Evolution and future perspectives in the treatment of locally advanced non-small cell lung cancer

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Introduction

Non-small cell lung cancer (NSCLC) represents the most common cause of cancer-related deaths in Western countries, with 50% of patients presenting with metastatic disease at diagnosis and about 40% of individuals with locally advanced disease (stage III), including resectable and unresectable tumours [1, 2]. Stage III includes a fairly heterogeneous group of tumours, ranging from T3 N1 to T4 N3 cancers, and across these subgroups prognosis is extremely variable and the choice of the optimal treatment strategy remains controversial. Although some patients with stage III disease and mediastinal involvement are technically resectable, the role of surgery is not yet fully defined due to the high rates of local and distant failure following radical resections. Therefore, multimodality approaches with the purpose of improving patient outcome have been investigated. The present review will discuss evolution and future perspectives in the treatment of stage III disease focusing on two distinct subgroups of patients: those with resectable and those with unresectable disease.

Induction chemotherapy in patients with resectable NSCLC

Patients with mediastinal lymph node involvement form the largest group of patients with stage III disease. Whether NSCLC individuals with IIIA (N2) cancer should undergo surgical resection is still controversial, although there is a tendency to consider those patients with non-bulky mediastinal node involvement as candidates for surgery. In fact, different trials indicated that the burden of mediastinal nodal disease is a critical prognostic factor, with more favourable 5-year survival rates for patients with minimal nodal disease compared with those with bulky mediastinal masses [3–5]. Therefore, accurate staging of the mediastinum including positron emission tomography (PET) scan, due to its excellent negative predictive value [6–8], and possibly mediastinoscopy in case of positive PET finding, is mandatory to properly select patients as candidates for surgery [9]. Moreover, selected T4 patients with N0 or minimal N1 disease (IIIB) may be considered amenable for surgical resection, including patients with satellite nodules in the same lobe or those with limited involvement of the carina [10–12]. However, due to the disappointing outcome of patients with locally advanced disease treated with surgery alone, multimodality approaches have been largely investigated in the last few decades, in order to gain either local and distant sites control.

Postoperative radiotherapy (PORT) has been investigated by several authors as a means to sterilize regions with increased risk of harbouring macroscopically undetectable disease. In a study conducted by the Lung Cancer Study Group, patients with resected stage I–III squamous cell carcinoma of the lung were randomly assigned to PORT or to observation. Although the addition of radiotherapy did not improve survival, it led to a reduction in local relapses that was statistically significant for individuals with N2 disease [13]. Similarly, the 1998 PORT metaanalysis did not show any improvement in survival for patients who received radiation treatment after surgery, addressing a possible detrimental effect of radiotherapy in patients with N0–1 disease, although an advantage favouring PORT was observed for patients with ipsilateral mediastinal involvement [14, 15]. A recent retrospective review of population-based data including 7465 patients showed that the use of PORT did not significantly impact on survival. However, the addition of radiotherapy significantly improved survival in N2 patients, while it had a detrimental effect in case of N0–1 disease [16].

Another strategy aimed at improving survival in patients with operable NSCLC has been the addition of chemotherapy, either in the preoperative (neoadjuvant or induction) or postoperative (adjuvant) setting. Induction chemotherapy, through immediate delivery of systemic therapy, might theoretically allow eradication of micrometastases and obtain reduction of tumour burden increasing cancer resectability, and offers the chance of in vivo assessment of tumour response or resistance.

Several phase II trials have explored the role of preoperative chemotherapy with old-generation cisplatin-based regimens in locally advanced lung cancer, mainly in pN2 tumours, showing that the delivery of induction anti-tumour treatment is feasible, with acceptable toxicity and encouraging response rates, although it is difficult to compare the different studies due to the large variability of inclusion criteria and treatment regimens [17–20]. A phase III trial from the MD Anderson Cancer Center compared three cycles of cisplatin/etoposide/cyclophosphamide followed by surgery and postoperative chemotherapy with the same regimen with upfront surgery alone [21]. The study, which also included patients with unresectable disease, was stopped prematurely due to the clear
survival advantage that emerged after an interim analysis in favour of the chemotherapy arm (64 versus 11 months, \( P < 0.008 \), Table 1). However, due to the early termination of the study, the sample size was small, with only 60 patients enrolled rather than the planned 130. Moreover, the induction treatment regimen proved extremely toxic, with 80% grade 3–4 neutropenia, 15% of neutropenic fever and with dose reduction being necessary in 70% of patients. Another criticism to the study has been the disappointing outcome of the surgery-only arm, as compared with historical controls.

Similarly, a Spanish study in which resectable stage III patients were randomized to preoperative cisplatin/ifosfamide/mitomycin versus upfront surgery, with PORT being administered in both groups, closed early due to the large survival difference observed in the interim analysis favouring the chemotherapy arm (26 versus 8 months, \( P < 0.001 \)) as illustrated in Table 1 [22]. Nevertheless, the higher incidence of k-ras mutations, a well-known negative prognostic factor in NSCLC, in the control arm (42 versus 15%) might have affected the extremely poor outcome of patients who received surgery alone.

Overall, these two studies, due to the limited sample size as a result of early closure and the heterogeneity of enrolled patients, are not conclusive about the role of preoperative chemotherapy in resectable locally advanced NSCLC. Moreover, a retrospective subgroup analysis of a large randomized French trial in which patients with early stage (IA–IIIB) and locally advanced disease (IIIA) were randomly assigned to preoperative chemotherapy or surgery alone, did not show any survival benefit for stage IIIA patients [23].

Third-generation platinum-based regimens including taxanes and/or gemcitabine have been tested in the preoperative setting in numerous phase II and III studies [24–31], with response rates ranging from 55 to 75% and resection rates from 29 to 80%. Particularly, in the study conducted by Betticher et al., the combination of cisplatin and docetaxel produced a 66% response rate with an impressive 19% rate of pathological complete responses [26]. In the multivariate analysis mediastinal clearance and complete surgical resection significantly predicted for longer survival, thus allowing identification of a subgroup of patients who are likely to derive a substantial benefit from surgery following induction chemotherapy. Large phase-III randomized trials exploring platinum–taxanes combinations in the preoperative setting are currently ongoing and will hopefully allow clarification of the role of induction chemotherapy and the most effective regimens.

Whether surgery might improve survival in potentially resectable patients with greater than minimal N2 disease after combined modality therapy has not yet been defined. In the Intergroup Trial 0139 patients with potentially resectable T1–3 N0 non-progressing after systemic administration of cisplatin and etoposide concurrent with 45 Gy of radiation treatment were randomly assigned to complete radiation treatment or to surgery [32]. Both groups received consolidation chemotherapy. Pathological complete response occurred in 18% of the patients and nodal clearance was observed in 46% of patients. Although progression-free survival was significantly longer in the surgery arm (14.0 versus 11.7, \( P = 0.02 \)), overall survival did not differ, as confirmed in a recent update of this study (Table 1) [33]. N0 status after surgery predicts for longer survival compared with patients with residual mediastinal disease. Moreover, patients who underwent lobectomy had improved survival when compared with patients in the non-surgical arm with similar characteristics. Conversely, individuals who underwent pneumonectomy had worse survival compared with controls in the non-surgical arm.

In a similarly designed EORTC trial, NSCLC patients with stage IIIA (N2) pathologically proven disease who obtained at least a minor response to three cycles of platinum-based induction chemotherapy were randomly assigned to radical radiotherapy or surgery [34]. Overall, a total of 579 patients was registered in the study, and 332 patients (57%) responding to preoperative chemotherapy were randomized. A pathological down-staging was observed in 42% of the patients who underwent surgery, with an operative mortality of 4%, which most often occurred following a pneumonectomy. No significant difference was observed between the two arms in terms of survival (16.4 versus 17.5 months, \( P = 0.60 \), Table 1) or progression-free survival (9.0 versus 11.3 months, \( P = 0.61 \)).

Overall, available data indicate that combination regimens including platinum and taxanes have shown promising activity in resectable locally-advanced NSCLC, although no prospective trial has addressed the question of which drug combination should be preferred in this setting. Patients obtaining nodal down-staging and/or those candidate to lobectomy may derive a substantial benefit from surgery after induction treatments.

### patients with unresectable nsclc

Stage III unresectable patients candidate to radical treatment include T4 without pleural effusion and/or bulky N2 or N3 tumours, although selected T4 patients, as previously discussed, may benefit from surgery. Radiotherapy alone was initially considered the standard of care for these patients, but the disappointing 5-year survival of no more than 5%, mostly due to distant site relapse, raised the need for systemic disease control. This observation led to further evaluations aimed at investigating the role of chemotherapy regimens in patients with unresectable disease, in order to eradicate the micro-metastatic disease and improve patient outcome.

The first combination studies explored a sequential approach, with chemotherapy followed by radiotherapy. The

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Treatment</th>
<th>OS (months)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roth et al. [21]</td>
<td>60</td>
<td>CT ( \rightarrow ) surgery ( \rightarrow ) CT</td>
<td>64</td>
<td>&lt;0.008</td>
</tr>
<tr>
<td>Rosell et al. [22]</td>
<td>60</td>
<td>CT ( \rightarrow ) surgery ( \rightarrow ) RT</td>
<td>26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albain et al. [33]</td>
<td>396</td>
<td>CT–RT ( \rightarrow ) surgery</td>
<td>23.6</td>
<td>0.24</td>
</tr>
<tr>
<td>Van Meerbeeck et al. [34]</td>
<td>332</td>
<td>CT ( \rightarrow ) surgery</td>
<td>16.4</td>
<td>0.60</td>
</tr>
</tbody>
</table>

OS, overall survival; CT, chemotherapy; RT, radiotherapy.
1995 metanalysis performed by the NSCLC Collaborative Group showed an advantage in survival favouring the addition of chemotherapy prior to radical radiation with a hazard ratio of 0.90 [35]. The role of induction chemotherapy has been further clarified in three randomized trials including more than 900 patients with NSCLC which randomly assigned patients with unresectable locally advanced disease to radiotherapy alone versus sequential chemoradiotherapy, as reported in Table 2 [36–38]. All trials included platinum-based regimens and demonstrated a significant survival advantage favouring the addition of chemotherapy to radiation treatment, with median overall survival up to almost 14 months, mostly due to better distant failure rates rather than local control.

Due to its radiosensitizing properties, single agent cisplatin has been investigated concurrently with radiotherapy in order to improve loco-regional disease control (Table 2). An EORTC trial randomly assigned 331 patients with unresectable stage III disease to radiotherapy alone, radiotherapy plus daily cisplatin (6 mg/m²) or radiotherapy plus weekly cisplatin (30 mg/m²), with the addition of cisplatin resulting in improved overall survival (P = 0.04). The study showed a local rather than systemic activity of the drug, probably due to suboptimal systemic dosage [39]. Conversely, a trial conducted by the Hoosier Oncology Group failed to demonstrate a survival advantage for patients receiving 3-weekly cisplatin concomitant with radiotherapy over those treated with radiotherapy alone [40]. More convincing data have risen with the use of combination platinum-based regimens, with different randomized studies providing evidence of significantly longer survival for patients who received concurrent chemoradiation over those treated with radiotherapy alone [41, 42].

Several randomized trials have addressed the question of whether a concomitant approach might be more effective than a sequential strategy including induction chemotherapy followed by radiation treatment [43–46]. The first of these studies was performed by the West Japan Lung Cancer Group, and showed that patients treated with cisplatin/vindesine/mitomycin concurrently with radiotherapy gained prolonged survival over the group who received the same chemotherapy regimen as induction treatment followed by radiotherapy (16.5 versus 13.3 months, P < 0.04), as reported in Table 2 [43]. Similarly, a French trial conducted by the GLOT and GFPC groups, which compared a sequential approach with cisplatin and vinorelbine followed by radiotherapy with concurrent chemoradiation including cisplatin and etoposide, showed a trend toward improved survival for the chemoradiation arm, although the difference did not reach statistical significance (Table 2) [44]. Similar results have emerged from a RTOG phase three-arm trial, comparing concurrent daily or hyperfractionated radiotherapy with sequential chemoradiation, with improved overall survival in favour of concurrent standard radiotherapy compared with the sequential approach (17 versus 14.6 months, P = 0.038), with no clear benefit for patients who received hyperfractionated radiation together with chemotherapy (Table 2) [45]. The superiority of concurrent strategies has emerged also in a Czech phase II study where patients who received cisplatin and vinorelbine in association with radiotherapy experienced a survival benefit of about 4 months compared with historical controls [48].

### Table 2. Phase III trials in unresectable locally advanced NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Treatment</th>
<th>OS (months)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dillman et al. [36]</td>
<td>155</td>
<td>CT → RT</td>
<td>13.7</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT</td>
<td>9.6</td>
<td></td>
</tr>
<tr>
<td>Sause et al. [37]</td>
<td>458</td>
<td>CT → HFX-RT</td>
<td>12.0</td>
<td>0.04*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT → RT</td>
<td>13.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT</td>
<td>11.4</td>
<td></td>
</tr>
<tr>
<td>Le Chevalier et al. [38]</td>
<td>353</td>
<td>CT → RT → CT</td>
<td>12.0</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>Schaake-Koning et al. [39]</td>
<td>331</td>
<td>RT-weekly CT</td>
<td>13%**</td>
<td>0.009*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT-daily CT</td>
<td>16%**</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT</td>
<td>2%**</td>
<td></td>
</tr>
<tr>
<td>Blanke et al. [40]</td>
<td>215</td>
<td>CT–RT</td>
<td>10.0</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT</td>
<td>10.7</td>
<td></td>
</tr>
<tr>
<td>Furuse et al. [43]</td>
<td>320</td>
<td>CT–RT</td>
<td>16.5</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fourmel et al. [44]</td>
<td>201</td>
<td>CT → RT</td>
<td>13.3</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT–RT</td>
<td>16.3</td>
<td></td>
</tr>
<tr>
<td>Curran et al. [45]</td>
<td>610</td>
<td>CT → RT</td>
<td>14.5</td>
<td>0.038***</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT–HFX RT</td>
<td>15.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT–RT</td>
<td>17.0</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>CT → RT</td>
<td>14.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT → CT-RT</td>
<td>18.7</td>
<td>0.091</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT → RT</td>
<td>14.1</td>
<td></td>
</tr>
<tr>
<td>Huber et al. [48]</td>
<td>303</td>
<td>CT → CT-RT</td>
<td>11.4</td>
<td>0.154</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT–RT</td>
<td>14.0</td>
<td></td>
</tr>
</tbody>
</table>

*, versus RT; **, 3-year survival; ***, versus CT → RT.

OS, overall survival; CT, chemotherapy; RT, radiotherapy; HFX, hyperfractionated.
unresectable stage III NSCLC were randomly assigned to historical controls [61]. The SWOG Cooperative Group has not shown any survival advantage when compared with with advanced NSCLC but failed to improve patient outcome since only selected patients may benefit from radical surgical resection. Several studies have addressed the superiority of concomitant chemoradiation for patients with unresectable stage III NSCLC regards to sequential strategies, with no established role for induction and consolidation chemotherapy. Tailoring treatments on the basis of the tumour molecular profile might help to identify patients who are more likely to benefit from targeted therapy.

targeted agents in stage III NSCLC

The availability of new targeted agents aiming at inhibition of critical pathways involved in cancer proliferation with proven activity in the metastatic setting prompted their testing in patients with locally advanced NSCLC.

Investigators have raised the question of how to best incorporate Epidermal Growth Factor Inhibitors (EGFR) into chemoradiotherapy paradigms for patients with stage III disease. Gefitinib and erlotinib, two orally active EGFR tyrosine kinase inhibitors, have shown single agent activity in patients with advanced NSCLC but failed to improve patient outcome in association with platinum-based chemotherapy [53–60]. A recent phase II study of maintenance gefitinib following induction chemotherapy and concurrent chemoradiotherapy did not show any survival advantage when compared with historical controls [61]. The SWOG Cooperative Group has performed a randomized phase III trial where 412 patients with unresectable stage III NSCLC were randomly assigned to concurrent chemoradiation and consolidation docetaxel followed by gefitinib or placebo [62]. An interim analysis showed a possible detrimental effect on survival of maintenance gefitinib compared with placebo (19 versus 29 months, \( P = 0.09 \)), and led to closure of the trial. These data indicate that EGFR tyrosine-kinase inhibitors are ineffective in unselected stage III NSCLC, although retrospective analysis will address whether proper biological patient selection should drive the future development of these drugs in this setting.

The encouraging results observed with cetuximab, an anti-EGFR monoclonal antibody, in association with radiotherapy in head and neck tumours [63], led investigators to design studies to explore its activity in association with platinum-based chemotherapy and radiation treatment in either resectable or unresectable stage III NSCLC. Particularly, in an ongoing RTOG phase II trial in unresectable tumours, patients are treated with concurrent chemoradiotherapy, cetuximab in combination with weekly carboplatin and paclitaxel, with subsequent consolidation therapy with cetuximab and systemic doses of carboplatin and paclitaxel. Another phase II trial performed by the CALGB is evaluating the use of carboplatin and pemetrexed with and without cetuximab concurrent with radiotherapy and consolidation therapy with pemetrexed.

Anti-angiogenic drugs have shown promising activity in advanced solid tumours, with bevacizumab, a monoclonal antibody directed against the vascular endothelial growth factor, being registered in association with chemotherapy as first-line treatment for colorectal cancer [64]. Moreover, a recent published ECOG trial showed that the addition of the drug to carboplatin–paclitaxel chemotherapy improved the outcome in terms of response rate, time to progression and overall survival in advanced NSCLC patients [65]. Based on these data and on the evidence that anti-angiogenic agents may increase the cytotoxicity of radiation therapy [66, 67], an ongoing phase II study is assessing bevacizumab in association with concurrent chemoradiation in patients with stage III disease.

conclusions

Presence of N2 nodal involvement represents the most relevant prognostic factor in patients with locally advanced NSCLC; therefore accurate mediastinal staging is critical to assess tumour resectability and plan the optimal treatment strategy. Since resectable stage III patients treated with surgery alone present disappointing results in terms of survival, especially in the presence of mediastinal lymph node disease, a multimodality approach involving complementary radiotherapy for N2 patients and induction chemotherapy with third generation platinum-based regimens should be considered. The role of surgery after an induction treatment for marginally resectable N2 cancers has not been fully defined, since only selected patients may benefit from radical surgical resection. Several studies have addressed the superiority of concurrent chemoradiation for patients with unresectable stage III disease regards to sequential strategies, with no established role for induction and consolidation chemotherapy. Tailoring treatments on the basis of the tumour molecular profile might help to identify patients who are more likely to
derive a benefit from an induction strategy, as recently observed in the adjuvant setting [68]. Even though available data are not encouraging, ongoing trials will probably allow proper association of chemoradiation strategies with new targeted agents in the locally advanced setting to further improve patient outcome.

references

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