Review Article

Management of stage IIIA non-small cell lung cancer (NSCLC): role of the chemotherapy

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Abstract: Lung cancer is the leading cause of cancer-related death, with an incidence that continues to increase in both sexes and all ages. Roughly 80–90% of lung cancers are non-small cell lung cancer (NSCLC), the remaining 10–20%, small cell lung cancer (SCLC), has seen its frequency going down globally over the two past twenty years. Adenocarcinoma is the most common histologic subtype of lung cancer in men and women in US, Canada, many European countries and Japan. Nearly 30% of patients with (NSCLC) will get diagnosed with early-stage (I-IIIA) and in spite of radical surgery the survival remains rather poor. Stage IIIA NSCLC is a very heterogeneous group, encompassing small primary T1a tumors with mediastinal lymph nodes (N2) to locally advanced T4 disease with or without any nodal involvement. Treatment remains challenging hence the need for a multidisciplinary management for all these cases. Oncologist, radiation oncologist and surgeon are essential to deliver the best possible care in this context. Here we have reviewed the evidence about the management of stage IIIA, with particular emphasis on the chemotherapy treatment.

Keywords: Non-small cell lung cancer (NSCLC); radio-chemotherapy; surgery; staging; multidisciplinary team

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Introduction

Lung cancer remains the leading cause of cancer-related death, with an incidence that continues to increase in both sexes and all ages (1). In women, rising lung cancer incidence has slowed in the US and UK, but rates continue to rise in central and eastern Europe. Tobacco smoking remains the main cause of lung cancer and the geographical and temporal patterns of the disease largely reflect tobacco consumption during the previous decades. Both smoking prevention and cessation can lead to a reduction in a large fraction of lung cancers (2).

Non-small cell lung cancer (NSCLC) accounts for 80-90% of lung cancers, while small cell lung cancer (SCLC) has been decreasing in frequency in many countries over the past two decades. Adenocarcinoma is the most common histologic subtype of lung cancer in men and women in US, Canada, many European countries and Japan.

Classification and staging of lung cancer is based on the 8th edition of the American Joint Commission on Cancer (AJCC). Nearly a third of the patients NSCLC will present with early-stage (I-IIIA) disease (3). Based on the 8th edition of TNM staging, 5-year overall survival (OS) rates range between 60% to 74% for stage I, 47% to 55% for stage II, and 38% for stage IIIA (4). In a high proportion of patients' surgery remains the cornerstone of treatment, in particular, in stage I and II. In this context the best approach remains surgery with the aim to completely resect the cancer. This offers the best chance of long-term survival (5). A tumor more than 4 cm is an unfavorable prognostic element, as well as lymph nodes involvement, and this leads to discuss the prescription of an adjuvant

therapy. Adjuvant chemotherapy is a well-established option in case of lymph nodes involvement and in case of tumors >4 cm. The OS benefit is approximately 5% at 5 years (6). For "locally advanced" disease, such as N3 or multi-station N2), concurrent definitive radio-chemotherapy has been accepted globally as a standard of care (7). Treatment for stage IV is systemic therapy depending on histology and genomic profiles. Recently, immunotherapy, namely immune checkpoint inhibitors, and targeted therapy have revolutionized the treatment paradigm in NSCLC (8). A possible exception could be oligometastatic disease where a more aggressive approach could be justified in case of initial response to systemic treatment (9). The management of patients with stage III disease remains quite challenging.

Management of NSCLC stage IIIA

Is there a standard of care?

Stage IIIA NSCLC is a very heterogeneous group, encompassing small primary T1a tumors with mediastinal lymph nodes (N2) to locally advanced T4 disease with or without any nodal involvement. This heterogeneity explains such a wide range for the 5-year survival rate of patients with stage IIIA NSCLC (<10% to 50%) (10).

A precise staging is also important, and a discussion in a multidisciplinary team is absolutely mandatory. Three modalities can be considered: definitive radio-chemotherapy versus radiotherapy and or chemotherapy followed by surgery. A meta-analysis of six trials (868 patients) published in 2015 evaluated survival outcomes of patients with N2 disease in multimodality trials of chemotherapy, radiotherapy and surgery (11). In trials where patients received surgery with chemotherapy or with chemo-radiotherapy, OS was not superior to the one with chemo-radiotherapy, either sequentially or concurrently. Two trials in the meta-analyses explored the trimodality treatments. One is an American trial, INT 0139, which explored induction by chemo-radiotherapy followed by surgery or further radiotherapy (12). There was no significant survival advantage with surgery after chemo-radiotherapy. Progression free survival (PFS) which was a secondary endpoint was improved with surgery (12.8 *vs.* 10.5 months, HR 0.77). The authors justified the lack of OS benefit with surgery by the high postoperative death rate following pneumonectomy, predominantly due to acute respiratory distress syndrome (ARDS) and other respiratory causes. An unplanned subgroup analysis which excluded patients who underwent pneumectomy, showed better survival in the surgical arm (median survivals: 33.6 *vs.* 21.7 months, logrank P=0.002, with 5-year survivals of 36.1% *vs.* 17.8%). In the European trial, EORTC 08941, patients received 3 cycles of platinum based induction chemotherapy before randomization between surgery and radiotherapy (13). Surgical resection did not improve OS or PFS compared to radiotherapy. Neither trial is very recent, patients were recruited between 1994 and 2001 for the US trial and between 1994 and 2002 for the European trial, and it is reasonable to ask ourselves if the results would be the same with the advances in both domains today. A more recent trial, ESPATUE (14), compared surgery with definitive chemo-radiotherapy in resectable stage IIIA (N2) and selected stage IIIB patients. They received induction chemotherapy with cisplatin and docetaxel followed by concurrent chemo-radiotherapy (45 Gy) with cisplatin and vinorelbine. Patients deemed resectable were randomized between chemo-radiotherapy boost (65/71 Gy) or surgery. The final result did not show any OS or PFS difference among the 2 modalities.

High morbidity and mortality rates can be observed with surgery, but it is also the case with chemo-radiotherapy, for instance, tumor cavitation (15). This phenomenon has been reported in 10–20% of all lung carcinomas and is due to tumor necrosis (16). More than 50% of patients with stage III NSCLC and tumor cavitation developed acute pulmonary toxicity of grade III or more, on chemo-radiotherapy. In this case, surgery would seem a valid alternative. No clear standard of care has emerged from these trials. As always, comorbidities and patient preferences are essential to identify the final therapeutic approach.

Role of the chemotherapy

As we discussed before, chemotherapy plays a very important role in stage IIIA NSCLC, either with radiotherapy or in induction therapy before surgery.

Induction chemotherapy

Several phase II trials have been published using induction chemotherapy with interesting findings (17), in particular showing higher complete resection rates in patients receiving chemotherapy up-front. Two major phase III trials assessing neoadjuvant chemotherapy

Table 1 Induction chemotherapy regimen

Induction chemotherapy regimen	Trial
Cisplatin, cyclophosphamide, vindesine	Dautzenberg *et al.* (France 1990)
Cisplatin, cyclophosphamide, etoposide	Roth *et al.* (MD Anderson 1994)
Cisplatin, mitomycin, ifosfamide	Rosell *et al.* (Spain 1994), Depierre *et al.*, MIP-91 (2002)
Cisplatin, vindesine	Nagai *et al.*, JCOG 9209 (2003)
Cisplatin, mitomycin, vinblastine	De Boer *et al.* (Netherlands 2000)
Cisplatin, mitomycin + ifosfamide or vinblastine, or cisplatin, vindesine, or cisplatin, vinorelbine	Waller *et al.*, MRC BLT (2004)
Cisplatin, mitomycin, vindesine	Yi *et al.*
Carboplatin, paclitaxel	Sorensen *et al.* (2006), Pisters *et al.*, SWOG S9900 (2010), Felip *et al.*, NATCH (Spain 2010)
Carboplatin, docetaxel	Wu *et al.* (China 2002)
Cisplatin, gemcitabine	Scagliotti *et al.*, CHEST (2012)
Docetaxel q3w	Mattson *et al.* (Finland 2003)

followed by surgery versus surgery alone were conducted in the 1990s (18,19). Both studies showed that neoadjuvant chemotherapy could improve surgical outcomes; those data were not confirmed in multicentric randomised phase III trials (20). Furthermore, a NSCLC meta-analysis Collaborative Group conducted a systematic review and meta-analysis (21). The analyses of 15 randomized controlled trials (2,385 patients) showed a small but significant benefit of preoperative chemotherapy on survival [hazard ratio (HR) 0.87, 95% CI 0.78–0.96, P=0.007], an absolute OS improvement of 5% at 5 years, from 40% to 45%. Induction chemotherapy regimen used in these trials are listed in *Table 1*. All of them used platinum-based chemotherapy, except one which used docetaxel alone. There was no clear evidence that the effect of chemotherapy on survival differed according to the type of chemotherapy regimen.

Given the paucity of data, neoadjuvant chemotherapy remains controversial. Several trials are exploring whether chemotherapy combined with immunotherapy may offer superior outcomes as neoadjuvant treatments.

Concurrent chemoradiotherapy

Platinum doublet is the backbone of concurrent chemotherapy regimens used with thoracic radiotherapy. As stated above, the two trials which assessed the role of concurrent radiochemotherapy versus surgery didn't find any difference. Chemotherapy regimen used with radiotherapy in these trials were cisplatin-etoposide in INT0139 and cisplatin-vinorelbine in ESPATUE. Another regimen often used is carboplatin-paclitaxel. One meta-analysis compared the efficacy of concurrent thoracic radiation therapy with either etoposide/cisplatin (EP) or carboplatin/paclitaxel (PC) in patients with stage III NSCLC and demonstrated similar efficacy between the 2 treatments (22). Nevertheless, only one randomized phase II trial directly compared the 2 chemotherapy regimens and found a 3-year OS significantly better in the cisplatin-etoposide arm than in the carboplatin-paclitaxel arm (23). A phase III trial published in the *Annals of Oncology* in 2017 showed that cisplatin-etoposide might be superior to weekly carboplatin-paclitaxel in terms of OS (24). Recently, an update of this study focused on the ECOG 2 patients and demonstrated that cisplatin-etoposide regimen had similar survival compared to carboplatin-paclitaxel regimen (25). Finally, for non-squamous NSCLC, the phase III PROCLAIM study showed that pemetrexed-ciplastin combined with thoracic radiation therapy was not superior to cisplatin-etoposid (26). On the other hand, less

hematologic toxicity (thrombocytopenia, neutropenia and febrile neutropenia) and more pneumonitis was noticed in the ciplastin-pemetrexed group.

Consolidation chemotherapy

There is no evidence for consolidation chemotherapy after concurrent chemoradiotherapy, as attested by a pooled analysis published in 2013 (27). Another phase III trial designed to determine the efficacy of consolidation chemotherapy with docetaxel and cisplatin after concurrent chemoradiotherapy with the same agents, failed to show prolong PFS (28).

Nodal response after induction chemotherapy is an important prognostic factors (29), and consolidation chemotherapy may improve survival outcomes, according to a retrospective trial (30). But we currently don't know what's the best consolidative treatment regimen in this situation.

Maintenance immunotherapy

PACIFIC, a randomized phase III trial has changed our practice in locally advanced, inoperable stage III NSCLC. In this trial, patients received durvalumab versus placebo every 2 weeks during one year, as consolidation therapy after definitive chemo-radiotherapy in unresectable stage III NSCLC. The majority of patients had stage IIIA and IIIB (respectively 52.9% and 44.5%) disease. PFS was significantly longer with durvalumab than with placebo [16.8 versus 5.6 months, hazard ratio 0.52 CI (0.42–0.65), P<0.001]. Data on OS, a secondary endpoint, were released in 2018 (31): durvalumab significantly prolonged OS, with a 24-month OS rate at 66.3% in the durvalumab group, compared to 55.6% in the placebo group (P=0.005). One question remains: what is the role of immunotherapy in case oncogenic driver mutations? It is known that giving targeted therapy straight after immune-checkpoint inhibitors can increase the adverse effects (24,32). Furthermore, immunotherapy seems to be less effective in tumors with driver mutations (22). In the PACIFIC trial, EGFR mutations were found in 6% of patients, 67.3% of the patients' tumors were EGFR-negative or wild-type and in about one third of the patients, EGFR status was unknown. In a subgroup analysis, most groups achieved OS improvement with durvalumab, including non –smokers. The number of events in patients with EGFR mutation positive was too small to assess OS. It remains therefore unclear whether these patients should be offered durvalumab.

Conclusions

There is no clear consensus about the management for patients with stage IIIA NSCLC. For the treatment of the primary tumor, options are radical chemo-radiotherapy, induction chemotherapy followed by surgery or surgery followed by adjuvant chemotherapy. No study has shown a clear benefit in favour of one option. As such, we must consider patients' fitness and preferences. In case of very fit patient, without notable comorbidities or actionable mutations, trimodality treatments can be discussed, in accordance with the results of the INT 0139 trial. Stage IIIA is and will remain a challenging situation for which staging and multidisciplinary discussion are fundamental in the choice of the most correct therapeutic procedure. Many options are available and, perhaps with immune-checkpoint inhibitors, the treatment paradigm in stage IIIA disease might become even more complex. A multidisciplinary approach is essential to ensure the best treatment possible, bearing in mind patients' fitness and preferences.

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Footnote

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