Radiotherapy in Lung Cancer

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Key Words
Small cell lung cancer (SCLC), Non-small cell lung cancer (NSCLC), radical, palliative, radiotherapy, prophylactic cranial irradiation (PCI), radiation induced pneumonitis, cyttoprotection.
Section I. Small cell lung Cancer

I.1. Introduction.
Small cell lung cancer (SCLC) accounts for 20% of all primary lung tumors. It has a high growth fraction and at diagnosis the disease is usually extended. Bronchial obstruction is present in 30%-40% of patients and in 14% of cases a solitary peripheral mass is found. Multiagent drug combinations are more effective than single agents, while SCLC tumors are normally sensitive to many chemotherapeutic drugs. Complete response to chemotherapy appears in 40-68% of patients with limited stage disease and in 18%-40% in those with extensive disease.

I.2. Limited stage
Thoracic irradiation: doses, fractionation, target volumes, beam arrangements.
Some medical oncologists question the indication of thoracic irradiation due to the high incidence of distant metastases. However, several trials have already shown the beneficial role of radiotherapy in terms of tumor control and survival [1-3]. Mira et al. [4] reported 30-60% of locoregional recurrences of patients receiving thoracic irradiation in contrast with 75-80% in patients treated with chemotherapy alone. Perez et al. [5] in a randomized study involving 304 patients, reported an intrathoracic failure rate of 52% in patients receiving chemotherapy alone compared with 36% in those receiving adjuvant radiotherapy. The 2-year survival was 40% in those receiving thoracic irradiation compared with 23% in the group receiving chemotherapy alone. Perry et al. [6] in prospective randomized trial of 399 evaluable patients reported a significant number of complete response in favor of radiotherapy (P=0.0013). Nevertheless, by reviewing the current literature in reported series comparing chemotherapy alone versus chemo-radiotherapy, data concerning response or failure rates are rather controversial [3,7]. The summary of reported series is shown in table 1. As it is shown, most of the randomized trials are reported a positive impact of thoracic irradiation in terms of survival and local control.
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The timing of chemotherapy and radiotherapy is also a matter of discussion. A meta-analysis of randomized trials by Pignon et al. [8] with or without radiotherapy, did not identify any optimal timing for thoracic irradiation. However, most trials showing no benefit of radiotherapy administered after or late in the treatment course, whereas many trials have shown a beneficial effect of concurrent or early thoracic irradiation, as shown in table 1. Moreover, Takada et al. [ ] in the recently published 9104 JCOG randomized trial, documented the beneficial effect of concurrent chemo-radiotherapy in limited stage of SCLC: median survival 19.7 months in the sequential arm versus 27.2 months in the concurrent arm. Beyond this, the superiority of early or concurrent thoracic irradiation over delayed is probably based on the prevention of distant micro-dissemination from chemotherapy-resistant tumor cells. Although, concurrent use of chemotherapy and radiotherapy with doxorubicin-based or cyclophosphamide-based regimens could not be combined with full doses of RT because of increased pulmonary toxicity, cisplatin plus etoposide was found to be the optimal regimen for combination with concurrent RT since it hardly accelerates toxicity at all and the is no recall phenomenon. We strongly propose the concurrent schedule, while the irradiation dose should be given with attention in levels over 50Gy.

Table 1. Comparisons of chemotherapy (CT) alone versus combined chemotherapy plus chest irradiation (RT) in patients with SCLC.
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<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Fraction</th>
<th>Chemotherapy</th>
<th>Tumor Volume</th>
<th>Tumor Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>[13] Looper et al.</td>
<td>123</td>
<td>35 Gy</td>
<td>CAV-CM</td>
<td>43, 60, 14, 29, 69, 26</td>
<td>Pos</td>
</tr>
<tr>
<td>[14] Carlson et al.</td>
<td>25-40</td>
<td>55</td>
<td>POCC/VAM</td>
<td>NS, 81, 78, 40, 40</td>
<td>Neg</td>
</tr>
<tr>
<td>[15] Souhami et al.</td>
<td>13</td>
<td>40 Gy</td>
<td>AV/CM</td>
<td>NS, similar, - , -</td>
<td>Neg</td>
</tr>
<tr>
<td>[16] Livingston et al.</td>
<td>333</td>
<td>48 Gy</td>
<td>VMVP/CAV-CVP</td>
<td>67, 97, - , -</td>
<td>Pos</td>
</tr>
<tr>
<td>[17] Kies et al.</td>
<td>12-17</td>
<td>48 Gy</td>
<td>VVPAMC</td>
<td>similar, similar, 72, 50</td>
<td>Neg</td>
</tr>
<tr>
<td>[18] Choi et al.</td>
<td>148</td>
<td>50</td>
<td>similar, similar, 44-54 Gy, 11, 13, 0, 21, 80, 25</td>
<td>Pos</td>
<td></td>
</tr>
<tr>
<td>[19] Greco et al.</td>
<td>1-6</td>
<td>45 &lt;.05</td>
<td>CAV</td>
<td>42, 48, 21, 29</td>
<td>Pos</td>
</tr>
<tr>
<td>[20] Creech et al.</td>
<td>8</td>
<td>50</td>
<td>CML</td>
<td>.003, 56, 68, 13, 19</td>
<td>Pos</td>
</tr>
</tbody>
</table>

fr: fractions; CAV: cytoxan, adriamycin, vincristine; CVP: cytoxan, vincristine, cisplatin, vinblastine; CAVM: cytoxan, adriamycin, vincristine, methotrexate; CMC/ProAV: cytoxan, methotrexate, procarbazine, adriamycin, vinblastine; CMV-CCNU: cytoxan, methotrexate, vincristine, lomustine; CM: cytoxan, methotrexate; AV/CM: adriamycin, vincristine, cytoxan, methotrexate; VMVP/CAV: vincristine, methotrexate, vinblastine, cisplatin, cytoxan, adriamycin, vincristine; CVP: cytoxan, vincristine, cisplatin; VVPAMC: vinblastine, vincristine, cisplatin, adriamycin, methotrexate, cytoxan;

Recently for limited stage SCLC, the common element in all positive randomized or simple prospective trials is the chemotherapy with etoposide+cisplatin combined with radiotherapy [21]. Takada et al. [22] in a randomized trial compared chemotherapy (etoposide+cisplatin) with either concurrent or sequential radiotherapy and reported beneficial results for the concurrent scheme.

Moreover, Turrisi et al. [23] in another randomized trial compared chemotherapy (etoposide+cisplatin) with either once daily or hyperfractionated radiotherapy and concluded that the twice daily scheme is significantly better (26% 5-year survival versus 16%). The definitions for the target volumes used in radiotherapy according to ICRU 50 guidelines are shown in table 2.

### Table 2. ICRU Planning Volume Terminology. ICRU= International Commission on Radiation Units and Measurements.

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Term</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTV</td>
<td>Gross Tumor Volume</td>
<td>Macroscope tumor volume as determined by clinical examination, surgical exploration and imaging studies.</td>
</tr>
</tbody>
</table>
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CTV  Clinical Target Volume  GTV plus additional volume to account for possible microscopic spread of disease to regional lymph nodes, adjacent soft tissues, along fascial planes, etc, according to the natural history of the particular neoplasm.

PTV  Planning Target Volume  CTV plus additional volume to account for variation in day-to-day setup, physiologic patient motion of tumor and other positional uncertainties.

The portal arrangements for SCLC are a subject of controversy. The main stream concerns portals that encompassing the prechemotherapy primary tumor with a 1-cm margin plus the high risk nodal bearing areas. Effective chemotherapy normally takes care of subclinical or microscopic disease. Kies et al. [17] in a randomized SWOG study of patients with limited stage SCLC analyzed patients treated with either large fields with the prechemotherapy primary tumor or small fields only the residual disease after two courses of multiagent chemotherapy. Patients treated with large fields had a slightly better survival and duration of response. Although the clinical target volume (CTV) and the optimal fractionation schedule have not been definitely established, we may argue that if a 3D-conformal technique is used, the radiation induced toxicity is minimal and the large fields technique (prechemotherapy tumor) should be used. The fractionation size should also be 1.8-2Gy 5 days a week. The total dose should be 50Gy to patients with complete response after chemotherapy and 60-66Gy to those with partial response. A typical anterior-posterior portal for SCLC based in pre-chemotherapy CT scans is shown in figure 1.
**Figure 1.** 3D conformal radiotherapy with anterior-posterior fields in SCLC (digital reconstructed radiography, DRR). The red lines represent the pre-chemotherapy bulky mass in the mediastinum as was shown in CT slices. The pre-chemotherapy mass is used for the PTV of the thoracic irradiation. The black line stands for the midline, as this line was used for the registration of CT-images and chest-radiography.

**Conclusions**

- Concomitant chemotherapy and 3D-conformal thoracic irradiation should be the treatment of choice, while the RT should be given with attention in levels over 50Gy.
- Attention with doxorubicin and methotrexate combined with irradiation due to higher toxicity rates

In terms of sequential chemo-irradiation:

- 54-56Gy of 3D conformal thoracic irradiation after complete response of chemotherapy
- 60-68Gy of 3D conformal thoracic irradiation after partial response of chemotherapy

In terms of consolidation or concomitant chemotherapy:
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- 46-50 Gy of 3D conformal thoracic irradiation should be given with precautions concerning radiation induced pneumonitis.
- In case of bulky disease remaining after the 50 Gy, a boost schedule encompassing only the gross tumor volume might be administered up to 60 Gy.


In patients with limited small-cell lung cancer, chemotherapy combined with thoracic radiotherapy yields complete response rates of 50 to 85 percent, a median duration of survival of 12 to 20 months, and 2-year disease-free survival rates of 15 to 40 percent [23,24]. Five-year survival rates may exceed 20 percent for patients who have complete responses [23]. With the combined treatment, the risk of a thoracic recurrence decreases, and as a result, brain metastasis becomes one of the main types of relapse. Although only 10 percent of patients have brain metastasis at the time of diagnosis, the cumulative incidence at two years is more than 50 percent, [25] which is consistent with the rate found in autopsy series [26]. Indeed, back to 1970 Mathews et al. [27] observed that 83% of patients with small-cell lung cancer (SCLC) who died one month after curative resection had residual disease on autopsy and in 50% of them had brain metastasis. Also in the early 70s Hansen [28] raised the question whether brain irradiation should be in conjunction with systemic chemotherapy for the treatment of patients with SCLC. From 1977 up to 1997 eleven prospective randomized clinical trials were published in which SCLC patients with or without limited disease and complete response were randomized to receive or not prophylactic cranial irradiation (PCI) [29-39]. These trials showed that PCI significantly decreased the risk of developing CNS metastases. Most of the trials reported total irradiation dose 30 to 36 Gy [40,41].

A thorough meta-analysis by Auperine et al. [42] published by the Prophylactic Cranial Irradiation Overview Collaborative Group evaluated prophylactic cranial irradiation in 987 patients with small-cell lung cancer in complete remission and showed that prophylactic cranial irradiation
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leads to a small but significant absolute reduction in mortality (5.4 percent), even after adjustment for the extent of initial disease. Additionally, irradiation not only significantly reduced the risk of brain metastasis, as previously shown in individual trials, but also improved overall and disease-free survival; these results confirm that prophylactic cranial irradiation prevents and does not simply delay the emergence of brain metastases. Meert et al. [43] in another meta-analysis of twelve randomised trials (1547 patients) revealed a decrease of brain metastases incidence (hazard ratio (HR): 0.48; 95 % confidence interval (CI): 0.39 - 0.60) for all the studies and an improvement of survival (HR: 0.82; 95 % CI: 0.71 - 0.96) in patients in complete response in favour of the PCI arm. Auperine et al. also identified a trend (P=0.01) toward a decrease in the risk of brain metastasis with earlier administration of cranial irradiation after the initiation of induction chemotherapy. Summary data of the survival rate and the relevant hazard ratio are shown in table 3.

Table 3. Results of two meta-analyses of PCI in patients with SCLC in complete remission.

*a* denotes for Auperine et al. and *b* denotes for Meert et al. Rate (%) is assessed over a 3-year of period.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Relative risk (95% confidence interval)</th>
<th>Rate (%) in the treated group</th>
<th>Rate (%) in the control group</th>
<th>Absolute benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>0.84(0.73-0.97)<em>a</em></td>
<td>20.7*^a*</td>
<td>15.3*^a*</td>
<td>5.4*^a*</td>
</tr>
<tr>
<td></td>
<td>0.82 (0.71-0.96)<em>b</em></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Disease free survival</td>
<td>0.75(0.65-0.76)<em>^a</em></td>
<td>23.3*^a*</td>
<td>13.5*^a*</td>
<td>8.8*^a*</td>
</tr>
<tr>
<td>Cumulative incidence of brain</td>
<td>0.46(0.38-0.57)<em>^a</em></td>
<td>33.3*^a*</td>
<td>58.6*^a*</td>
<td>-25.3*^a*</td>
</tr>
<tr>
<td></td>
<td>0.49(0.39-0.62)<em>^b</em></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Radiation induced neurotoxicity comes as the main argument of the opponents of PCI [44]. From a radiobiological point of view, concerning the early injury of central nervous system, van der Kogel [45] reported some reactions within the first 6 months after radiation. These radiation injuries comprise demyelination (somnolence syndrome) or leukoencephalopathy. The pathogenesis is focused on damages in oligodendrocytes and astrocytes. Some reviews of PCI studies since 1980 investigated neuropsychological effects of brain irradiation and reported cognitive disabilities, mental abnormalities and neurological disorders [46,47]. Conflicting reports exist regarding the cognitive effects of prophylactic brain irradiation. Retrospective analyses performed in the 1980s reported neuropsychological modifications after PCI [48-50]. On the contrary, several randomized trials [46,51] showed no significant evidence of neurotoxicity. All these years two major questions are coming trough persistently: is PCI beneficial for SCLC and also is PCI neurotoxic?

Pedersen et al. [52] in a thorough review among 715 patients states that the incidence of central nervous system relapse in those not receiving PCI was 22% versus 6% in those receiving irradiation. However the neurological sequelae for a PCI course of 30Gy in ten fractions ranges from 0-12.5%, when chemotherapy is administered concomitant with the PCI. In table 4, the fractionation and the neurological toxicity of several PCI courses are shown. There are articles emphasizing the impact of radiotherapy schedule to the incidence of neurotoxicity by means of a critical value of 3 Gy per fraction and up to 30 Gy for total dose [39,41]. Moreover, the toxicity rate after PCI is rather minimized in the first year of follow-up [41]. Additionally, previous studies suggested that the concurrent chemotherapy in conjunction with total radiation dose more than 30 Gy in the brain might affect higher function modifications [47,48,53,54]. Along with this, the younger the patient, the greater the side effects of the treatment [44,55-59].
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Table 4. Neurological sequelae of PCI in small cell lung cancer patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>No. patients</th>
<th>Clinical (%)</th>
<th>Radiological CT</th>
<th>Concomitant</th>
<th>Dose/fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al. [60]</td>
<td>24</td>
<td>12.5</td>
<td>yes</td>
<td></td>
<td>30Gy/10</td>
</tr>
<tr>
<td>Looper et al. [13]</td>
<td>13</td>
<td>77</td>
<td>yes</td>
<td></td>
<td>30Gy/10</td>
</tr>
<tr>
<td>Licciardello et al. [61]</td>
<td>7</td>
<td>42</td>
<td>yes</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Livingston et al. [16]</td>
<td>17</td>
<td>6-12</td>
<td>yes</td>
<td></td>
<td>30Gy/10</td>
</tr>
<tr>
<td>Van Oosterhout et al [62]</td>
<td>32</td>
<td>0</td>
<td>0</td>
<td>No</td>
<td>30Gy/10</td>
</tr>
<tr>
<td>Laukkanen et al.[63]</td>
<td>12</td>
<td>50</td>
<td>50</td>
<td></td>
<td>30Gy/10</td>
</tr>
<tr>
<td>Twijnsta et al.[64]</td>
<td>14</td>
<td>Yes</td>
<td></td>
<td></td>
<td>30Gy/10</td>
</tr>
<tr>
<td>Johnson et al.[65]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parageorgiou et al. [66]</td>
<td>11</td>
<td>0</td>
<td>No</td>
<td></td>
<td>30Gy/10</td>
</tr>
</tbody>
</table>

A typical PCI is shown in figure 2.
**Figure 2.** Typical PCI with isodose-lines. The red line stands for the Reed’s line representing the base of the scalp.

**Conclusions**

- Concurrent chemotherapy and PCI should be avoided.
- The schedule of 30Gy in 10 fractions seems safe if concurrent chemotherapy is excluded and performance status is good.
- PCI should be administered in case of complete response of the primary tumor without any distant metastases. Performance status should not be poor for the administration of PCI.
- PCI should be administered early after the completion of chemotherapy.
- PCI decreases relapses by 23% and prolongs survival by 5%.
- Radiation induced neurotoxicity of PCI seems minimal. Many confounding factors, such as age, long-term tobacco use, paraneoplastic syndromes, micrometastases, and the neurotoxicity of anticancer drugs, may have effects erroneously attributed to irradiation.

I.4. SCLC: extensive disease

Intensive initial chemotherapy induces a complete response rate of 18% to 40% in patients with extensive disease in contrast with 40% to 70% in those with limited disease. The role of radiotherapy in patients with extensive disease SCLC is not well documented [3]. Delaney et al. [67] in a decision making model proposed thoracic irradiation only in symptomatic patients with good performance status. The management of bone or brain metastases definitely includes the administration of palliative irradiation with conventional or short-term schedules (either 5X400cGy or 10X300cGy). In general the prognosis is dismal and hardly extends beyond 6 months [3]. Details of the proposed treatment schedules depending on the stage and performance status are given in figure 3.
Section II. Non Small Cell Lung Cancer

II.1. Introduction

Non-Small Cell Lung Cancer (NSCLC) accounts for 70–80% of all lung cancers. Unfortunately 2/3 of them are diagnosed in advanced stages. Stage III or locally advanced cancer comprises approximately 40% of all NSCLC and consists a major therapeutic problem in every day clinical practice for the radiation oncologist. Stage III NSCLC represents a heterogeneous group of disease with a great variation of the clinical extent. To add to controversy the borders between resectable and unresectable Stage III tumors have recently become less clear. New techniques (3D
conformal), fractionation schedules (hyperfractionation, CHART etc), combined Chemotherapy-Radiotherapy (CHT-RT) have been tried with encouraging results, although long term results are not available yet.

II.2. Postoperative adjuvant radiotherapy

Generally, postoperative radiotherapy has been advocated for positive or close surgical margins. The definitions of positive/close or clear margins are rather arbitrary. If tumor cells are found in the surgical margins these are called positive. If less than 0.5cm of normal tissue is present adjacent to the tumor edge, the surgical margin is usually considered close. More than 1cm of normal tissue is considered a clear margin. In situations of not clear margins a course of 60 to 66 Gy (2Gy/fraction) is usually recommended. If during thoracotomy, a complete and thorough resection of mediastinal nodes is performed and all nodes are negative, then the portal of irradiation should encompass only the tumor bed with 1.5-2cm safety margins due to respiratory movements.

It is generally agreed that in patients after complete resection and with clear margins as well as without nodal involvement (T1N0, T2N0), no adjuvant postoperative treatment is needed. Van Houtte et al. [68] in a randomized trial with 222 patients (T1,2N0) with complete resection, no beneficial effect of postoperative irradiation was noted. However, there are conflicting reports on the beneficial effect of postoperative irradiation in patients with N1 disease. Ferguson et al. [69] reported on 34 patients with T1,2N1 with a 10% survival for surgery alone and 40% for postoperative radiation therapy. On the other hand Martini et al. [70] reported negative results with 45% for surgery alone and 13% for postoperative radiotherapy. Recommendations for N2 patients are less controversial. The Lung Cancer Study Group (LCSG) [71] reported in 1986 the results of randomized trial in patients with stage II to III epidermoid carcinoma of the lung after complete resection receiving either postoperative radiotherapy or no treatment. The postoperative radiotherapy significantly reduced the rate of local recurrence but without any benefit to survival. In general the causes of controversy for postoperative radiotherapy concerning the randomized trials are mainly due to the following: lack of proper selection of patients, lack of uniformity in anatomic description of nodal regions or nodal surgical resection, lack of uniformity in radiotherapeutic target volume or radiation dose. The survival with postoperative irradiation in NSCLC is shown in table 5.

Table 5. Survival with postoperative irradiation in NSCLC.

<table>
<thead>
<tr>
<th>Study</th>
<th>Years</th>
<th>Surgery alone</th>
<th>Radiotherapy</th>
<th>Median dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Tumors</th>
<th>Doses</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choi et al. [72]</td>
<td>5 (adeno-Ca) 8</td>
<td>43</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>4 (squamous) 33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chung et al. [73]</td>
<td>3</td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>Green et al. [74]</td>
<td>5</td>
<td>3</td>
<td>35</td>
</tr>
<tr>
<td>Israel et al. [75]</td>
<td>3</td>
<td>50</td>
<td>70</td>
</tr>
<tr>
<td>Kirsh et al. [76]</td>
<td>5</td>
<td>0</td>
<td>23</td>
</tr>
<tr>
<td>Paterson et al. [77]</td>
<td>3</td>
<td>36</td>
<td>33</td>
</tr>
<tr>
<td>Pavlov et al. [78]</td>
<td>5</td>
<td>24</td>
<td>38</td>
</tr>
<tr>
<td>Van Houte [68]</td>
<td>5</td>
<td>45</td>
<td>20</td>
</tr>
<tr>
<td>Wesenburger et al.</td>
<td>5</td>
<td>53</td>
<td>56</td>
</tr>
</tbody>
</table>

II.3. Radical Radiotherapy

Definitive radiotherapy is indicated for approximately 40% of patients presenting with newly diagnosed non-small cell cancer. Two groups deserve comment: medically inoperable patients with early stage NSCLC and those with local recurrence. Studies with stage I,II NSCLC medically inoperable report excellent results in patients with tumors smaller than 2-4cm, good performance status and doses of 60Gy or more [79]. In terms of postoperative thoracic recurrence, patients with more favorable outcome included those with a recurrence more than 1 year after surgery, a bronchial rather than a nodal or chest wall recurrence, younger age, female gender, good performance status, absence of weight loss and squamous histology. The addition of chemotherapy did not improve survival.

The portals of radiation fields should include the gross tumor volume (GTV) and the subclinical disease in terms of regional lymphnodes and/or median carcinomatous pneumonitis. The planning target volume (PTV) should take into account the respiratory movements of the lungs. The RT schedule should normally be divided into 2 or more phases, with the technique of shrinking fields. A typical scheme of target volumes for NSCLC is shown in figure 4.
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Figure 4. Theoretical diagram of target delineation; GTV = gross tumor volume; PTV2 = planning target volume around the GTV; CTV = clinical target volume (elective treated areas thought to contain micrometastasis); PTV1 = planning target volume around CTV.

It is common practice to design treatment portals with a 2cm margin around any gross tumor seen on posterior-anterior radiographs and approximately 1cm margin around electively treated regional lymphnode areas. Multiple beams and oblique portals are required to deliver adequate tumor dose with sparing the spinal cord in order to keep the dose below 45Gy. When traditional portals are used to cover potential lymphatic drainage, the following guidelines are suggested:

If the primary tumor is in the upper lobe the ipsilateral supraclavicular region should be included in the treatment portal. The inferior portal should be 5 to 6 cm below carina. If the primary tumor is located in a middle or lower lobe and no mediastinal lymphadenopathy is present, there is no need to treat the supraclavicular areas. Examples of portals used for irradiation of NSCLC depending on the anatomic location of the primary tumor are showed in figures 5,6,7. The two phases of treatment (phase I with tumor, microscopic disease and regional lymphnodes; phase II with gross tumor volume) are also shown.
Figure 5. Portals used for anterior-posterior fields for NSCLC. CTV1 encompasses regional lymphnodes of the mediastinal area and CTV2 encompasses mainly the primary tumor. CTV3 encompasses the supraclavicular node (boost).
Figure 6. **A**: 3D conformal radiotherapy for Non Small Cell Lung Cancer. The red lines are for the PTV. The brown lines are for the organs at risk: spinal cord and contralateral lung. **B**: Isodose lines in a representative CT slice. The spinal cord and the contralateral lung are sparing safely.

Figure 7. A verification portal (anterior-oblique field for sparing the spinal cord) of a residual mass of NSCLC after chemotherapy. The energy used is 18MV.
In a recent paper Komaki et al. [80] performed a recursive partitioning analysis (RPA) of 1547 patients with inoperable NSCLC included in 4 RTOG trials and were treated by radical RT. Patients in class I (Median Survival Time, MST, of 12.6 months) where those with Karnofsky Performance Status (KPS) 80–100, negative nodes, age younger than 70, weight loss <5% and radiation dose ≥66 Gy and they had a 2-year survival rate of 25%. In class II (MST 8.3 months) patients were of KPS 80–100, node positive, age ≤60 years old, WL<5% and radiation dose <66Gy and they experienced a 2-year survival rate of 13%. Classes III and IV carried the most dismal prognosis (table 6).

Table 6. The four classes of recursive partitioning analysis (RPA), by Komaki et al. [80] for patients treated by radiotherapy alone (WL: Weight Loss, KPS: Karnofski Performance Status).

<table>
<thead>
<tr>
<th>Class</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS:80–100</td>
<td>KPS:80–100</td>
<td>KPS≤70</td>
<td>KPS ≤70</td>
<td></td>
</tr>
<tr>
<td>Node negative</td>
<td>Node positive</td>
<td>Pleural effusion</td>
<td>Pleural effusion (+)</td>
<td></td>
</tr>
<tr>
<td>Age &lt;70</td>
<td>Age &gt;60</td>
<td>(-)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WL &lt;5%</td>
<td>WL &gt;5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT Dose ≥66Gy</td>
<td>RT Dose &lt;66Gy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Survival Time (Months)</td>
<td>12.6</td>
<td>8.3</td>
<td>6.2</td>
<td>3.3</td>
</tr>
<tr>
<td>2-year survival rate</td>
<td>25%</td>
<td>13%</td>
<td>8%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Most studies agree that PS is a prognostic factor of absolute significance in inoperable NSCLC are in agreement on the absolute significance of PS on patients’ prognosis. Most trials include patients with PS of 0 or 1 and WL <5% when treating patients with radical intent. But there are also some that include patients with Karnofski PS ≥70 or even 60 [81], which corresponds to PS ≤2 in ECOG scale. Therefore, it seems logical to start with a careful evaluation of KPS even before the staging of these patients. Those with high PS are candidates for radical treatment. Elderly patients—in case of radical treatment—should also be treated by conventional RT schedule. Movsas et. al re-evaluated six Phase II and III RTOG trials and found that the elderly patients (i.e. those >70 years old) were better treated by the conventional scheme of 60 Gy [82].

If radical RT is planned, we have to decide upon the optimal RT scheme. In UK it is a rather common practice to treat radically patients with stages I-IIIa with a hypofractionated RT scheme of
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20 fractions, while patients with ‘bulky’ stage IIIa,b are usually treated with palliative intent [83]. For this group of patients radical RT is not recommended in UK outside randomized clinical trials. In the USA more radical treatments are usually given even for those with bulky disease. The ‘golden standard’ of 60 Gy in 30 fractions is useful, however all authors agree that higher doses are needed to eradicate NSCLC; on the other hand a higher incidence of morbidity is associated with a dose above 60 Gy given by conventional fractionation. In some studies dose escalation has a positive impact on tumor control; promising results have been reported by Armstrong et al from the 3D conformal RT for NSCLC (median dose 70.2 Gy); the authors propose that total dose increase, results in a better outcome (MST 15.7 months and 2-year survival rate 32%) [84]. 3D conformal RT demands for high-tech equipment, although in some centers, special techniques have been developed; Wurstbauer et al. [85] described an interesting technique (target splitting by asymmetric collimation) which can be easily applied by departments without available 3D planning systems.

Indication exists that some subtypes of NSCLC proliferate rapidly with a potential doubling time of about 5 days. So there is a clear need for these tumors to be treated by a high dose in a shorter total treatment time. Such RT schemes are termed accelerated fractionation.

RTOG 83 11 was a phase II dose escalation trial in which patients were randomized to receive total doses of 60, 64.8, 74.4, and 79.2 Gy hyperfractionated. This trial suggested that there was a favorable subgroup with good PS, WL<5% and received total dose of greater than 69.6 Gy [86].

The published CHART-lung trial [87] reported 2-year survival rates of 20% for standard RT of 60 Gy/30 fr., and 29% for the CHART arm. In the subgroup of patients with non-squamous cell histology, the conventional RT resulted in a better 2-year survival of 27 vs. 21%, but it did not reach statistical significance. Some authors have criticized the inclusion of stage I and II patients (30 and 7% respectively). These earlier stage patients frequently had unfavorable features such as older age, coincidental disease, etc; all patients had to be of PS 0.1. A modified CHART scheme, the CHARTWELL (weekend less) i.e. 60 Gy in 18 days is currently being tested [88]. The option for CHT given with CHART is also considered [87].

II.4. Chemoirradiation

Combined chemotherapy and radiation is now considered the treatment of choice for locally advanced inoperable non-small cell lung cancer in patients with good performance status and absence of weight loss. The results of most randomized trials showed the superiority of sequential chemo-radiotherapy or combined chemo-radiotherapy versus radiotherapy alone [3]. Trials that
failed to show a difference in survival did not use cisplatin-based chemotherapy or gave low doses of irradiation [89,90].

Despite the promising results of modified fractionation schemes both local control and distant metastases rate are far from satisfactory. Therefore combined modality treatment is being investigated. Chemotherapy is administered as inductive, alternating, concurrent or various combinations with RT. A meta-analysis with updated data on individual patients, involving 52 randomized clinical trials has recently been published. Trials comparing RT with RT plus CHT gave a 13% reduction in the risk of death (absolute benefit of 4% at 2 years) [91]. Numerous other trials advocate the combination of RT-CHT reporting acceptable toxicities (table 6) while the few trials reporting negative results have been criticized [92,93]. The majority of these trials include patients with KPS of ≥70. Komaki et.al. compared the three arms of trials RTOG 88–08/ECOG 4588 and they concluded that the addition of chemotherapy decreases the risk of distant metastases and increases survival for non-squamous NSCLC; survival rates were similar among the treatment arms for patients with squamous-cell carcinomas [94].

Cox et. al. in a similar study performed an evaluation of the influence of chemotherapy on therapeutic result of the combined treatments for various histologies of stage III NSCLC [95]. They analyzed data from 4 RTOG RT-alone studies (1415 patients) and 5 RTOG combined- treatment studies (350 patients). The main conclusions were very important:

Conclusions

- Patients with low PS should be treated by short-term palliative RT courses
- Chemotherapy reduces distant metastases in all types of NSCLC
- Chemotherapy has different effects on the primary tumor by cell type
- Chemotherapy has no effect on the development of brain metastases
- Squamous cell carcinomas should be approached in a different manner than the other histological types. Dose escalation studies from the radiotherapeutic point of view might be the key point
- The high risk of brain metastases in patients with non squamous-cell NSCLC probably justifies the use of prophylactic cranial irradiation in these patients.

Similar conclusions are drawn by Movsas et al. [83], who have re-evaluated the 979 patients treated in 6 prospective Phase II and III clinical trials from 1982 to 1995. Treatment regimens ranged from conventional, to hyperfractionated (69.6 Gy), induction chemotherapy plus conventional RT,
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induction+concomitant+conventional RT, etc. Patients with low KPS (50–70) had the lowest MST (7.8 months), patients <70 years of age had improved survival with the use of aggressive therapy, while those with >70 years of age were better treated by the conventional schedule. A dramatic improvement was seen in patients with squamous cell histology who received induction+concomitant chemotherapy plus conventional RT (median survival 25.7 months).

Trials RTOG 88 08 and ECOG 45 88 [96] compared in a three arm study conventional RT, induction chemotherapy – conventional RT and hyperfractionated. The 2-year survival rates were 20%, 31% and 24% and the MST 11.4, 13.6 and 12.3 months respectively. There was a consistent difference between radiation alone and chemo-irradiation that was statistically significant (log-rank p = 0.05), while hyperfractionated RT was better than conventional RT at every time point but differences were not statistically significant. Primary tumor was equally controlled with the use of either induction chemotherapy or hyperfractionated RT. Distant metastases were less for chemo-irradiation compared to RT alone groups. Survival rates were similar among the treatment arms for patients with squamous cell neoplasms. Among patients with non-squamous histologies, failure patterns did not differ by treatment group, but survival was significantly better in those treated by induction chemotherapy (p = 0.04).

Jeremic et. al. [97] have reported a significant improvement in median survival time (MST) and 2-year survival probability for patients treated with hyperfractionated RT plus weekly concurrent chemotherapy (VP16, Carboplatin). The arm treated by hyperfractionated RT only gave results similar to that given by the RTOG 83 11 trial. Toxicity of combined treatment was acceptable. None patient died of treatment related toxicity. The same authors conducted a second trial with two arms [98]. Hyperfractionated RT in a dose of 69.6 Gy was given in both, while chemotherapy was given to the second arm, but it was administered in a more continuous way on each RT day and using a lower dose per administration. The combined treatment arm experienced a MST of 22 months and a 2-year survival of 43% vs 14 months and 26% in the RT alone arm. The problem of controlling distant metastases remains. The additional use of intensive sequential chemotherapy should be considered. Komaki et.al. studied two different combinations of RT and chemotherapy in a randomized trial with two arms [99]. Patients in the first arm were treated with induction chemotherapy followed by concurrent chemo-irradiation: Vinblastine was administered weekly and cisplatin on days 1.29.50.71.92; RT started on day 50. 63 Gy were given in 34 fractions/7 weeks. In the second arm, patients received concurrent chemo-irradiation: RT started on day 1 and a total dose of 69.6 Gy /58 fr. was given. DDP was given in days 1 and 8 and VP16 was given during the first 10 days. Patients had to be of PS ≥70 and WL<5%.The first arm showed greater haematologic toxicity while the
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second greater acute and late esophageal toxicity. The MST was 15.5 and 14.4 months respectively; 1-year survival 65% and 58% and 2-year survival were approximately 28% for each arm. Therapeutic outcome was similar for both groups and similar in absolute numbers to the ‘concurrent' arms of other trials (table 2) [100–103]. The ‘every-two-weeks’ concurrent chemo-irradiation was tested in a trial conducted by Blanke et. el. [104]. The MST and 2-year survival rates were similar between arms of RT, and chemo-RT (table 7). The alternating hyperfractionated RT – chemotherapy (rather similar to the above-mentioned schedule) was tested in GOTHA I and II trials [105], giving an MST of 13.6 months and 2-year survival of 27% with acceptable toxicity. The rates were better than those reported by Blanke et.al., although the study included patients with KPS of 70–100.

The reported results in terms of 2-year survival rates are rather in favor of lower daily doses of chemotherapeutic agents. In this way chemotherapeutic agents seem to behave like radiosensitizers. Nevertheless such a regimen failed to control effectively distant metastases. To improve overall survival further, additional use of CHT should also be considered in future randomized clinical trials.

Table 7. Trials of combined chemotherapy-radiotherapy (CHT-RT).

<table>
<thead>
<tr>
<th>AUTHORS</th>
<th>ARMS</th>
<th>CHT</th>
<th>RT SCHEME</th>
<th>RT DOSE</th>
<th>Nm Patient</th>
<th>1-year survival</th>
<th>2-year survival</th>
</tr>
</thead>
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<tr>
<td>Soresi et al. [106]</td>
<td>1</td>
<td>-</td>
<td>25X5</td>
<td>50</td>
<td>50</td>
<td>48</td>
<td>25</td>
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<td></td>
<td>2</td>
<td>Cisplatin</td>
<td>45</td>
<td>73</td>
<td>40</td>
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<td></td>
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<tr>
<td>Schaake-Konig et. al. [107]</td>
<td>1</td>
<td>-</td>
<td>10X3-, 3 week rest-10x2.5</td>
<td>55</td>
<td>110</td>
<td>46</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Cisplatin</td>
<td>55</td>
<td>110</td>
<td>54</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Trovo et. al. [92]</td>
<td>1</td>
<td>-</td>
<td>15x3</td>
<td>45</td>
<td>85</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>2</td>
<td>Cisplatin,</td>
<td>45</td>
<td>86</td>
<td></td>
<td></td>
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<tr>
<td>Arriagada et. al. [100]</td>
<td>1</td>
<td>-</td>
<td>26X2.5</td>
<td>65</td>
<td>177</td>
<td>14</td>
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<td>2</td>
<td>VCPC</td>
<td>65</td>
<td>176</td>
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<tr>
<td>Dillman et. al. [101]</td>
<td>1</td>
<td>Cisplatin Vinblastine</td>
<td>30X2</td>
<td>60</td>
<td>78</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Regimens</td>
<td>Dose</td>
<td>Tumor</td>
<td>Lymph</td>
<td>1YOS</td>
<td></td>
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<td></td>
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<tr>
<td>Blanke et. al [104]</td>
<td>Cisplatin 30X2</td>
<td>60–65</td>
<td>105</td>
<td>45</td>
<td>13</td>
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<td>Cisplatin</td>
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<tr>
<td>Komaki et. al [86]</td>
<td>Cisplatin/VP16 Hyperfractionated</td>
<td>69.6</td>
<td>203</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Cisplatin</td>
<td>69.6</td>
<td>76</td>
<td>22</td>
<td>35</td>
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<td>Komaki et. al [99]</td>
<td>Vinblastine Cisplatin 35X1.8</td>
<td>63</td>
<td>80</td>
<td>65</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td>VP16 Hyperfractionated Cisplatin</td>
<td>69.6</td>
<td>82</td>
<td>58</td>
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<tr>
<td>Komaki et. al [94]</td>
<td>Cisplatin-VP16 30X2</td>
<td>60</td>
<td>152</td>
<td>20</td>
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<tr>
<td></td>
<td>Cisplatin-Vinblastine</td>
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<td>152</td>
<td>31</td>
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<tr>
<td></td>
<td>VP16 Hyperfractionated</td>
<td>69.6</td>
<td>154</td>
<td>24</td>
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<td></td>
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<tr>
<td>Jeremic et. al [98]</td>
<td>Carboplat VP16 Concurrent/daily</td>
<td>69.6</td>
<td>65</td>
<td>74</td>
<td>43</td>
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<td></td>
<td>Carboplat</td>
<td>69.6</td>
<td>66</td>
<td>68</td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>VP16, Concurrent /weekly</td>
<td>64.8</td>
<td>52</td>
<td>73</td>
<td>35</td>
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</tr>
<tr>
<td></td>
<td>Carboplat</td>
<td>64.8</td>
<td>56</td>
<td>50</td>
<td>27</td>
<td></td>
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</tr>
<tr>
<td>Miramanoff et. al. [105]</td>
<td>Hyperfractionated</td>
<td>63</td>
<td>65</td>
<td>56</td>
<td>27</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>63</td>
<td>67</td>
<td>56</td>
<td>27</td>
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<td></td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Clamon et. al. [102]</th>
<th>Vinblast + Cis-platine + carbo</th>
<th>30X2</th>
<th>60</th>
<th>130</th>
<th>56</th>
<th>29</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Saunders et. al. [88]</th>
<th>CHART</th>
<th>NO</th>
<th>30X2</th>
<th>60</th>
<th>225</th>
<th>21</th>
</tr>
</thead>
</table>

The locoregional or intrathoracic failure rate within the irradiated volume is dose dependent. It is a common secret that local recurrences especially in the gross tumor volume are the main problem in NSCLC. In all trials with irradiated dose less than 60 Gy the local recurrence is ranging from 40% to 48% [3,108]. The rates of recurrences after chemoradiotherapy is shown in table 8.

**Table 8.** Local failure rates. The failure rate is apparently dose dependent.

<table>
<thead>
<tr>
<th>Irradiated dose</th>
<th>Local failure rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>40Gy continuous dose</td>
<td>48%</td>
</tr>
<tr>
<td>40Gy split course</td>
<td>38%</td>
</tr>
<tr>
<td>50Gy continuous</td>
<td>38%</td>
</tr>
<tr>
<td>60Gy</td>
<td>27%</td>
</tr>
<tr>
<td>70Gy</td>
<td>&lt;20%</td>
</tr>
</tbody>
</table>

As a boost to the primary tumor seated inside the bronchus (endobroncial disease) the radiation oncologist may also administer intraluminal irradiation as brachytherapy [109].

II5. Stage IIIA-N2. Chemo-irradiation, surgery or combination?
RT or surgery alone have had limited success in treating patients with both occult and marginally resectable overt N2 disease. Current investigations are exploring various means of integrating surgery, RT, and chemotherapy. To date, no studies have established the optimal chemotherapy or chemotherapy/RT regimen for N2 patients, but most induction regimens have used platinum-based chemotherapy.
In the only other trial comparing surgical and nonsurgical treatment in this setting, Shepherd and associates [110] have reported a randomized trial of chemotherapy plus surgery vs. RT alone for biopsy-proven Stage IIIA NSCLC. Thirty-one patients were randomized. The median survival was 16.2 and 18.7 months for RT alone and chemotherapy plus surgery, respectively, with no improvement in long-term survival seen with combined-modality surgical treatment.

Do any other data suggest that RT with or without chemotherapy is a reasonable alternative to surgery with or without chemotherapy? A common conception is that RT alone is significantly inferior to surgery alone for N2 disease. However, N2 patients referred for RT are not a comparable group of patients to those who undergo surgery; such patients are usually rejected for surgery because of disease bulk or medical contraindications. Accordingly, few RT data are available for a surgically suitable group of N2 patients. The existing evidence suggests that hyperfractionated RT to 69.6 Gy in 6 weeks yields survival results surprisingly close to those for surgery. On analysis of completed RTOG lung trials using RT alone, a group of patients was identified that had clinical N2 disease, favorable prognostic factors (Karnofsky performance score >70, and <5% weight loss), and a T-stage distribution similar to surgical series. For standard fractionation RT, the 3-year survival rate was only 7%, but for hyperfractionated RT it was 20% [111]. This result is similar to that in several of the surgical series [112-113]. There will not likely ever be a direct comparison of RT and surgery for N2 disease. [114]. Thus, even with the best locoregional treatment, one could not expect to control the disease in more than 40% of patients. For patients with overt N2 involvement, even if nonbulky, the risk of systemic disease is even higher, and locoregional treatment alone would fail in 90% of patients.

Some promising results have come from two small Phase III trials of chemotherapy induction followed by surgery, with and without RT. The median survival in the first study was 26 months for induction chemotherapy followed by surgery and RT and was 8 months without induction chemotherapy [115]. In the second study, the median survival had not yet been reached using induction chemotherapy followed by surgery compared with 18 months for surgery alone [116]. Moreover, Arriagada et al. [117] in a well documented meta-analysis concluded that there was no effect of postoperative radiotherapy in patients with N2 disease, while there was no doubt for the deleterious effect of post-RT in N0,N1 patients. These results suggest that the optimum scheme of combined treatment for N2 patients is the following: chemo-irradiation (up to 50Gy) and in case of respectability, then surgery. In case of unresectability, then chemotherapy in consolidation therapy.

Conclusions
Radiotherapy after chemotherapy and surgery for N2 patients is not recommended.
Concomitant chemo-irradiation ±surgery might be the treatment of choice
The dose of pre-operative radiotherapy should not exceed 50Gy.

II.6. In the context of chemoradiotherapy: sequential, concomitant, induction or consolidation chemotherapy?
Cancer and Leukemia Group B (CALGB) study 8433 compared induction chemotherapy consisting of cisplatin and vinblastine followed by daily radiation to daily radiation alone [101]. The induction chemotherapy-containing arm showed improvement in median survival from 9.7 to 13.8 months. The benefit of sequential induction chemotherapy followed by daily radiation was confirmed in an inter-group trial (RTOG 8808, ECOG 4588, SWOG 8992) [118]. Sequential chemoradiotherapy appears to improve survival by lowering the rate of systemic relapse and does not appear to improve local control compared to radiotherapy alone [119]. Concomitant chemoradiotherapy also improves survival compared to radiation alone and appears to improve survival primarily by improving local control [120].

Sequential or concurrent chemotherapy added to daily radiation has now been compared in phase III randomized trials. A trial by the West Japan Group compared sequential full dose mitomycin, vindesine and cisplatin followed by daily radiation to a dose of 56 Gy to the same chemotherapy given concurrently with a split course of daily radiation to a dose of 56 Gy [119]. The concomitant therapy arm had a median survival of 16.5 months compared to 14.2 months in the sequential treatment arm. Radiation Therapy Oncology Group (RTOG) trial 9410 compared sequential versus concomitant chemotherapy as used in CALGB 8433 added to daily radiation of 2 Gy to a total dose of 60 Gy [120]. The third arm of RTOG 9410 was concomitant cisplatin and oral etoposide with twice-daily radiation of 1.2 Gy to a total dose of 69.6 Gy. Median survival was 17 months for concomitant chemotherapy with daily radiation versus 14.6 months for sequential therapy (P=0.038) and 15.6 months for concomitant chemotherapy and twice daily radiation. A French randomized phase III trial compared sequential chemoradiotherapy consisting of cisplatin and vinorelbine followed by radiation to 66 Gy to concurrent chemoradiotherapy with cisplatin and etoposide followed by cisplatin and vinorelbine and reported a trend toward improved survival for the concurrent therapy arm [121]. A Czech randomized phase II trial comparing sequential versus concurrent chemoradiotherapy with cisplatin and vinorelbine showed a median survival of 396 and 619 days, respectively [122]. The results of these studies suggest that the current standard of care should be concomitant platinum-based chemotherapy and once daily radiation for patients with good
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performance status. Patients with poor performance status, significant weight loss or pleural effusion were excluded from RTOG 9410 and there have been no randomized trials comparing sequential to concurrent chemoradiotherapy in that group of patients. Adding full dose chemotherapy to eradicate occult micrometastases before or after concomitant chemoradiotherapy that improves local control has the potential to improve survival in locally advanced NSCLC.

Giving full dose systemic chemotherapy prior to concomitant chemoradiotherapy treats micrometastatic disease immediately before it has the opportunity to progress or become resistant to the lower doses of chemotherapy that are typically given concomitantly with radiation. In addition compared to consolidation therapy, induction chemotherapy is delivered at a time when the patient will better tolerate side effects and bone marrow suppression. CALGB 9431 is a randomized phase II trial in which all patients received two cycles cisplatin based induction doublet chemotherapy and 2 cycles of cisplatin based doublet chemotherpay concurrent with daily radiation 2 Gy per fraction to a total dose 66 Gy [123]. Patients were randomized to receive gemcitabine, paclitaxel or navelbine as the second chemotherapeutic agent. The median survival for all patients was 17 months and there was no clear superiority to any of the recent generation chemotherapy agents. A phase II trial that evaluated induction chemotherapy with paclitaxel and carboplatin followed by concomitant chemoradiotherapy with weekly paclitaxel, carboplatin and conformal radiation therapy to a dose of 74 Gy had a median survival of 26 months with 1-, 2-, 3- and 4-year survival rates of 71, 52, 40, and 36%, respectively [124]. CALGB 30105 is an ongoing randomized phase II trial with one arm being the above regimen and the other consisting of induction carboplatin and gemcitabine followed by concomitant chemoradiation with twice weekly gemcitabine 35 mg/m2 also with conformal thoracic radiation to a dose of 74 Gy.

Beginning therapy with concomitant chemoradiotherapy utilizes what appears to be the most important component of the combination immediately before the often bulky local tumor can become larger or become chemoradioresistant. Southwest Oncology Group (SWOG) 9019 gave concurrent chemoradiation with cisplatin and etoposide followed by consolidation with 2 cycles of cisplatin and etoposide. In 50 patients with stage IIIB NSCLC the median survival was 15 months [125]. SWOG 9504 used the same concomitant chemoradiotherapy as SWOG 9019 but replaced two cycles of cisplatin and etoposide consolidation with two cycles of docetaxel. SWOG 9504 had an encouraging median survival of 27 months, with 1- and 2-year survivals of 76 and 53%, respectively [126]. The Locally Advanced Multimodality Project or LAMP trial is a randomized phase II trial with three arms of paclitaxel and carboplatin chemoradiation: arm 1 induction chemotherapy followed by radiotherapy alone, arm 2 induction chemotherapy followed by concomitant chemoradiotherapy, and arm 3 concomitant chemoradiotherapy followed by consolidation [127]. The reported median
survivals for the three arms of the LAMP trial are arm one 13 months, arm two 12.8 months, and arm three 16.1 months.

Conclusions

- Chemoradiotherapy is superior to radiation alone for locally advanced unresectable stage III NSCLC.
- Concomitant chemoradiotherapy appears to be superior to sequential chemoradiotherapy for good performance status patients.
- Encouraging results from phase II trials suggest that induction or consolidation chemotherapy added to concomitant chemoradiation may improve outcome

II.6. Superior vena cava syndrome

Superior vena cava syndrome is a medical emergency that requires immediate therapeutic action. The syndrome is produced by extrinsic compression of the superior vena cava or intracaval thrombosis which is seen in approximately 40-50% of patients with this syndrome. Although it is generally believed that these patients have an extremely poor prognosis approximately 10% - 20% survive longer than 2 years [128]. Therefore in the absence of distant metastases, aggressive management and support are indicated. Radiotherapy should be initiated as soon as possible. Patients should initially be given high dose fractions (4Gy per fraction) for 2-3 days, followed by conventional radiotherapy [129]. The recommended total dose for patients with localized bronchogenic carcinoma should be 60-70Gy while in patients with malignant lymphoma should be 40-45Gy. Radiation therapy portals (fig. 8) should include the mediastinal, hilar, supraclavicular nodal areas and any adjacent parenchymal pulmonary lesions.

Alternatively, superior vena cava syndrome secondary to malignant disease is preferentially treated by endovascular stenting with highly palliative effect [130]. Adjuvantly, external beam radiation and/or chemotherapy would also be administered for tumor mass reduction.
II.7. Palliative RT

According to all publications and most of the radiation oncologists agree that patients with low PS must be treated palliatively with short hypofractionated RT schedules. In everyday clinical practice radiation oncologist is called to treat patients with local disease too extensive for radical treatment. According to MRC studies an effective palliative treatment could be a 2 x 8.5 Gy one-week apart regimen [131]. In case of a low PS a single fraction of 10 Gy could be administered [132]. These studies have significantly influenced clinical practice in the UK and other countries [133], since they offer fast and effective palliation. It should be emphasized that the large dose per fraction does not produce unacceptable toxicity; especially for the widely used 2x8.5 Gy scheme the risk of radiation myelitis is extremely low if the spinal cord is blocked in the posterior field of the second fraction [134].

A third MRC study [135] comparing 2x8.5 Gy with 13x3 Gy for patients with good PS showed no difference in palliation, more severe and prolonged oesophagitis and a small but statistically significant increase in 2-year survival for the higher dose regimen (13 vs 9%). It is concluded that it is difficult to decide the trade-off between the increased toxicity and relative inconvenience against a modest increase in survival for an individual patient. The option between radical and palliative treatment may be based on the presence of the unfavorable patient and disease characteristics. Low PS (<60), WL >5%, positive pleural effusion, TNM stage of T4 or N3 and intensive symptomatology advocate the use of short course-palliative RT schemes. Nevertheless the 10x3 Gy course is widely used in the USA as the schedule of choice with palliative intent.
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Particularly for patients with supraclavicular node metastases (when there is lack of other adverse prognostic factors) Machtay et al. [136] reported that when treated with modern chemoradiotherapy these patients appear to have similar prognosis to other stage IIIb patients. Platinum-based chemotherapy is also recommended for patients with metastatic NSCLC and good performance status, while short term hypofractionated radiation therapy should also be considered for symptoms relief in these patients [137].

Conclusions

- CTV to PTV margins are 2cm around GTV and 1cm around regional lymphnodes.
- Spinal cord dose should be kept below 45Gy.
- 3D conformal should be the treatment of choice for irradiation. Traditional anterior-posterior fields should be used only for phase I of irradiation schedule or palliative radiotherapy.
- The lung volume received dose of 20Gy (V_{20}) should not exceed the 30% of total lung volume in order to minimize the radiation induced pneumonitis.
- The most important unfavorable characteristics of patients with NSCLC are: low KPS, weight loss>5%, positive pleural effusion, intensive symptomatology and distant metastases.
- For patients with unresectable stage IIIa,b and a PS of 70–100, a radical treatment should be given in terms of combined chemo-radiotherapy.
- Results from randomized clinical trials advocate the use of intensive RT (e.g. CHART or HFXRT).
- In case of radical RT alone the general recommendation is to administer as high dose as possible in as short as possible overall treatment time.
- The dose of 60 Gy in 30 fractions should be the least therapeutic dose to eradicate such a bulky disease, while it is the recommended RT schedule for patients over the age of 70 years.
- A high dose hyperfractionated RT scheme, or the CHART (in case of squamous cell carcinoma) could be employed.
- In all randomized clinical trials it is always reproduced that combined RT+CHT gives better therapeutic results that RT alone, and that HFX/ACCRT yields better results than STDRT alone.
- Results from randomized trials advocate the use of combined RT-CHT as a continuous way as possible. Platinum based chemotherapy can be combined to radiation therapy as inductive, concurrent or in consolidation.
If the above-mentioned therapeutic modalities are not available a tumor dose of at least 60 Gy in 6 weeks (or shorter) or its radiobiological equivalent could be employed.

For patients with PS of 70 with either locally too advanced disease or positive pleural effusion, a palliative (e.g. 2 x 8.5 Gy or 13 x 3Gy) RT regimen can be given.

Concurrent CHT+RT and intensified RT schedules (hyperfractionated-accelerated) should be administered for radical irradiation.

In terms of 3D conformal, positive are regional lymphnodes with diameter more than 1.5cm (probability 90% of having pathological involvement).

The GTV – CTV margins are depending on the histology: 6mm for adenocarcinoma and 8mm for squamous cell.

The acute side effects after RT are: acute pneumonitis, acute esophagitis, cough, Lhermitte syndrome. The management consists of bed/rest-bronchodilators-corticosteroid-O_2 (pneumonitis), mucosal anesthetics-liquid antacids (esophagitis), antitusive therapy (cough), antibiotics (secondary infection), antifungal medication (esophagitis). In severe esophagitis, nasogastic tube or intravenous hyperalimentation. In severe acute pneumonitis, hospitalization due to high percent of mortality.

Spinal cord myelopathy with doses >45

Esophagitis as a late complication (stenosis, ulceration, perforation, fistula) occurs in 5% or more of patients with 60Gy dose delivery in esophagus. Very careful with cis-platin combined with RT, since the previous incidence is higher.

Doxorubicin plus RT have synergistic effect with RT for the induction of cardiotoxicity.

**Figure 9.** Decision tree for radiotherapy in non small cell lung cancer [3,125].
The general outcome to the treatment of lung cancer according to stage is shown in table 9.

**Table 9.** General approach to the treatment of lung cancer and outcome [21,126].
### Stage Treatment Outcome

**Non small cell cancer**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Surgical resection, ± chemotherapy</td>
<td>5-year survival &gt;60-70%</td>
</tr>
<tr>
<td>II</td>
<td>Surgical resection, ± chemotherapy</td>
<td>5-year survival &gt;40-50%</td>
</tr>
<tr>
<td>IIIA</td>
<td>Surgical resection, +chemo-irradiation</td>
<td>5-year survival &gt;15-30%</td>
</tr>
<tr>
<td>IIIA,N2</td>
<td>Chemo-irradiation ± surgery</td>
<td></td>
</tr>
<tr>
<td>IIIB without pleural effusion</td>
<td>Chemo-irradiation</td>
<td>Median survival 8-10mo</td>
</tr>
<tr>
<td>IIIB with pleural effusion or IV</td>
<td>Chemo-irradiation</td>
<td>1-year survival 30-35%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-year survival 10-15%</td>
</tr>
</tbody>
</table>

**Small Cell Cancer**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited stage</td>
<td>Chemo-irradiation</td>
<td>5-year survival 15-25%</td>
</tr>
<tr>
<td>Extensive disease</td>
<td>Chemotherapy + palliative irradiation</td>
<td>5-year survival &lt;5%</td>
</tr>
</tbody>
</table>

### Section III. Radiation induced pneumonitis

Radiation pneumonitis (RP), which manifests within a period of 1–8 months after radiotherapy (RT), is one of the most significant complications. RT-induced pulmonary symptoms occur in about 20% of all PTs irradiated for lung cancer or other thoracic neoplasms, while subclinical functional and radiological changes are seen in an even larger fraction of patients [140-143].

Several studies have investigated the relationship between a number of clinical factors including age, gender, performance status, pulmonary comorbidity, tumour site, changes in plasma, cytokine transforming growth factor-β levels, histology and the development of severe RP [144-147]. Some authors have focused their analyses on patients treated with combined modality treatment (chemoradiotherapy), for which an increased risk of RP has been postulated [98,107,108,148-150].

However, most of these studies did not take into account 3D dosimetry data.

Some reports have identified `simple' dosimetric risk factors for RP [150]. Based on the detailed dosimetric information provided by three-dimensional (3D) treatment planning tools, other researchers have related the risk and severity of RP to specific Dose Volume Histogram (DVH)
parameters [151-155], and a few studies have characterised the dose–response curve for RP following RT by means of biological models [156-158].

While there is a number of differences in the published reports, there is some consensus about the association between a few of the dosimetric factors (mainly the mean lung dose $D_{\text{mean}}$) and the incidence of RP [152,159]. Most lung cancer patients showed poor pre-treatment pulmonary function and among those patients, chronic obstructive pulmonary disease (COPD) was not an uncommon clinical finding. However, the role of pre-treatment lung function and the influence of covariates such as chemotherapy agents are still under debate. According to several publications, the incidence of clinical pneumonitis is correlated with parameters from the DVH of the total lung volume (figure 10).

![Figure 10. Representative DVH for total lung. The indices of V20 and V30 are shown.](image)

In general, the most statistically significant factor predicting pneumonitis seems to be the percent volume of the total lung exceeding 20 Gy ($V_{20}$). According to Graham et al. [151], there was a strong correlation between $V_{20}$ and the severity of pneumonitis (table 10). When the $V_{20}$ was less than 22% there was no pneumonitis. When the $V_{20}$ was 22–31% there was an 8% Grade 2 pneumonitis, but no higher severity. It was not until $>32\%$ $V_{20}$ where high-grade pneumonitis ($\geq$ Grade 3) was encountered. The highest incidence of severe ($\geq$ Grade 3) pneumonitis was in patients with a $V_{20} > 40\%$, where there was a 23% crude incidence of Grade 3–5 pneumonitis and 3 patients died of unequivocal radiation-induced pneumonitis.
It seems that there is little correlation between the tumor size (measured by the GTV in cc) and the $V_{20}$ [151]. This implies that the potential ability to give escalated radiation doses is not limited to small tumors, but rather to the patient's unique anatomy and the treatment planning in order to keep the $V_{20}$ as low as possible. The $V_{20}$ parameter is easily identified on all treatment planning systems and can be quickly utilized as a parameter to judge whether a plan is acceptable or whether the plan is better than a computing plan.

Marks et al. [150] reviewed the results of 100 patients after 3D CRT for the development of pneumonitis, pulmonary fibrosis, and/or pulmonary symptoms. Although the authors looked at additional biologic (transforming growth factor-β [TGF-β]) and functional (PFTs and ventilation–perfusion scans) parameters, the best predictors of "pulmonary symptoms" after radiation therapy (RT) were the $V_{30}$ and the Normal Tissue Complication Probability (NTCP, Lyman model). This is most consistent with our presented data in this paper. The $V_{20}$ and $V_{30}$ parameters may be nearly identical parameters particularly when "traditional" plans are used. They may differ in the future if new treatment modalities are created that use nonconventional beam arrangements, or intensity modulation.

In a study involving the pooled data of five institutions with 540 patients, Kwa et al. [158] reported that the mean lung dose, (NTD$_{\text{mean}}$) was a useful predictor of the risk of pneumonitis. Future studies are indicated to further identify and refine these DVH data in predicting not just "risks" of pneumonitis, but who exactly will develop pneumonitis. It is anticipated that there are unique and individual biologic/physiologic responses to radiation that will not be well predicted by this empiric dose–volume relationship. Further modeling taking into account other biologic markers, such as cytokine changes [159-164] underlying lung function, may be necessary.

In addition, it is clear that there are other pulmonary outcomes worth evaluating after 3D treatment, such as lung fibrosis, long symptomatic pulmonary function, and quality of life as it relates to lung function. However, because the $V_{20}$ seems to be the most important predictor of

### Table 10. Correlation between $V_{20}$ and severity of pneumonitis

<table>
<thead>
<tr>
<th>$V_{20}$ (%)</th>
<th>Grade 2 (%)</th>
<th>Grade 3-5 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;22</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>22-31</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>32-40</td>
<td>13</td>
<td>5 (1 fatal)</td>
</tr>
<tr>
<td>&gt;40</td>
<td>19</td>
<td>23 (3 fatal)</td>
</tr>
</tbody>
</table>
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pneumonitis, this implies to us that the volume effect in the development of acute pneumonitis is a much more important factor than the physiologic lung function and response to radiation of the affected parts of the lung.

Until further investigations of this nature can be performed, we recommend that the total lung volume DVH be assessed when evaluating the "goodness" of a 3D radiation plan in the treatment of NSCLC patients. In the clinic of Carlos Perez, some practical guidelines are used for the routine lung radiotherapy:

Conclusions and recommendations

- When the total lung $V_{20}$ is <25%, we might be comfortable with tumor dose escalation and the very low risk of pneumonitis. These plans are considered "acceptable."
- If a plan has a total lung $V_{20}$ of >25% to 37%, alternative plans should be made with an attempt at reducing the $V_{20}$. This may be achieved by different beam arrangements, noncoplanar beams, less or no elective nodal irradiation, or smaller margins around the target volumes. This last technique is applied only as a last resort and should be carried out with great caution as it may decrease the dose delivered to the tumor.
- If a treatment plan gives a $V_{20}$ of >35–40%, we do not use that plan for treatment. All fatal pneumonitis occurred in patients with a $V_{20} \geq 35\%$.
- Similarly, all high-grade pneumonitis occurred in patients with a $V_{20}$ of $\geq 32\%$. The risk of pneumonitis seems too great. Options for treatment then include: (1) changing the plan, as outlined above, (2) administering neoadjuvant chemotherapy in an attempt to reduce the volume of the tumor and treat the postchemotherapy tumor volume, and (3) treating the patient palliatively with lower doses.

As we move into the era of intensity-modulated radiation therapy (IMRT) and potentially more unconstrained beam arrangements, these data may not be valid. Further work in confirming these data with higher doses and IMRT is indicated.

Section IV. Cyttoprotection – Amifostine

Efforts to develop pharmacologic agents that protect normal tissues from the effects of radiation are long-standing. One very promising radioprotector that has emerged from these efforts is amifostine,
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an organic thiophosphate developed by the United States Army (WR [Walter Reed]-2721) in the post–World War II era to protect against the possible effects of radioactive fallout. The active metabolite (WR-1065) is a free thiol that is thought to provide an alternative target for reactive species from alkylating agents that would otherwise target DNA. The free thiol is also believed to scavenge the free radicals released during the interaction of ionizing radiation and water. With regard to its tissue selectivity, amifostine has been shown to protect both the salivary glands from the damaging effects of RT [165] and the kidneys from the nephrotoxic effects of cisplatin [166]. Nonetheless, amifostine's ability to protect normal tissue is not well understood, and the dosage required to reduce specific toxicities has not been established [167]. However, it appears to protect normal tissues, including the esophagus, lung, kidney, liver, bone marrow, immune system, skin, colon, small bowel, salivary glands, oral mucosa, and testes, from radiation damage; the brain and spinal cord, however, were not protected. In addition, no evidence has shown that it caused tumors to be spared the effects of RT or chemotherapy. Also in its favor, amifostine has been shown to protect normal tissues against the toxic effects of several classes of cytotoxic agents, including the alkylating and organo-platinum agents, anthracyclines, and taxanes [168]. All these qualities, therefore, indicate amifostine's potentially broad applicability as a cytoprotective agent. Amifostine is already approved for use as a radioprotector in the United States as the result of an international multi-institutional Phase III comparative trial that showed a significant reduction in the severity of acute and late xerostomia in patients given intravenous amifostine before each fraction of RT [165].

Several prospective randomized comparative studies of RT with and without amifostine have been published all these years. Komaki et al. [169] in a study conducted in M. D. Anderson Cancer Center reported a significant radioprotective effect of amifostine against radiation induced pneumonitis and esophagitis. All the randomized studies are shown in table 11.

**Table 11.** Randomized trials with amifostine in lung cancer

<table>
<thead>
<tr>
<th>Reference</th>
<th>Radiation dose</th>
<th>Chemotherapy</th>
<th>Amifostine dose</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Movsas et al. (<em>n</em> = 242) [170]</td>
<td>69.6 Gy at 1.2 Gy (hyperfractionation)</td>
<td>Induction PC</td>
<td>500 mg i.v. 4_/wk between RT fractions</td>
<td>No difference by NCI-CTC esophagitis, Swallowing diaries (<em>p</em> &lt; 0.03) and weight loss (<em>p</em> &lt; 0.05) favour amifostine (median survival, 15.6 and 15.8 mo)</td>
</tr>
<tr>
<td>Leong et al. (<em>n</em> = 60) [171]</td>
<td>60–66 Gy at 2.0 Gy</td>
<td>Induction PC</td>
<td>740 mg/m^2 with each chemo (Days 1, 22, 43, 50, 57, 64, 71, 78)</td>
<td>Esophagitis Grade 2–3: 43% in amifostine, 70% in control (not significant) (median survival, 12.5 and 14.5 mo)</td>
</tr>
<tr>
<td>Senzer et al. (<em>n</em> = 63) [172]</td>
<td>64.8 Gy at 1.8 Gy</td>
<td>Concurrent PC, gemcitabine and cisplatin X 3 after</td>
<td>500 mg i.v. before weekly chemo; 200 mg i.v. daily before RT</td>
<td>No difference in toxicity, no survival data (ongoing trial)</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Gy Dose</th>
<th>Chemoradiation Details</th>
<th>Chemoradiation Duration</th>
<th>Pneumonitis Improvement</th>
<th>Esophagitis Improvement</th>
<th>Survival Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antonadou et al.</td>
<td>55–60 Gy at 2.0 Gy</td>
<td>None</td>
<td>340 mg/m²/d before RT</td>
<td>↓</td>
<td>↓</td>
<td>(no survival data)</td>
</tr>
<tr>
<td>Antonadou et al.</td>
<td>55–60 Gy at 2.0 Gy</td>
<td>Concurrent weekly Por C</td>
<td>300 mg/m²/d before</td>
<td>↓ (p &lt;0.001)</td>
<td>↓ (p = 0.009)</td>
<td>(no survival data)</td>
</tr>
<tr>
<td>Komaki et al.</td>
<td>69.6 Gy at 1.2 Gy (hyperfractionation)</td>
<td>Concurrent i.v. cisplatin Days 1, 8, 29, 36; Oral etoposide Days1–5 8–12, 29–33, 36–40</td>
<td>500 mg i.v. 1st, 2nd day each wk before chemo and 1st RT fraction</td>
<td>↓ Degree of esophagitis, ↓ Pneumonitis, ↓ Neutropenic fever (median survival, 19 and 20 mo)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** P = paclitaxel; C = carboplatin; RT = radiotherapy; NCI-CTC = National Cancer Institute-Common Toxicity Criteria.

As general guidelines:

- Amifostine should be administered only to patients with good performance status, no cardiovascular diseases, no severe hypotension, normal kidney and liver function and age up to 70 years.
- Amifostine as intravenous infusion should be administered with an intermediate time from Rt 15 minutes (maximum).
- In case of concomitant chemotherapy-radiotherapy, amifostine should be administered before chemotherapy.
References

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33. Cox, J.D.; Stanley, K.; Petrovich, Z.; Paig, C.; Yesner, R. Cranial irradiation in cancer of the lung of all cell types. JAMA 1981;245: 469-472


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