Small Cell Lung Cancer*

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Among patients with lung cancers, the proportion of those with small cell lung cancer (SCLC) has decreased over the last decade. SCLC is staged as limited-stage disease and extensive-stage disease. Standard staging procedures for SCLC include CT scans of the chest and abdomen, bone scan, and CT scan or MRI of the brain. The role for positron emission tomography scanning in the staging of SCLC has yet to be defined. Limited-stage disease is treated with curative intent with chemotherapy and radiation therapy, with approximately 20% of patients achieving a cure. The median survival time for patients with limited-stage disease is approximately 18 months. Extensive-stage disease is treated primarily with chemotherapy, with a high initial response rate of 60 to 70% and a complete response rate of 20 to 30%, but with a median survival time of approximately 9 months. Patients achieving a complete remission should be offered prophylactic cranial irradiation. Currently, there is no role for maintenance treatment or bone marrow transplantation in the treatment of patients with SCLC. Relapsed or refractory SCLC has a uniformly poor prognosis. In this section, evidence-based guidelines for the staging and treatment of SCLC are outlined.

Key words: carboplatin; chemotherapy; cisplatin; etoposide; irinotecan; paclitaxel; prophylactic cranial irradiation; radiation therapy; small cell lung cancer

Abbreviations: CAV = cyclophosphamide, Adriamycin, and vincristine; CODE = cyclophosphamide, vincristine, doxorubicin, and etoposide; CR = complete response; ECOG = Eastern Cooperative Oncology Group; G-CSF = granulocyte colony-stimulating factor; NSCLC = non-small cell lung cancer; PCI = prophylactic cranial irradiation; PET = positron emission tomography; SCLC = small cell lung cancer; TEP = paclitaxel, etoposide, and cisplatin; TRT = thoracic radiotherapy

This document is the result of a comprehensive review of the existing guidelines, meta-analyses, and relevant randomized clinical trials on the subject of small cell lung cancer (SCLC).

Among lung cancers, the proportion of patients with SCLC has decreased from 17.4% in 1986 to 13.8% in 1998.1 Like non-SCLC (NSCLC), it has a strong association with tobacco use, but its clinical characteristics tend to be more aggressive than NSCLC, and median survival time without treatment is between 2 and 4 months.

Staging of SCLC

Patients are staged according to a two-stage system, which was developed by the Veterans Administration Lung Cancer Study Group, as having limited-stage disease or extensive-stage disease. Patients with limited-stage disease have involvement restricted to the ipsilateral hemithorax within a single radiation port. Extensive-stage disease is defined as the presence of obvious metastatic disease. Patients with limited-stage disease with the presence of contralateral hilar and/or supraclavicular nodes and/or with malignant pericardial and/or pleural effusions are excluded from clinical trials for limited-stage SCLC.

A complete evaluation of a patient newly diagnosed with SCLC should consist of a medical history and physical examination, a review of the histopathology specimens, a CT scan of the chest and upper abdomen to include the whole liver and the adrenal glands, a bone scan, and a CT scan or MRI examination of the brain. Additionally, complete blood counts, measurement of electrolyte, BUN, and creatinine levels, liver function tests, and measurement of lactate dehydrogenase levels should be performed in all patients at baseline. The utility of positron emission tomography (PET) scanning in patients with SCLC has been recently reported in two small prospective studies.2,3 In a study reported by Hauber et al,2 PET scans detected all primary lesions, lymph node metastases, and distant metastases that had been detected by other standard staging procedures. In a second study,3 30 patients with SCLC were evaluated with 36 PET scan examinations, and the
results were compared with the sum of the other staging procedures. The results of 23 of the 36 PET scan examinations were concordant with those of the other staging procedures. In seven cases, the PET scan examination resulted in upward staging of the patient, and in one instance the PET scan revealed the presence of a viable tumor when conventional staging procedures had revealed no residual disease. PET scan identified all areas of tumor involvement detected by other staging procedures. A third study\textsuperscript{102} looked at the accuracy of PET scanning in detecting bony metastases in patients with SCLC and NSCLC, comparing the PET scans to bone scans and single-photon emission CT scans. In this study, PET scans were found to be the most accurate whole-body imaging modality for the screening of bone metastases. These studies suggested that PET scanning is likely to be a useful staging tool in patients with SCLC. However, all the above studies were small, and the experience with PET scan as a staging tool remains largely limited. Until larger prospective studies become available, PET scanning cannot be recommended for routine use in the staging and restaging of patients with SCLC.

**Recommendation**

1. In all patients, the routine staging of SCLC should include medical history and physical examination, complete blood counts, comprehensive chemistry panels, CT scans of the chest and abdomen, a CT scan or MRI of the brain, and a bone scan. Level of evidence, good; benefit, substantial; grade of recommendation, A

2. For the routine staging of patients with SCLC, PET scanning is not recommended outside of a clinical trial. Level of evidence, fair; benefit, none/negative; grade of recommendation, D

**TREATMENT OF EXTENSIVE STAGE SCLC**

**First-Line Treatment**

Platinum-based chemotherapy remains the mainstay of treatment for extensive SCLC. In a meta-analysis\textsuperscript{4} of randomized trials (19 trials and 4,054 evaluable patients) comparing a cisplatin-based regimen with a non-cisplatin-based regimen, patients randomized to a regimen containing cisplatin had a significant increase in the probability of response and survival with no significant increase in toxicity. Detailed analyses of the roles of etoposide and cisplatin in the treatment of SCLC have been performed by Berghmans et al\textsuperscript{8,9} and were reported in abstract form in September 1999. Thirty-six eligible trials that were performed between 1980 and 1998 were classified into the following four groups: (1) cisplatin vs no cisplatin (1 trial); (2) etoposide (without cisplatin) vs no etoposide (17 trials); (3) cisplatin/etoposide vs no cisplatin/etoposide (9 trials); and (4) cisplatin/etoposide vs etoposide (9 trials). The authors concluded that the use of cisplatin and/or etoposide offered a significant survival advantage to patients with SCLC.\textsuperscript{5}

In another meta-analysis, Chute et al\textsuperscript{6} evaluated all 21 cooperative group trials performed in North America from 1972 to 1993. Patients with extensive-stage SCLC who were treated during a similar time interval and were listed in the Surveillance, Epidemiology, and End Results database also were examined. Trends were tested in the number of trials and the survival of patients over time. In this analysis, a modest 2-month prolongation in median survival was demonstrated in patients with extensive-stage SCLC. This improvement in survival was independently associated with both cisplatin-based therapy and in the improvement of best supportive care. This meta-analysis again establishes that cisplatin-based chemotherapy should be the cornerstone of first-line chemotherapy for patients with extensive-stage SCLC.

The issue of carboplatin vs cisplatin was recently reviewed by Brahmer and Ettinger,\textsuperscript{7} who concluded that carboplatin plus etoposide is as effective as cisplatin plus etoposide but is less toxic (except for increased myelosuppression). The Hellenic Oncology Group conducted a phase III trial\textsuperscript{103} comparing cisplatin and etoposide with carboplatin and etoposide. In this study, containing patients with both limited-stage and extensive-stage disease, the median survival time was 11.8 months for cisplatin plus etoposide and 12.5 months for carboplatin plus etoposide. The difference was not statistically significant, although the study was not powered to show equivalence.\textsuperscript{103}

A recent Japanese trial\textsuperscript{8} compared cisplatin and irinotecan with cisplatin and etoposide. Patients randomized to the cisplatin/irinotecan arm did (statistically) significantly better than the group that was randomized to the cisplatin/etoposide arm (median survival time, 420 vs 300 days, respectively). Confirmatory trials are underway in the United States. Several phase II trials with irinotecan, topotecan, and paclitaxel in combination with either cisplatin or etoposide have been reported, and these have been summarized in Table 1.

The issue of adding a third drug to cisplatin and etoposide has been investigated. The Hoosier Oncology Group evaluated the addition of ifosfamide to cisplatin and etoposide in a phase III trial of 171 patients with extensive-stage disease. At the expense of increased toxicity, the 2-year survival rate increased from 5 to 13% with the addition of ifos-
famide. Mavroudis et al compared the use of paclitaxel, etoposide, and platinum (TEP) with the use of etoposide and platinum. The study was terminated early, secondary to a higher number of toxic deaths in the TEP arm. Despite a statistically significant improvement in the time to progression for TEP, there was no difference in overall survival. Recently, another phase III intergroup trial (Cancer and Leukemia Group B 9732) was reported comparing cisplatin and etoposide with or without paclitaxel in patients with extensive-stage SCLC. No significant survival advantage was seen with the addition of paclitaxel to cisplatin and etoposide in this study. On the other hand, there was an increased incidence of deaths from toxicities in the paclitaxel arm.

Recommendations

3. Patients with extensive-stage disease should receive platinum-based chemotherapy. Level of evidence, good; benefit, substantial; grade of recommendation, A

4. Patients achieving a complete remission (CR) should be offered prophylactic cranial irradiation (PCI). Level of evidence, fair; benefit, small; grade of recommendation, C

**Maintenance Treatment**

The topic of maintenance therapy in patients with SCLC was extensively reviewed in the journal *Lung Cancer* in 1998. Several randomized trials have demonstrated that 4 to 6 months of treatment is equal to prolonged treatment when survival is considered as the end point. In the meta-analysis reported by Sculier et al, published randomized trials were included. One showed a statistically significant difference in survival in favor of maintenance therapy, 5 studies showed survival advantage in subgroups of patients, 1 study showed significantly shorter survival times with maintenance therapy, and 6 studies showed no difference. The Eastern Cooperative Oncology Group (ECOG) conducted a phase III trial in which patients showing a response to therapy or patients whose disease stabilized after receiving four cycles of cisplatin and etoposide were randomized to observation alone or to four cycles of topotecan therapy. Despite an improvement in progression-free survival, there was no difference in overall survival between the two groups.

Treatments other than chemotherapy for maintenance are currently being investigated in ongoing clinical trials. A phase III randomized trial is currently underway testing the efficacy of anti-GD3 immunization as maintenance treatment. Metalloproteinase inhibitors and inhibitors of angiogenesis also are being investigated in this fashion.

 Recommendation

5. For patients with extensive-stage or limited-stage SCLC achieving a partial or CR, there is no evidence, outside of a clinical trial, for

<table>
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<tr>
<th>Treatment</th>
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<th>CR</th>
<th>PR</th>
<th>Total</th>
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<td>10</td>
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<td>12</td>
<td>100</td>
<td>74–100</td>
<td>85</td>
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*CEC = cisplatin-etoposide-carboplatin; MMC = mitomycin C; RA = retinoic acid; CL = confidence limits; CPT = cisplatin-paclitaxel-topotecan; EPE = etoposide-paclitaxel-epirubicin; PR = partial response.

†Values given as median.

‡Includes 14 patients with stage IIIB and stage IV disease.
maintenance treatment. Level of evidence, good; benefit, none/negative; grade of recommendation, D

TREATMENT OF RELAPSED OR REFRACTORY SCLC

Despite high initial response rates to chemotherapy (ie, 45 to 75% CRs) reported in patients with limited-stage disease and 20 to 30% CRs in patients with extensive-stage disease, the response duration is usually short with a progression-free survival time of approximately 4 months for patients with extensive-stage disease and 12 months for patients with limited-stage disease. Most patients are destined to relapse, and the prognosis of this group of relapsed patients is poor. Patients who relapse < 3 months after first-line therapy are commonly called refractory, and patients who relapse 3 months after therapy are called sensitive. Patients with late relapses after receiving initial therapy may be retreated with the same induction regimen used initially.

Patients whose disease progresses early after induction therapy and who are in satisfactory clinical condition, should be offered a second-line regimen. In a randomized multicenter study, von Pawel et al101 compared cyclophosphamide, Adriamycin, and vincristine (CAV) with topotecan as a single agent in patients who relapsed within 60 days after the completion of initial therapy. A total of 211 patients were enrolled in the study. The response rate was 24.3% in patients who were treated with topotecan and was 18.3% in patients treated with CAV (p = 0.285). The median times to disease progression were 13.3 weeks for patients in the topotecan arm and 12.3 weeks for patients in the CAV arm. The median survival time was 25 weeks for patients receiving topotecan and 24.7 weeks for those receiving CAV. The proportion of patients who experienced symptom improvement was greater in the topotecan arm than in the CAV group for four of the eight symptoms evaluated. The authors concluded that topotecan was at least as effective as CAV in the treatment of patients with recurrent SCLC and resulted in improved control of several symptoms. However, toxicity rates were high in both arms of the study, and alternative dose schedules of topotecan are currently being evaluated. Several recently reported phase II trials in patients with relapsed/refractory SCLC are summarized in Table 2.

Recommendation

6. Patients with SCLC who have relapsed following an initial response to treatment or who are refractory to the initial treatment should be offered further chemotherapy. The chemotherapy offered will depend on the duration of response after receiving first-line chemotherapy or the lack of response to first-line chemotherapy (ie, sensitive relapses vs refractory patients). Level of evidence, fair; benefit, small/weak; grade of recommendation, C

TREATMENT OF ELDERLY PATIENTS WITH EXTENSIVE-STAGE SCLC

Approximately 25% of patients with SCLC are > 70 years of age (ie, elderly). The performance status and the physiologic status of the patient should guide treatment decisions rather than the patient’s chronologic age. It is clear that patients with good performance status (ECOG level 0 or 1) and normal organ function should be treated with optimal chemotherapy (and with radiotherapy, if indicated) as in their younger counterparts. Similar outcomes of elderly patients with limited-stage SCLC have been shown in the intergroup trial 0096 in which cisplatin, etoposide, and thoracic radiotherapy were administered once a day or twice daily.14 The National Cancer Institute of Canada performed a retrospec-

<table>
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<th>Treatment</th>
<th>Patients, No.</th>
<th>CR</th>
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<th>Survival Mo</th>
<th>1 Yr Rate, %</th>
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<td>3</td>
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</table>

*See Table 1 for abbreviations not used in the text.
†Values given as median.
tive review\textsuperscript{15} of their BR3 and BR6 trials and also concluded that age did not appear to impact the delivery, tolerance, or efficacy of thoracic irradiation in the combined-modality management of patients with limited-stage SCLC. Greater myelosuppression is to be expected since equivalent exposure to a drug will lead to more myelosuppression in the elderly compared to their younger counterparts. This has been shown to be the case at least for etoposide.\textsuperscript{16} Greater ancillary support will be required in the elderly. However, despite treatment delays elderly patients with good performance status have similar prognoses to those of younger patients.

Elderly patients with poor performance status or with compromised organ function may be offered single-agent chemotherapy or polychemotherapy in attenuated doses. However, several randomized studies\textsuperscript{17,18} have indicated that such "gentler" chemotherapy is inferior to optimal combination chemotherapy. Options available to these patients include the following: oral etoposide for 14 days combined with carboplatin on day 1 every 28 days\textsuperscript{19}; abbreviated chemotherapy with CAV in full doses followed 3 weeks later by chemotherapy with cisplatin and etoposide in optimal doses\textsuperscript{20}; or chemotherapy with platinum, Adriamycin, vincristine, and etoposide in reduced doses.\textsuperscript{21} A recently reported phase III trial\textsuperscript{22} compared carboplatin-gemcitabine therapy with cisplatin-etoposide therapy in patients with SCLC who had poor prognoses, with carboplatin-gemcitabine therapy exhibiting a more favorable overall toxicity profile at the expense of increased myelotoxicity. Another phase III trial compared the use of single-agent carboplatin with CAV\textsuperscript{23} with carboplatin producing response rates, relief of tumor-related symptoms, and survival similar to that seen with CAV. There was a lower risk of life-threatening sepsis and less need for hospitalization in the group that received carboplatin.

Recommendations

7. Elderly patients with good performance status and with intact organ function should be treated with platinum-based chemotherapy. Level of evidence, good; benefit, moderate; grade of recommendation, B

8. Elderly patients with poor prognostic factors such as poor performance status or severe concomitant comorbid disease still may be considered for chemotherapy. Level of evidence, poor; benefit, small; grade of recommendation, C

9. Elderly patients achieving a CR should be offered PCI. Level of evidence, fair; benefit, small; grade of recommendation, C

Dose Intensity in SCLC

The issue of dose intensity has been subjected to extensive clinical investigation in recent years primarily due to the initially chemosensitive nature of the disease and also owing to the almost universal lack of durable responses and cure, despite the initial responses. Several randomized trials\textsuperscript{24–26} however, have failed to show a survival advantage with dose-intensive chemotherapy. On the basis of promising results from a pilot trial reported by Murray et al,\textsuperscript{27} the Southwest Oncology Group reported the results of their phase III trial comparing therapy with cisplatin, vincristine, doxorubicin, and etoposide (CODE) with alternating therapy using CAV then cisplatin and etoposide. The study was stopped early owing to an excessive mortality rate in the CODE arm (8%) compared to the standard arm (1%). The response rates with CODE were higher than that of patients in the standard arm of the study, but progression-free survival and overall survival were not statistically significantly improved. Furnese et al\textsuperscript{28} and Skarlos et al\textsuperscript{29} compared more dose-intensive weekly regimens with standard or alternating non-cross-resistant regimens and again failed to show a survival advantage for the weekly, more dose-intensive arms. Pujol et al\textsuperscript{30} compared therapy with cyclophosphamide, epirubicin, etoposide, and cisplatin in higher doses with recombinant human granulocyte-macrophage colony-stimulating factor vs the same drugs in lower doses without granulocyte-macrophage colony-stimulating factor and failed to show a survival advantage for the more dose-intense arm. However, Steward et al\textsuperscript{31} comparing therapy with the combination of vincristine, ifosfamide, carboplatin, and etoposide every 3 weeks vs the same regimen every 4 weeks, showed a significant survival advantage for patients receiving the intensified regimen. Another trial, which was conducted by Thatcher et al\textsuperscript{32} and that also showed positive results for the dose-intense approach, compared standard therapy with adriamycin, cyclophosphamide, and etoposide administered every 3 weeks with dose-dense therapy with adriamycin, cyclophosphamide, and etoposide administered every 2 weeks along with granulocyte-colony stimulating factor (G-CSF) support. The overall survival rate was statistically significantly better in the dose-dense group (1-year survival rate, 47% vs 39%, respectively [p = 0.04]; 2-year survival rate, 13% vs 8%, respectively). Progression-free survival, nonhematologic toxicity, and quality of life were similar in the two groups.

Interestingly, Arriagada et al\textsuperscript{33} conducted a randomized trial of 105 patients with limited-stage SCLC who were randomized to receive a higher...
A dose of cisplatin (100 vs 80 mg/m²) or cyclophosphamide (300 vs 225 mg/m²) initially. All patients then were treated with the same dose of doxorubicin and etoposide, and radiotherapy. There was an improved disease-free survival rate (2-year survival rate, 28% vs 8%, respectively; p = 0.02) and an improved overall survival rate (2-year survival rate, 46% vs 26%, respectively; p = 0.02) among patients in the higher dose arm. The issue of dose intensity may need further evaluation in the limited-stage disease setting.

**Recommendation**

10. For patients with either extensive-stage SCLC or limited-stage SCLC, there is no role for dose-dense/intense initial/induction, or maintenance treatment outside of a clinical trial. Level of evidence, good; benefit, none/negative; grade of recommendation, D

**The Role of Growth Factor and the Use of Stem Cell Support in SCLC**

The use of G-CSF in the treatment of SCLC has been analyzed carefully by Chouaid et al. They did a retrospective review of their experience and also analyzed published data from three randomized trials that evaluated the effectiveness of primary therapy with G-CSF in patients with SCLC. The use of G-CSF for primary prophylaxis was not found to be cost-effective, did not improve palliation, and hence is not recommended for routine use.

**Recommendation**

11. In patients with SCLC who are receiving chemotherapy, the routine use of G-CSF is not recommended. Level of evidence, good; benefit, none/negative; grade of recommendation, D.

**Treatment of Limited-Stage SCLC**

**Radiation Therapy in SCLC**

SCLC has long been recognized to be clinically responsive to radiation, and in vitro radiation of SCLC cell lines has shown that they often have a greater intrinsic radiosensitivity than adenocarcinomas or squamous cell lung cancer cell lines. Because of these observations, many early trials of combining radiation with chemotherapy in patients with SCLC used low total radiation doses. More recently, it has become increasingly clear that higher doses than the old regimens of 30 Gy in 10 fractions or 45 Gy in 25 fractions are needed to provide durable local control.

A number of trials conducted in the 1970s and 1980s compared chemotherapy alone to chemotherapy plus thoracic radiation therapy (TRT) in patients with limited SCLC. These varied in radiation dose, timing, and choice of chemotherapeutic agents (but most were performed with an alkylating agent and doxorubicin-based therapy rather than with cisplatin and etoposide). The analysis by Warde and Payne showed improved local control and survival with the addition of TRT, particularly in patients < 60 years. Pignon et al. obtained individual patient data from these trials and were able to update analyses from the time of the original publication. They found that the addition of TRT resulted in an increase in the 3-year survival rate from 8.9 to 14.3%, an absolute improvement of 5%, and a relative improvement of nearly 50%. With the publication of these two meta-analyses, the debate shifted from whether or not to employ TRT to how best to integrate it with chemotherapy.

**Sequencing and Timing of Thoracic Radiation and Chemotherapy**

The issues here are whether to administer radiation therapy and chemotherapy concurrently, sequentially, or in an alternating fashion, and whether radiation should be administered early or late in the overall course of treatment. Murray and Coldman performed a meta-analysis of trials that combined chemotherapy and TRT, using progression-free survival at 3 years as a surrogate end point for long-term survival. The best results were seen with TRT beginning 3 to 5 weeks from the start of chemotherapy. As radiation was further delayed, the benefit decreased and survival approached that seen with chemotherapy alone.

There have been at least nine randomized trials that have addressed the issue of the timing of radiation in patients with limited-stage SCLC (Table 3). There are major differences in trial design, choice of chemotherapeutic agents, radiation dose, and fractionation schedules. With those caveats, several reasonable conclusions emerge from these data, as follows:

1. Trials that used alkylating agents and doxorubicin-based chemotherapy showed little effect of radiation timing and sequencing. They also reported significant difficulty in delivering planned treatment (both chemotherapy and radiation) when radiation was given concurrently with or alternated between cycles of chemotherapy. Long-term survival in most of
these trials was in the range of 10% that is minimally different from that seen with chemotherapy alone.

2. When platinum-etoposide regimens are used for chemotherapy, concurrent chemotherapy-TRT is superior to sequential TRT, where TRT is administered after chemotherapy.

3. When platinum-etoposide chemotherapy and concurrent TRT are combined, the data are divergent as to whether early TRT (ie, in week 1) is better than delayed TRT (ie, week 6 or week 13).

**Radiation Dose**

Relatively few trials have addressed the issue of optimal TRT dose in patients with SCLC. A retrospective analysis of patients treated at the Massachusetts General Hospital showed an improvement in local control as radiation doses were increased from 30 to 50 Gy. The Cancer and Leukemia Group B has tried to define the maximal tolerated dose for concurrent TRT and cisplatin-etoposide chemotherapy when these are administered after three courses of induction chemotherapy with cyclophosphamide-cisplatin-etoposide. They examined both a once-a-day radiation therapy schedule with 2-Gy fractions and a twice-daily schedule with 1.5-Gy fractions. The limiting toxicity was acute esophagitis, and the maximum tolerated dose was reported to be 45 Gy in 3 weeks for twice-daily fractionation and 70 Gy in 7 weeks for daily fractionation. As the best local control rates in current trials do not exceed 70%, the exploration of dose escalation seems warranted, and a recent trial proposed by the ECOG to the National Cancer Institute would compare the regimen of twice-daily 45-Gy doses for 3 weeks to that of a daily 70-Gy dose for 7 weeks. Studies in patients with NSCLC clearly have shown the feasibility of giving even higher radiation doses to conformal planned fields with concurrent chemotherapy, and this approach may also be feasible in patients with SCLC.

**Radiation Fractionation**

The rapid growth of many SCLC cell lines encouraged the exploration of treatment acceleration by giving two fractions per day with a modest reduction in fraction size from the usual 1.8 to 2.0 Gy to 1.5 Gy. Two prospective trials have compared this approach to conventional daily fractionation. The North American Intergroup trial compared doses of 45 Gy administered in 25 fractions for > 5 weeks to the investigational arm of doses of 45 Gy administered in

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**Table 3—Randomized Trials of Radiation-Chemotherapy Sequencing and Timing in Limited-Stage SCLC**

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
<th>Chemotherapy</th>
<th>Result</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perry et al</td>
<td>TRT day 1 vs day 64</td>
<td>CAV/CEV</td>
<td>Delayed TRT gave best survival</td>
<td>Planned dose reduction in arm with day 1 TRT</td>
</tr>
<tr>
<td>Murray et al</td>
<td>TRT cycle 2 vs cycle 6</td>
<td>CAV/PE</td>
<td>Median and 4-yr survival favored early TRT</td>
<td>Greatest difference in patterns of failure was in CNS relapse</td>
</tr>
<tr>
<td>Schultz et al</td>
<td>TRT day 1 vs day 120</td>
<td>CAV/PE</td>
<td>Delayed TRT nonsignificantly better (MST, 12.9 vs 10.7 mo)</td>
<td>No long-term follow-up reported</td>
</tr>
<tr>
<td>Tsukada et al</td>
<td>TRT concurrent with cycle 1 or following cycle 4</td>
<td>PE</td>
<td>3-yr survival significantly better for early concurrent vs late sequential (30.9% vs 20.7%, respectively)</td>
<td>Double comparison of timing and concurrency</td>
</tr>
<tr>
<td>Gregor et al</td>
<td>TRT alternating between cycles 2, 3, 4, and 5 or following cycle 5</td>
<td>CAE</td>
<td>Nonsignificant trend favoring delayed TRT</td>
<td>More toxicity with resultant drug dose reduction and delay in alternating arm</td>
</tr>
<tr>
<td>LeBean et al</td>
<td>TRT concurrent with cycle 2 or alternating among cycles 2, 3, 4, and 5</td>
<td>CAE</td>
<td>No difference in median survival</td>
<td>No long-term data: poor compliance in alternating arm</td>
</tr>
<tr>
<td>Work et al</td>
<td>TRT starting week 1 vs week 18</td>
<td>CAV and PE</td>
<td>No difference in median or 5-yr survival</td>
<td>Early RT preceded chemotherapy and was not concurrent with it</td>
</tr>
<tr>
<td>Samantas et al</td>
<td>TRT starting week 1 vs week 13</td>
<td>ChpE</td>
<td>No difference in median or 2-yr survival</td>
<td>Reasonably good 2-year survival rate (35%)</td>
</tr>
<tr>
<td>Jeremic et al</td>
<td>TRT starting week 1 vs week 6</td>
<td>ChpE</td>
<td>MST significantly better for early TRT (34 vs 26 mo, respectively)</td>
<td>Local control better with early TRT</td>
</tr>
</tbody>
</table>

*A = doxorubicin; C = cyclophosphamide; Chp = carboplatin; E = etoposide; P = cisplatin; V = vincristine; MST = median survival time; RT = radiation therapy. Table modified and expanded from Wagner.*

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These trials can be categorized according to their treatment sequence and timing, and the results are shown in Table 3.
30 fractions for > 3 weeks. Chemotherapy consisted of four cycles of cisplatin-etoposide. The accelerated regimen resulted in improved local control (intrathoracic failure: accelerated therapy arm, 36%; standard therapy arm, 52%) and long-term survival, which was 26% for the twice-daily regimen and 16% for the standard regimen. There was an increased rate of grade 3 esophagitis (26% vs 11%, respectively), but there were no other significant differences in toxicity.40

The North Central Cancer Treatment Group41 also compared twice-daily fractionation to daily fractionation but with a significantly different twice-daily regimen and overall study design. In both arms of the study, radiation therapy was administered concurrently with the fourth and fifth cycles of chemotherapy. The standard radiation regimen was 50.4 Gy in 28 fractions for > 5 weeks. Patients in the twice-daily arm of the study received 48 Gy in three fractions, with a 2.5-week split after the initial 24-Gy dose. Thus, unlike the above-mentioned North American Intergroup trial, there was no overall acceleration of the radiation course. In this trial, there were no differences in local control or survival between patients in the two arms of the study.

**Radiation Target Volume**

SCLC often presents with bulky mediastinal adenopathy and often with a confusing mixture of tumor and atelectasis in lung parenchyma. Radiation target volumes are often large, limiting the achievable doses. In attempting to define the minimal appropriate dose, the following two issues can be considered:

1. Is elective radiation applied to normal-appearing lymph nodes required? This has not been studied prospectively. However, the North American Intergroup trial, which produced the best 5-year survival rate reported by a cooperative group, limited elective radiation to no intentional radiation to the contralateral hilum or to supraclavicular nodes, unless there was bulky superior mediastinal adenopathy.42

2. If TRT is started after several cycles of chemotherapy, can the target volume comprise the postchemotherapy rather than the prechemotherapy tumor volume? A retrospective review41,43,44 of data from the Mayo Clinic and the North Central Cancer Treatment Group suggests that this can be done, as recurrences tended to be at the center of the tumor rather than at the periphery. An earlier trial by the Southwest Oncology Group,45 which randomized patients having partial responses to radiation to prechemotherapy or postchemotherapy volumes, also reported no difference in recurrence rates.

**Recommendations**

12. Patients with limited-stage SCLC should be referred to a radiation oncologist and a medical oncologist for chemotherapy and radiation therapy. Level of evidence, good; benefit, substantial; grade of recommendation, A

13. Patients with limited-stage SCLC achieving a CR should be offered PCI. Level of evidence, good; benefit, substantial; grade of recommendation, A

**PCI**

Brain metastases are common in SCLC. In patients who achieve a CR to induction therapy, CNS metastases will emerge over the next 2 years in about 50 to 60% of patients, and 20 to 30% of these metastases will be the sole site of disease recurrence.40 Overt metastatic disease in the brain, while often responding temporarily to radiation or chemotherapy, is rarely if ever cured. The hypothesis that moderate doses of radiation given to patients without detectable CNS involvement might eradicate occult metastatic disease has been entertained for > 20 years,47 but only in the past few years have data emerged to allow a reasonable consensus that PCI can reduce the risk of CNS failure and improve survival, and can do so without excessive toxicity.48–50 A meta-analysis of randomized trials of PCI in complete responders (patients predominately with limited disease) concluded that it significantly reduced CNS failure by about 50% and produced a modest (about 5%) but also significant improvement in the 3-year survival rate. There was a trend toward better results with higher doses (ie, 30 to 36 Gy using 2-Gy fractions) than with 20-Gy doses, but this was not a randomized comparison. An intergroup trial is currently comparing 25-Gy doses administered in 10 fractions to 36-Gy doses administered in 18 fractions.

Earlier trials of PCI had variably reported late neurotoxicity, with deterioration in memory, calculation ability, and quality of life. The relation of these toxicities to treatment was unclear. In several more recent trials51 in which cognitive function was assessed prospectively, significant differences between SCLC patients and age-matched and gender-matched control subjects have been observed prior to any treatment, with up to 40% of patients showing significant impairment. Significant further deterioration following PCI was not seen in a large 1997 trial.
in the United Kingdom. Van Oosterhout et al performed careful neurologic and neurophysiologic examinations of 59 survivors who were alive > 2 years after receiving a diagnosis and who underwent a cranial CT or MRI scan. Groups were neurophysiologically compared with matched control subjects. The authors concluded that although more intensively systemically treated patients showed more neurologic impairment, there was no statistical evidence for additional neurotoxicity with PCI.

**Recommendations**

14. Patients with limited-stage SCLC achieving a CR or patients who have undergone resection who have stage I disease should be offered PCI. Level of evidence, good; benefit, substantial; grade of recommendation, A

15. Patients with extensive-stage SCLC achieving a CR should be offered PCI. Level of evidence, fair; benefit, small; grade of recommendation, C

**Role of Surgery in Early Stage SCLC**

The role of surgery in the treatment of early-stage SCLC recently has been reviewed. Surgery as a primary modality of treatment was abandoned after the British Medical Counsel published the results of their study comparing primary radiation therapy with surgery in patients with resectable SCLC with a 10-year follow-up. The overall survival was better for patients in the radiation therapy-alone arm of the study, and there were no long-term survivors among patients in the surgery arm of the study. However, subsequent reports published in the 1970s and early 1980s showed long-term survival in patients who had been treated with surgery alone who had very early-stage disease. The most favorable subset of patients had T1N0 tumors that had been identified either at the time of surgery or at the time of postoperative pathologic examination. Even though the role of adjuvant therapy has not been evaluated in prospective randomized trials, there are several reports suggesting a benefit for adjuvant chemotherapy even in the earliest stages of the disease.

The role of surgery in node-positive patients was evaluated prospectively by the Lung Cancer Study Group. Patients with stage I disease (ie, T1–2, N0 tumors) were excluded from this trial. Patients were initially treated with five cycles of CAV. Responding patients were randomized to undergo surgery or not to undergo surgery. All patients received radiation therapy to the chest and brain. There was no difference in survival between the arms of the study. For all patients, the median survival time was 15 months and the 2-year survival rate was 20%.

All patients who are being worked up for surgery should have undergo mediastinoscopy prior to undergoing resection. The utility of mediastinoscopy in SCLC patients has been validated recently in a small prospective Japanese trial.

**Recommendations**

16. For the rare patient with very limited-stage disease (ie, T1–2, N0 tumors), surgical resection followed by a platinum-based chemotherapy could be offered. Level of evidence, fair; benefit, small; grade of recommendation, C

17. Mediastinoscopy should be performed in all patients undergoing surgical resection. Level of evidence, poor; benefit, moderate; grade of recommendation, C

18. PCI should be offered to patients achieving a CR. Level of evidence, fair; benefit, small; grade of recommendation, C

**Conclusion**

The incidence of SCLC has been decreasing, and in 1998 it was reported to be 13.8% of all lung cancers. A two-stage staging system is generally utilized. Limited-stage SCLC is optimally treated with a concurrent chemotherapy and radiation therapy approach, and approximately 20% of patients are cured. A platinum-based chemotherapy is the standard for treating extensive-stage SCLC. PCI provides a small absolute benefit in survival in patients achieving CRs. Future research should be focused on optimizing chemotherapy regimens and radiation therapy schedules.

**Summary of Recommendations**

**Staging of SCLC**

1. In all patients, routine staging of SCLC should include history and physical examinations, complete blood counts, a comprehensive chemistry panel, a CT scan of the chest and abdomen, a CT or MRI scan of the brain, and a bone scan. Level of evidence, good; benefit, substantial; grade of recommendation, A

2. For the routine staging of patients with SCLC, PET scanning is not recommended outside of a clinical trial. Level of evidence, fair; benefit, none/negative; grade of recommendation, D
Treatment of Extensive-Stage SCLC

First-Line Treatment:
3. Patients with extensive stage disease should receive platinum-based chemotherapy. Level of evidence, good; benefit, substantial; grade of recommendation, A
4. Patients achieving CRs should be offered PCI. Level of evidence, fair; benefit, small; grade of recommendation, C

Maintenance Treatment:
5. For patients with extensive-stage or limited-stage SCLC achieving a partial response or a CR, there is no evidence, outside of a clinical trial, for the use of maintenance treatment. Level of evidence, good; benefit, none/negative; grade of recommendation, D

Treatment of Relapsed or Refractory SCLC
6. Patients with SCLC who have relapsed following an initial response to treatment or who are refractory to the initial treatment should be offered further chemotherapy. The chemotherapy offered will depend on the duration of the response after receiving first-line chemotherapy or the lack of response to first-line chemotherapy (i.e., sensitive relapses vs refractory patients). Level of evidence, fair; benefit, small/weak; grade of recommendation, C

Treatment of Elderly (> 70 years of age) Patients With Extensive-Stage SCLC
7. Elderly patients with good performance status and with intact organ function should be treated with platinum-based chemotherapy. Level of evidence, good; benefit, moderate; grade of recommendation, B
8. Elderly patients with poor prognostic factors such as poor performance status or severe concomitant comorbid disease may still be considered for chemotherapy. Level of evidence, poor; benefit, small; grade of recommendation, C
9. Elderly patients achieving CRs should be offered PCI. Level of evidence, fair; benefit, small; grade of recommendation, C

Dose Intensity in SCLC
10. For patients with either extensive-stage or limited-stage SCLC, there is no role for the administration of dose-dense/intense, initial/induction, or maintenance treatment outside of a clinical trial. Level of evidence, good; benefit, none/negative; grade of recommendation, D

The Role of Growth Factor and the Use of Stem Cell Support in SCLC

11. In patients with SCLC who are receiving chemotherapy, the routine use of growth factor is not recommended. Level of evidence, good; benefit, none/negative; grade of recommendation, D

Treatment of Limited-Stage SCLC
12. Patients with limited-stage SCLC should be referred to a radiation oncologist and a medical oncologist for chemotherapy and radiation therapy. Level of evidence, good; benefit, substantial; grade of recommendation, A
13. Patients with limited-stage SCLC achieving CRs should be offered PCI. Level of evidence, good; benefit, substantial; grade of recommendation, A

PCI
14. Patients with limited-stage SCLC achieving CRs or patients who have undergone resection who have stage I disease should be offered PCI. Level of evidence, fair; benefit, small; grade of recommendation, C
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Role of Surgery in Early-Stage SCLC
16. For the rare patient with very limited-stage disease (i.e., T1–2,N0 tumors), surgical resection followed by platinum-based chemotherapy could be offered. Level of evidence, fair; benefit, small; grade of recommendation, C
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