Review article

Combined modality therapy of non-small cell lung cancers

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Summary

Lung cancer represents the leading cause of cancer mortality. Non-small cell lung cancer (NSCLC) accounts for about 75% to 80% of lung cancer cases and carries a 5-year survival of about 10% to 15% for all stages. Approximately one-third of NSCLC patients present with stage III disease, which is defined as locally advanced tumour confined to the chest without distant metastasis. The traditional treatment for stage III patients has been thoracic radiotherapy (RT). However, the impact of thoracic RT alone has been minimal with published studies showing median survival <1 year and 5-year survival of 5% to 7%. Thus, the treatment of stage III NSCLC remains a significant challenge. The metastatic nature of this disease has been responsible for the poor survival statistics and emphasises the need for effective systemic treatment. In recent years, cisplatin-containing combination chemotherapy has emerged as a viable option in the treatment of NSCLC. Combined modality therapy employing systemic (chemotherapy) and local (RT with or without surgery) approaches has shown favourable results in patients with stage III disease. Randomised studies have demonstrated the benefit of concurrent or sequential chemoradiation in selected patients with a good performance status and minimal weight loss. The exact sequence has yet to be determined. Moreover, randomised studies in stage IIIA potentially resectable disease show survival advantage for patients receiving combined modality treatment. Thus, combined modality treatment has the potential to improve overall survival by increasing both local and distal control. These recent reports of randomised clinical trials of combined modality therapy for stage III NSCLC form the basis for this report. Several new agents, like the taxanes, CPT-11 and gemcitabine show promising activity in NSCLC treatment. Ongoing studies are evaluating the potential role of these new agents in combined modality treatment but since the phase III trials have not been reported yet these studies will not be discussed.

Introduction

Lung cancer represents the most frequent lethal neoplasm in males whilst its incidence increases progressively in females. In many respects, it is a self-induced illness, i.e., 85% to 90% of lung cancer is caused by chronic cigarette smoking [1-3]. Histogenetically, lung carcinoma derives from a progenitor pluripotent stem cell of bronchiolar epithelium. The malignant transformation is a result of chronic exposure of these cells to inhaled carcinogens. The precise sequence of genetic and/or molecular events leading to the development of an invasive cancer has not yet been established. The genetic predisposition presumably is important, because of all smokers, only 10% to 20% develop lung cancer. Depending on the carcinogen exposure and the host’s ability to handle xenobiotic injury, the natural history of cancer varies. Lung cancer should be considered a heterogeneous collection of diseases with different biological properties [4].

Lung cancer treatment is far from ideal. Surgery offers the best chance for long-term survival and cure if the tumour is confined within the lung and is resectable. Unfortunately, the majority of patients present with disease not amenable to surgery because it is either locally advanced or has metastasised [1, 5-7].

It is clinically useful to broadly categorise lung cancers into two groups which reflect their biology and therapeutic management: small cell lung cancers (SCLC) and non-small cell lung cancers (NSCLC) [1, 5, 6].

SCLC represent 20%-25% of all newly diagnosed lung cancer cases. SCLC cells have relatively rapid cell proliferation and tendency for early distant dissemination. Hence, patients with SCLC are usually considered to have systemic disease unless proven opposite. Chemotherapy or chemoradiation therapy are the primary and main treatment modalities for this group of lung cancers [1, 6-8].

NSCLC is a heterogeneous aggregate of at least three distinct histologies of lung cancer including squamous, adenocarcinoma, and large cell carcinoma [1, 5]. The most important prognostic factor in NSCLC is the stage of disease [1, 5]. The recently updated TNM staging system (Tables 1 and 2) [9] predicts relatively well for survival (Table 3) [1, 5, 9]. Within a given disease stage, the next most important prognostic factors are performance status and recent weight loss [1, 5]. These parameters are often indicative of advanced and/or metastatic disease. At diagnosis, patients with NSCLC can be divided into three groups that reflect the extent of disease and treatment approach [1, 5, 8, 10].

The first group of patients (less than a quarter) has tumours that are surgically resectable (generally stages I and II). This is the group with the best prognosis, depending on a variety of tumour and host factors [1, 5, 11]. Patients with resectable disease who have medical contraindications to sur-
The second group of patients diagnosed with NSCLC (25% to 40%) has either locally (T3–T4) or regionally (N2–N3) advanced disease (stages IIIA and IIIB; 'locally advanced (LA) lung cancer') (Table 1 and 2). Their disease is too extensive for primary surgical resection yet limited to the chest [1, 5, 10]. Historically, the standard treatment for patients having stage IIIA or IIIB disease has been fractionated external-beam thoracic radiation therapy (RT) delivered in a continuous fashion (60 Gy in 30 fractions; 2 Gy daily, 5 days a week, for 6 weeks) [15]. A boost to the cone-down field of the primary tumour is frequently used to further enhance local control. Careful treatment planning with precise definition of target volume, and avoidance of critical normal structures to the extent possible is needed for optimal results and requires the use of a simulator [7, 10, 13].

Precise data on the relationship between tumour size (or volume) and the degree of local control are not available. Multiple parameters such as total radiation dose, fraction size, volume and type of normal tissues to be irradiated, definition of target volume, and quality control of radiotherapy techniques should be taken into account [10, 16, 17]. Overall, the dose-response relationship in NSCLC is evident only for tumours of 3 cm or smaller, at least within the range of doses of 60 to 65 Gy. In patients with larger tumours, doses much greater than 40 Gy may have to be used [10].

Table 1: TNM descriptors.

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM Subset</th>
<th>Clinical stage 1 y</th>
<th>3 y</th>
<th>5 y</th>
<th>Pathologic stage 1 y</th>
<th>3 y</th>
<th>5 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1 NO M0</td>
<td>91</td>
<td>71</td>
<td>61</td>
<td>94</td>
<td>80</td>
<td>67</td>
</tr>
<tr>
<td>IB</td>
<td>T2 NO M0</td>
<td>72</td>
<td>46</td>
<td>38</td>
<td>87</td>
<td>67</td>
<td>57</td>
</tr>
<tr>
<td>IIA</td>
<td>T1 N1 M0</td>
<td>79</td>
<td>38</td>
<td>34</td>
<td>89</td>
<td>64</td>
<td>55</td>
</tr>
<tr>
<td>IIB</td>
<td>T2 N1 M0</td>
<td>61</td>
<td>34</td>
<td>24</td>
<td>78</td>
<td>47</td>
<td>39</td>
</tr>
<tr>
<td>IIA</td>
<td>T3 N1 M0</td>
<td>55</td>
<td>31</td>
<td>22</td>
<td>76</td>
<td>47</td>
<td>38</td>
</tr>
<tr>
<td>IIB</td>
<td>T4 NO-2 M0</td>
<td>37</td>
<td>10</td>
<td>7</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IV</td>
<td>T1-4 N1-3 M1</td>
<td>20</td>
<td>2</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IVA</td>
<td>T1-4 N1-3 M1</td>
<td>20</td>
<td>2</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

1. The uncommon superficial tumour of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1.

2. Most pleural effusion associated with lung cancer are due to tumour. However, there are few patients in whom multiple cytopathologic examinations of pleural fluid show no tumour. In these cases, the fluid is nonbloody and is not exudative. When these elements and clinical judgment dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging element and the patient's disease should be staged T1, T2, or T3. Pericardial effusion is classified according to the same rules.

3. Separate metastatic tumour node(s) in the ipsilateral nonprimary-tumour lobe(s) of the lung are also classified as M1.
higher than 65 Gy would likely be necessary for local control. Delivery of such doses is difficult, given the constraints of toxicity to the surrounding normal tissues, mostly the lung, spinal cord, and heart [10, 16]. Selected patients with T3 or N2 disease can be, like patients with stage I and II of disease, also treated effectively with surgical resection alone [1, 5, 18].

Long-term survival in a majority of patients with stage III disease is poor, in the range of 5%–10%. The analysis of the failure patterns in locally advanced NSCLC indicates that both persistent or recurrent intrathoracic disease and appearance of distant metastases are responsible for such a poor long-term survival [1, 5, 10, 13].

The final group of patients (45%–50%) will have metastatic disease (M1; stage IV) at the time of diagnosis. The 5-year survival for this stage of disease is less than 1%. Patients with stage IV disease can be treated with radiotherapy and chemotherapy for palliation of symptoms from the primary tumour. Patients with good performance status, women, and patients with distant metastases confined to a single site appear to live longer than others [1, 5, 10].

**Combined modality therapy**

Since most patients with LA-NSCLC succumb to the disease, either due to unsatisfactory local control or from the appearance of metastases, the inclusion of chemotherapy, in addition to radiation therapy in their management was a logical step [8, 13, 17]. Until recently, the role of combined modality therapy (radiotherapy and chemotherapy) in the treatment of stage III NSCLC was controversial, in part because early clinical trials were too small to reliably detect benefits and thus often provided contradictory results. In addition, trials performed in the 1970s evaluating the benefits of radiotherapy alone versus combined radiotherapy and chemotherapy often involved long-term administration of alkylating agents, which appeared to be detrimental to patients with advanced NSCLC and are no longer used [10, 13, 14, 17, 19]. Within the past 10 years, however, several randomised trials have validated the importance of chemotherapy in the treatment of LA-NSCLC [20–22]. These results have been achieved with cisplatin combined with a plant alkaloid such as etoposide or one of the *Vinca* alkaloids. These phase III clinical trials have demonstrated that in selected patients with good performance status and minimal weight loss combined modality therapy improves survival compared with radiotherapy alone [8, 23–25]. Moreover, some studies employing neoadjuvant chemotherapy followed by local surgery indicate that chemotherapy can eradicate NSCLC micrometastases [26–29].

Recently, several new agents, including the taxanes paclitaxel and docetaxel, the novel pyrimidine gemcitabine, and camptothecin analogue irinotecan (CPT-11), have demonstrated an impressive preliminary activity in NSCLC (response rate as single-agents in 30% or more). The potential role of these new agents in NSCLC, especially in combination with platinum analogues, and in combination with radiotherapy, is undergoing intense evaluation worldwide. Phase III studies with these newer chemotherapeutic agents interdigitated with radiation and surgery are still pending [8, 25, 30, 31].

**Combined approaches to locally advanced NSCLC**

The aim of combining chemotherapy and radiotherapy is to optimise local control and control of distant micrometases [10, 13, 17, 23, 32]. Studies employing systemic (chemotherapy) and local (radiotherapy) therapy have reported varying results, probably due to the differences in the composition of chemotherapy regimens and different criteria for patient inclusion and performance status employed by each. The exact sequence of chemotherapy and radiotherapy has yet to be determined. In general, chemotherapy is given either sequentially followed by RT or concurrently with RT. Besides survival or disease-free interval, one of the main concerns when combining drugs and radiation, remains the potential interference between both modalities leading to increased toxicity, which may outweigh all potential benefits. On the other hand, simultaneous administration of chemotherapy and radiotherapy might be more effective ('dose intensification') in local tumour control than radiotherapy alone or radiotherapy after induction chemotherapy [10, 17, 23, 32, 33].

Sequential chemotherapy and radiation provide an early opportunity to treat micrometastatic disease without compromising the chemotherapy dose intensity, and reduction in local tumour bulk increases chances of tumour sterilization with subsequent RT. An alternative to the sequential administration of chemotherapy and radiotherapy is a simultaneous use of these two treatment modalities. This management concept is based on the rationale that chemotherapeutic agents may improve the antitumour activity of radiotherapy at the primary disease site, either by acting as a radiosensitiser or through the additive effect of chemotherapy on radiotherapy. On the other hand, increased toxic effects, including esophagitis and pulmonary toxicity, may ensue. These effects can result in treatment delays and/or dose reduction in radiotherapy or chemotherapy, or both, thereby reducing 'dose intensity.' Chemotherapy after RT has not found favour, as overall responses in previously irradiated lesions are generally low [10, 17, 23, 32, 33].

Randomised trials of combined modality therapy for unresectable stage III NSCLC with benefit in combined modality arm are shown in Table 4.

One of the first randomised studies reporting the successful use of combined modality therapy appeared at the beginning of this decade. Dillman and associates [20] in the Cancer and Leukemia Group B study (CALGB 8433 trial), compared standard radiotherapy alone with radiotherapy preceded by a brief course of chemotherapy (induction chemotherapy) consisting of two cycles of cisplatin and five weeks of vinblastine. Enrolled patients had minimal weight loss (maximum of 5%) and Karnofsky index of at least 70. Patients receiving combined modality treatment experienced...
Table 4. Randomised trials of combined modality therapy for unresectable stage III NSCLC with benefit in combined-modality arm.

<table>
<thead>
<tr>
<th>Investigators</th>
<th>N</th>
<th>Therapy</th>
<th>MST</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dillman et al., 1990, seq.</td>
<td>77</td>
<td>RT (60 Gy)</td>
<td>9.6</td>
<td>6 (7)</td>
</tr>
<tr>
<td>LeChevalier et al., 1991, seq.</td>
<td>176</td>
<td>VCPC (3x) + RT + VCPC (3x)</td>
<td>12</td>
<td>12*</td>
</tr>
<tr>
<td>Shaake-Koning et al., 1992, conc.</td>
<td>109</td>
<td>RT (55 Gy) + weekly P</td>
<td>-</td>
<td>16*</td>
</tr>
<tr>
<td>Sause et al., 1995, seq.</td>
<td>149</td>
<td>RT (60 Gy)</td>
<td>11.4</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Jerome et al., 1996, conc.</td>
<td>66</td>
<td>hRT (69.6 Gy / 1.2 bid)</td>
<td>14</td>
<td>9 (4)</td>
</tr>
<tr>
<td></td>
<td>65</td>
<td>hRT + CE daily with hRT</td>
<td>22</td>
<td>14*</td>
</tr>
</tbody>
</table>

Legend: N, number of patients; MST, median survival time in months; OS, overall survival with the year following treatment in parenthesis; seq, sequential chemotherapy; cone, concurrent chemotherapy; PVb, cisplatin and vinblastine; VCPC, vindesine, cyclophosphamide, cisplatin, lomustine; P, cisplatin; RT, radiotherapy; hRT, hyperfractionated RT; bid, twice daily.

*Statistically significant

Improvement in median survival (13.7 months vs 9 months) and in long-term survival rate (at 7 years 13% vs 6%) (Table 4) [20, 34].

Concomitantly with the above CALBG 8433 trial, Le Chevalier and associates (French Multicenter Trial) [21, 35] and Shaake-Koning and associates (European Organization for Research and Treatment of Cancer, EORTC) [22] also reported similar results with cisplatin-based therapy in their randomised studies.

In the French Multicenter Trial [21, 35] combined modality treatment consisted of three intensive cycles of induction chemotherapy followed by locoregional irradiation and then, if disease had not progressed, three chemotherapy consolidation cycles. Median survival time for chemoradiotherapy group was 12 months versus 10 months for thoracic RT alone (P=0.02) (Table 4). The metastasis rate was significantly lower in the combined modality arm (P<0.001). Despite the use of a dose of 65 Gy in both treatment arms, local control, as evaluated at 3 months was low (15%-17%). During the first 2 years the difference in overall survival was marginal (for example, 2-year survival rate 21% vs 14%), but in the third year it became significant (Table 4).

In their three-arm study Shaake-Koning and associates [22] reported that concurrent chemoradiotherapy schedule of low-dose daily cisplatin provides a statistically significant survival benefit over thoracic RT alone (3-year survival of 16% vs 2%; P=0.009) (Table 4). The survival benefit derived from the improved control of local disease.

Several published studies, however, did not support the conclusion that chemotherapy in addition to RT provides superior survival [36–38]. The issue was investigated further by two meta-analyses of data extracted from all of the published randomised trials comparing radiotherapy alone with radiotherapy and cisplatin-based chemotherapy [14, 39]. Both meta-analyses report a small improvement in survival (absolute benefit of 4% at 2 years and 2% at 5 years, or a 13% reduction in the risk of death).

Survival can be also improved by the addition of chemotherapy to hyperfractionated RT [40, 41] (Table 4).

In summary, although the observed benefits of chemotherapy in addition to thoracic radiotherapy are modest, they offer hope of progress. The optimal and most effective chemotherapeutic regimen in the combined modality setting continues to be a subject of clinical investigation. The exact sequence and schedule of incorporation of chemotherapeutic agents with thoracic radiation has yet to be determined. The combined modality approach should become the standard care for patients who have a good performance status and <5% loss in body weight. Radiation alone is appropriate for patients with stage III NSCLC who are otherwise not good candidates for chemoradiation, e.g., those with ≥5% weight loss during the preceding 3–6 months and/or those whose Karnofsky index is ≤70-80% or ECOG performance is ≥2 [8, 10, 23, 24].

Preoperative therapy for stage III NSCLC

The role of surgery for patients with stage IIIA (N2) as a standard disease remains controversial [5, 18]. The presence of metastases in any of the mediastinal lymph nodes (N2 disease) is indicative of advanced disease and is thought by some to represent a contraindication to surgery. However, many surgeons recommend resection if the N2 disease is limited to a single lymph node level. Disseminated disease is the cause of death in most patients with stage III NSCLC treated with surgical resection. The administration of postoperative radiation reduces the risk of recurrence in the chest from 20% to 3% but does not significantly improve disease-free or overall survival. Trials of adjuvant chemotherapy were also unsatisfactory and the obtained results have not led to the standard use of adjuvant therapies [5, 13, 23, 28].

Because of these unsatisfactory results induction or neoadjuvant chemotherapy (with or without RT) followed by surgery for stage III NSCLC is under evaluation. Induction or neoadjuvant therapy can be defined as cytoreductive therapy administered before definitive locoregional therapy. Cytoreductive therapy consists of either chemotherapy or RT or combined RT and chemotherapy. The intent of cytoreductive therapy is to downstage primary tumour and hence, increase the resectability rate. Earlier administration of chemotherapy may eradicate micrometastasis, improve overall survival, and provide accurate pathological assessment of response to induction therapy. Moreover, chemotherapy might be better tolerated in the preoperative setting. Many phase II trials have demonstrated improved response, resection and survival rates with induction therapy before surgery. A variety of cisplatin-based chemotherapy regimens with 30 to 45 Gy of radiation in the preoperative setting have been reported. In general, the response rate to induction
therapy in these studies was approximately 50%, with pathologic complete responses seen in about 10% of patients. At the end of therapy, complete surgical resection was possible in about 60% of patients, and 2- to 3-year survival was approximately 30%. Several factors, such as inconsistently used mediastinoscopy, different chemotherapy and radiation regimens, and definitions of complete resection, have hampered interpretation and comparison of phase II trials of induction chemotherapy with or without radiotherapy [5, 23, 25, 29].

From the prospective phase III trials three studies have been published (Table 5) [26-28]. The first one was conducted by Pass and associates in 1992 [26]. It was closed with only 27 patients due to the slower-than-anticipated accrual of patients. All patients had histologically confirmed N2 disease and they were randomised either to the neoadjuvant arm or to immediate surgery. The resectability rate was about 85% in both groups, with no operative mortality. Neoadjuvant therapy in this trial did not result in statistically significant survival advantage but it demonstrated the feasibility of this approach. Two other studies were published in 1994, one by Rosell and associates from the University of Barcelona [27] and the other by Roth and co-workers at M.D. Anderson Cancer Center (MDACC), Houston [28]. Each study enrolled 60 patients, and both were terminated early after an interim analyses indicated a survival advantage in the chemotherapy arm. Cisplatin-based chemotherapy was administered for three cycles in each trial, and an additional three cycles of postoperative chemotherapy were given to the patients in the MDACC study. Postoperative irradiation was given to all patients in the Barcelona trial but only to incompletely resected patients in the MDACC trial. Response rates to induction chemotherapy were 60% in the Barcelona study and 35% in the MDACC study. Resectability rates were similar in both arms of each trial; in the Barcelona trial between 60% to 70% and in the MDACC trial between 85% to 90%. Both studies showed a significant improvement in survival in patients who received induction chemotherapy. This survival advantage persisted with multivariate analysis.

Table 5. Randomised trials of preoperative therapy for stage III NSCL with benefit in preoperative therapy arm.

<table>
<thead>
<tr>
<th>Investigators</th>
<th>N</th>
<th>Therapy</th>
<th>RR %</th>
<th>MST (mos.)</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pass et al., 1992</td>
<td>14</td>
<td>S + RT (54-60 Gy)</td>
<td>86</td>
<td>15.6</td>
<td>-</td>
</tr>
<tr>
<td>Rosell et al., 1994</td>
<td>30</td>
<td>S + RT (50 Gy)</td>
<td>90</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>Roth et al., 1994</td>
<td>32</td>
<td>CEP (3x) + S + CEP (3x)</td>
<td>66</td>
<td>11</td>
<td>15 (3)</td>
</tr>
</tbody>
</table>

Legend: N, number of patients; RR, resection rate; MST, median survival time in months; OS, overall survival with the year following treatment in parenthesis; PE, cisplatin, etoposide; MIP, mitomycin, ifosfamide, cisplatin; CEP, cyclophosphamide, etoposide, cisplatin; RT, radiotherapy. *Statistically significant

In summary, based on the results of the above studies, we conclude that chemotherapy plays an important role, adding to the survival of patients with stage III (N2) NSCLC. Whether surgery is of benefit in these patients continues to be a point of debate among lung cancer oncologists [10, 23, 25, 29]. Also, studies have been designed to evaluate the role of chemotherapy before surgery in early-stage NSCLC [42, 43]. The results of these studies are still not mature.

In general, the results suggest that modern chemotherapy regimens may have a role in the treatment of all stages of NSCLC, although further research is needed to confirm the degree of benefit (Table 6) [8, 13, 14].

Table 6. Feasible combined modality treatment in NSCLC.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Combined modality treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB, II</td>
<td>Small impact for postoperative chemotherapy or radiation; postoperative chemotherapy under continued study</td>
</tr>
<tr>
<td>IIA</td>
<td>Chemotherapy plus surgery appears better for resectable patients</td>
</tr>
<tr>
<td>IIA, IIB</td>
<td>Chemotherapy plus radiation better than radiation alone, role of surgery not proven</td>
</tr>
</tbody>
</table>

In conclusion, the results of the above studies support the role of chemotherapy in improving survival in patients with stage III NSCLC. Further research is needed to confirm the degree of benefit and to determine the optimal combination of chemotherapy and surgery. The authors thank Mrs. Morana Simat for editorial assistance.

References


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