IIIA non-small cell lung cancer

| Trial | Year | Overall survival HR (95% CI) | | | |
|---|---|---|---|---|---|
| | | All stages | Stage I | Stage II | Stage IIIA |
| ALPI (39) | 2002 | 0.96 (0.81–1.13) | 0.97 (0.71–1.33) | 0.80 (0.60–1.06) | 1.06 (0.82–1.38) |
| IALT (40) | 2004 | 0.86 (0.76–0.98) | 0.95 (0.74–1.23) | 0.93 (0.72–1.20) | 0.79 (0.66–0.95) |
| BLT (41) | 2004 | 1.02 (0.77–1.35) | Not tested | Not tested | Not tested |
| CALGB9633 (42) | 2004 | 0.80 (0.60–1.07) | 0.80 (0.60–1.07) | Not tested | Not tested |
| UFT/Kato (43) | 2004 | 0.71 (0.52–0.98) | 0.71 (0.52–0.98) | Not tested | Not tested |
| JBR.10 (44) | 2005 | 0.69 (0.52–0.91) | 0.94 | 0.59 (0.42-0.85) | Not tested |
| ANITA (45) | 2006 | 0.80 (0.66–0.96) | 1.14 (0.83–1.57) | 0.67 (0.47–0.94) | 0.60 (0.44–0.82) |

and N1 disease (HR, 1.097; $P = 0.0196$) but significantly improved survival for patients with N2 disease (HR, 0.8555; $P = 0.0077$). In addition, an unplanned subset analysis of patients who received PORT in the Adjuvant Navelbine International Trialist Association (ANITA) (45) randomized study of adjuvant chemotherapy suggested PORT had a positive effect in patients with pN2 disease and a negative effect in patients with pN1 disease. In summary, these data suggest that PORT may be appropriate for patients with Stage IIIA (N2) disease. At a minimum, PORT reduces the risk of loco-regional recurrence and might improve overall survival for these patients.

## Induction or adjuvant chemotherapy?

Which is the better treatment, induction or adjuvant chemotherapy? Some concern has arisen regarding adjuvant chemotherapy compliance, with most trials involving cisplatin doublets reporting delivery of only 60% of the planned treatments. The (Neo) adjuvant Taxol/Carboplatin Hope (NATCH) trial (10) compared the prognosis of patients who received neoadjuvant chemotherapy, adjuvant chemotherapy, and surgery alone. The NATCH trial was conducted between April 2000 and March 2007, and a total of 624 patients from 42 centers in Spain, Germany, Portugal, Sweden, and Switzerland were randomly assigned to one of three arms. A total of 212 patients were assigned to the surgery arm, 201 to the preoperative chemotherapy group, and 211 to the adjuvant group. There were no statistical differences in the prognosis between these three groups. However, the NATCH trial compared induction and adjuvant chemotherapy only for Stage I, II and some Stage IIIA (T3N1) patients. No Phase III study has compared induction and adjuvant chemotherapy for Stage III-N2 patients. Nevertheless, induction chemotherapy seems better tolerated with more than 80% of patients receiving the full planned treatment, which is an improvement over adjuvant chemotherapy. In the LACE meta-analysis (47), 33% of patients in the chemotherapy arm did not receive the planned chemotherapy regimen, reflecting the difficulty of administering taxing adjuvant chemotherapy to a postoperative population.

## Consolidative therapies (PORT and chemotherapy after induction chemotherapy)

Amini et al. (51) reported the role of consolidation therapy for resected Stage III NSCLC with persistent N2 disease after induction chemotherapy. They concluded that aggressive consolidative therapies (PORT and chemotherapy) may improve outcomes for patients with persistent N2 disease after induction chemotherapy and surgery. However, the data from Phase III trials are lacking and there is no evidence regarding the efficacy of consolidative therapy.

## Future directions

In order to improve dismal surgical outcome of IIIA-N2 disease, the administration of chemotherapy and/or radiotherapy before or after the surgical procedure should be considered by multidisciplinary team. Optimal adjuvant or neoadjuvant therapy regimens should be evaluated by multi-institutional large-scale RCTs. For cN0-1pN2 disease, adjuvant chemotherapy with molecular-targeted agents and adjuvant immunotherapy should be explored. For cN2 disease, induction chemotherapy or immunotherapy with or without radiotherapy followed by surgery can be considered for a selective group of patients

## Conclusions

Multimodality therapy is an appropriate treatment approach for Stage IIIA NSCLC patients; although, optimal treatment strategies are still evolving. When N2 nodal involvement is discovered postoperatively, adjuvant cisplatin-based chemotherapy confers an overall survival benefit. The addition of PORT might be considered for patients with hilar or mediastinal nodal metastases. Although definitive chemoradiation remains a standard of care for cN2 NSCLC, alternative approaches such as induction chemotherapy with or without radiotherapy and surgery can be considered for a selective group of patients. When surgical resection can be performed after induction therapy with low risk and a good chance of complete resection, the outcome may be optimal. The decision to proceed with resection after induction therapy must include a detailed preoperative pulmonary function evaluation as well as a critical intraoperative assessment of the feasibility of complete resection.

## Conflict of interest statement

None declared.

## References


1. Martini N, Flehinger BJ. The role of surgery in N2 lung cancer. *Surg Clin North Am* 1987;67:1037–49.
2. Martini N, Kris MG, Flehinger BJ, et al. Preoperative chemotherapy for stage IIIa (N2) lung cancer: the Sloan-Kettering experience with 136 patients. *Ann Thorac Surg* 1993;55:1365–74.
3. Pass HI, Pogrebniak HW, Steinberg SM, Mulshine J, Minna J. Randomized trial of neoadjuvant therapy for lung cancer: interim analysis. *Ann Thorac Surg* 1992;53:992–8.
4. Roth JA, Fossella F, Komaki R, et al. A randomised trial comparing perioperative chemotherapy and surgery and surgery alone in resectable stage IIIA non-small cell lung cancer. *JNCI* 1994;86:673–80.
5. Rosell R, Gómez-Codina J, Camps C, et al. A randomized trial comparing pre-operative chemotherapy plus surgery with surgery alone in patients with non-small cell lung cancer. *N Engl J Med* 1994;330:153–8.
6. Depierre A, Milleron B, Moro-Sibilot D, et al. Pre-operative 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;20:247–53.
7. Nagai K, Tsuchiya R, Mori T, et al., Lung Cancer Surgical Study Group of the Japan Clinical Oncology Group. A randomised trial comparing induction chemotherapy followed by surgery with surgery alone for patients with stage IIIa N2 non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2003;125:254–60.
8. Gilligan D, Nicolson M, Smith I, et al. Preoperative chemotherapy in patients with resectable non-small cell lung cancer: results of the MRC LU22/NVALT 2/EORTC 08012 multicentre randomised trial and update of systematic review. *Lancet* 2007;369:1929–37.
9. Pisters KM, Vallières E, Crowley JJ, 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.
10. Felip E, Rosell R, Maestre JA, et al., Spanish Lung Cancer Group. Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non-small-cell lung cancer. *J Clin Oncol* 2010;28:3138–45.
11. Scagliotti GV, Pastorino U, Vansteenkiste JF, et al. Randomized phase III study of surgery alone or surgery plus preoperative cisplatin and gemcitabine in stages IB to IIIA non-small-cell lung cancer. *J Clin Oncol* 2012;30:172–8.

12. Burdett S, Stewart LA, Rydzewska L. 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.
13. NSCLC Meta-analysis Collaborative Group. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. *Lancet* 2014;383:1561–71.
14. Van Zandwijk N, Smit EF, Kramer GW, et al. Gemcitabine and cisplatin as induction regimen for patients with biopsy-proven stage IIIA N2 non-small-cell lung cancer: a phase II study of the European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group (EORTC 08955). *J Clin Oncol* 2000;18:2658–64.
15. Betticher DC, Hsu Schmitz SF, Tötsch 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.
16. De Marinis F, Nelli F, Migliorino MR, et al. Gemcitabine, paclitaxel, and cisplatin as induction chemotherapy for patients with biopsy-proven Stage IIIA(N2) nonsmall cell lung carcinoma: a Phase II multicenter study. *Cancer* 2003;98:1707–15.
17. O'Brien ME, Splinter T, Smit EF, et al., EORTC Lung Cancer Group. Carboplatin and paclitaxol (Taxol) as an induction regimen for patients with biopsy-proven stage IIIA N2 non-small cell lung cancer. an EORTC phase II study (EORTC 08958). *Eur J Cancer* 2003;39:1416–22.
18. Cappuzzo F, Selvaggi G, Gregorc V, et al. Gemcitabine and cisplatin as induction chemotherapy for patients with unresectable Stage IIIA-bulky N2 and Stage IIIB nonsmall cell lung carcinoma: an Italian Lung Cancer Project Observational Study. *Cancer* 2003;98:128–34.
19. Biesma B, Manegold C, Smit HJ, et al., EORTC Lung Cancer Group. Docetaxel and cisplatin as induction chemotherapy in patients with pathologically-proven stage IIIA N2 non-small cell lung cancer: a phase II study of the European organization for research and treatment of cancer (EORTC 08984). *Eur J Cancer* 2006;42:1399–406.
20. Garrido P, González-Larriba JL, Insa A, et al. Long-term survival associated with complete resection after induction chemotherapy in stage IIIA (N2) and IIIB (T4N0-1) non small-cell lung cancer patients: the Spanish Lung Cancer Group Trial 9901. *J Clin Oncol* 2007;25:4736–42.
21. Pless M, Stupp R, Ris HB, Stahel RA, Weder W, Thierstein S, et al. Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial. *Lancet* 2015;386:1049–56.
22. Shah AA, Berry MF, Tzao C, et al. Induction chemoradiation is not superior to induction chemotherapy alone in stage IIIA lung cancer. *Ann Thorac Surg* 2012;93:1807–12.
23. Girard N, Mornex F, Douillard JY, et al. Is neoadjuvant chemoradiotherapy a feasible strategy for stage IIIA-N2 non-small cell lung cancer? Mature results of the randomized IFCT-0101 phase II trial. *Lung Cancer* 2010;69:86–93.
24. Fleck J, Carmargo J, Godoy D, Teixeria P, Braga Fiho A, Banetta A. Chemoradiation therapy (CRT) versus chemotherapy (CT) alone as a neoadjuvant treatment for stage III non-small cell lung cancer (NSCLC). Preliminary report of a phase III prospective randomized trial. *Proc Am Soc Clin Oncol* 1993;12:333.
25. Sauvaget J, Rebischung J, Vannetzel J, et al., GEARC, France; Fondation Hosp Saint Joseph, Paris, France. Phase III study of neo-adjuvant MVP versus MVP plus chemo-radiation in stage III NSCLC. *Proc Am Soc Clin Oncol* 2000;19:495a.
26. Thomas M, Rübe C, Hoffknecht P, et al., German Lung Cancer Cooperative Group. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer. *Lancet Oncol* 2008;9:636–48.
27. Pezzetta E, Stupp R, Zouhair A, et al. Comparison of neoadjuvant cisplatin-based chemotherapy versus radiochemotherapy followed by resection for stage III (N2) NSCLC. *Eur J Cardiothorac Surg* 2005;27:1092–8.
28. Li J, Dai CH, Shi SB, Chen P, Yu LC, Wu JR. Prognostic factors and long term results of neo adjuvant therapy followed by surgery in stage IIIA N2 non-small cell lung cancer patients. *Ann Thorac Med* 2009;4:201–7.
29. Higgins K, Chino JP, Marks LB, et al. Preoperative chemotherapy versus preoperative chemoradiotherapy for stage III (N2) non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2009;75:1462–7.
30. Rusch VW, Giroux DJ, Kraut MJ, et al. Induction chemoradiation and surgical resection for superior sulcus non-small-cell lung carcinomas: long-term results of Southwest Oncology Group trial 9416 (Intergroup trial 0160). *J Clin Oncol* 2007;25:313–8.
31. Kunitoh H, Kato H, Tsuboi M, et al., Japan Clinical Oncology Group. Phase II trial of preopeperative chemoradiotherapy followed by surgical resection in patients with superior sulcus non-small-cell lung cancers: report of Japan Clinical Oncology Group trial 9806. *J Clin Oncol* 2008;26:644–9.
32. 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.
33. Katayama H, Ueoka H, Kiura K, et al. Preoperative concurrent chemoradiotherapy with cisplatin and docetaxel in patients with locally advanced non-small-cell lung cancer. *Br J Cancer* 2004;90:979–84.
34. Eberhardt WE, Wilke H, Stamatis G, et al. Preoperative chemotherapy followed by concurrent chemoradiation therapy based on hyperfractionated accelerated radiotherapy and definitive surgery in locally advanced non-small-cell lung cancer: mature results of a phase II trial. *J Clin Oncol* 1998;16:622–34.
35. 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;374:379–86.
36. Eberhardt WE, Pöttgen 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;33:4194–201.
37. Weder W, Collaud S, Eberhardt WE, et al. Pneumonectomy is a valuable treatment option after neoadjuvant therapy for stage III non-small-cell lung cancer. *J Thorac Cardiovasc Surg* 2010;139:1424–30.
38. Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. *BMJ* 1995;311:899–909.
39. Scagliotti GV, Fossati R, Torri V, et al. Adjuvant Lung Project Italy/European Organisation for Research Treatment of Cancer-Lung Cancer Cooperative Group Investigators. Randomized study of adjuvant chemotherapy for completely resected stage I, II, or IIIA non-small-cell Lung cancer. *J Natl Cancer Inst* 2003;95:1453–61.
40. Arriagada R, Bergman B, Dunant A, et al., International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med* 2004;350:351–60.
41. Waller D, Peake MD, Stephens RJ, et al. Chemotherapy for patients with non-small cell lung cancer: the surgical setting of the Big Lung Trial. *Eur J Cardiothorac Surg* 2004;26:173–82.
42. Strauss GM, Herndon JE 2nd, 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;26:5043–51.
43. Kato H, Ichinose Y, Ohta M, et al., Japan Lung Cancer Research Group on Postsurgical Adjuvant Chemotherapy. A randomized trial of adjuvant chemotherapy with uracil-tegafur for adenocarcinoma of the lung. *N Engl J Med* 2004;350:1713–21.
44. Winton T, Livingston R, Johnson D, et al., National Cancer Institute of Canada Clinical Trials Group. National Cancer Institute of the United States Intergroup JBR.10 Trial Investigators. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. *N Engl J Med* 2005;352:2589–97.
45. 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.
46. 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.
47. Pignon JP, 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;26:3552–9.
48. NSCLC Meta-analyses Collaborative Group. Arriagada R, Auperin A, Burdett S, et al. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. *Lancet* 2010;375:1267–77.
49. PORT Meta-analysis Trialists Group. Post-operative radiotherapy in non-small cell lung cancer: systematic review and meta-analysis of individual patient data from 9 randomised controlled trials. *Lancet* 1998;352:257–63.
50. Lally BE, Zelterman D, Colasanto JM, et al. Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results database. *J Clin Oncol* 2006;24:2998–3006.
51. Amini A, Correa AM, Komaki R, et al. The role of consolidation therapy for stage III non-small cell lung cancer with persistent N2 disease after induction chemotherapy. *Ann Thorac Surg* 2012;94:914–20.