Thoracic and Cranial Radiotherapy for Limited-Stage Small Cell Lung Cancer*

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Chemotherapy remains the mainstay of treatment for small cell lung cancer (SCLC). For patients with limited-stage disease, the addition of thoracic radiotherapy confers a moderate improvement in local control and a modest survival benefit, but these improvements come at the cost of increased toxic reactions. The optimal method for integrating chemotherapy and thoracic radiotherapy is unresolved. Concurrent and alternating strategies are appealing because they allow uninterrupted delivery of chemotherapy, but they have not been proven to be superior to conventional sequential approaches. Based on limited data, delivery of thoracic radiation early in the treatment course may be preferable to delivery later in the course. There is evidence of a radiation dose-response effect for SCLC, and, in standard regimens, thoracic radiation doses in the range of 50 to 60 Gy are recommended. The use of limited radiation fields (to postchemotherapy tumor volumes) appears reasonable. Results for alternative thoracic radiation fractionation schedules such as accelerated hyperfractionation are promising and worthy of further investigation. The role of prophylactic cranial irradiation (PCI) is controversial and should be individualized. It should be considered for the favorable subgroup of patients with limited-stage disease who achieve a complete response to chemotherapy and thoracic radiotherapy. If given, we recommend a total dose of 30 to 36 Gy in 2-Gy fractions; PCI should not be delivered concomitantly with chemotherapy.

(CHEST 1995; 107:2498-2545)

The natural history of small cell lung cancer (SCLC) is one of rapid proliferation and early dissemination. About one third of patients with SCLC present with clinically determined limited disease, although, in fact, most of these patients probably have micrometastatic disease at the time of diagnosis. Because of this proclivity for early dissemination, chemotherapy is the mainstay of treatment for patients with SCLC. Considerable effort is appropriately being devoted to the development of more efficacious chemotherapeutic strategies to control systemic disease.

In addition to chemotherapy, there is a significant role for radiotherapy in the treatment of SCLC. Local tumor progression occurs in up to 80% of patients with limited-stage disease who are treated with chemotherapy alone. This high recurrence rate can be significantly reduced with the addition of thoracic radiotherapy, as will be described. Furthermore, there may be a role for prophylactic cranial irradiation (PCI) in certain patients to prevent intracranial relapse.

The following report will review the current roles and optimal administration schedules of thoracic radiotherapy and PCI in patients with limited-stage SCLC.

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Is There a Role for Thoracic Radiotherapy?

Several randomized clinical trials have been performed to address the role of thoracic radiotherapy for limited-stage SCLC, but these studies yield conflicting results with respect to whether the addition of thoracic radiotherapy to chemotherapy is beneficial. This is partly explained by the fact that these trials have differed significantly in terms of total radiation dose, dose fractionation, timing of radiotherapy, and radiation treatment fields, as well as chemotherapy utilized. Two recent meta-analyses of these randomized trials have shown that the addition of thoracic radiotherapy to chemotherapy results in a small, statistically significant improvement in survival compared with chemotherapy alone in patients with limited-stage SCLC. However, these small benefits are realized at the cost of increased toxic reactions.

The meta-analysis by Warde and Payne included 11 randomized trials that examined treatment of patients with limited-stage SCLC by chemotherapy alone compared with chemotherapy and thoracic radiotherapy. The chemotherapeutic regimens differed between studies, as did the radiation doses and delivery schedules. Combining the results of these studies, the investigators found that the addition of thoracic radiotherapy resulted in a significant overall benefit in 2-year survival of 5.4% (p<0.05). Local control results were reported for 9 of the 11 studies. The meta-analysis showed an overall benefit in local control of 25% (95% confidence interval, 16.5 to 34.1%); among
the 9 studies, local control for patients treated with chemotherapy alone was 23% (172/737) compared with 48% (376/784) for patients who received both chemotherapy and thoracic radiotherapy.

Pignon et al\(^5\) performed a slightly larger meta-analysis that included many of the same studies as those assessed by Warde and Payne.\(^2\) Pignon and colleagues included two additional trials and obtained further follow-up data that increased the power of their analysis. They reported that the use of combined chemotherapy and thoracic radiotherapy resulted in a statistically significant relative survival benefit of 5.4% (±1.4%) at 3 years. The survival benefit appeared to be greatest for patients younger than 55 years of age. This benefit, however, was achieved at the cost of increased toxic reactions in those patients given thoracic radiotherapy. Analysis of local control was not performed.

In summary, it appears the addition of thoracic radiotherapy to chemotherapy for the treatment of patients with limited-stage SCLC yields moderate benefits in terms of local control and survival. Further optimization of chemotherapy, thoracic radiotherapy, and the integration of the two modalities may add to these benefits. Future advances in the control of micrometastatic disease may increase the importance of local-regional control, since patients may be at increased risk of thoracic failure if they do not have failure first in distant sites.

**Sequential, Concurrent, or Alternating Integration of Chemotherapy/Thoracic Radiotherapy?**

The question of how best to integrate chemotherapy and thoracic radiotherapy remains controversial. Sequential, concurrent, and alternating approaches have all been studied. Sequential therapy refers to treatment with one modality at a time whereby chemotherapy is delayed until completion of radiotherapy or vice versa. Concurrent therapy indicates that chemotherapy and radiotherapy are delivered simultaneously. Alternating therapy refers to delivery of radiotherapy on days when chemotherapy is not given, in such a fashion that the timing of the next chemotherapy cycle is not altered; in this treatment scheme, thoracic radiotherapy is by definition delivered as a split course.

Although to our knowledge no randomized trials have directly compared these treatment integration schemes, some suggest that a nonsequential approach may be more efficacious. In the meta-analysis of Pignon et al,\(^3\) indirect comparisons of sequential vs alternating or concurrent treatment integration were performed, but no statistically significant differences between the sequential vs nonsequential approaches were found. However, it is interesting to note that, among the 13 individual trials in this meta-analysis, 4 showed a significant survival benefit for chemotherapy and thoracic radiotherapy,\(^4,7\) of which used an alternating or concurrent schedule.\(^4,5,7\) Of the nine randomized trials that did not report a significant survival advantage for the combined modality, seven employed a sequential approach. Furthermore, a multivariate analysis of six Southwest Oncology Group (SWOG) limited-stage SCLC trials showed concurrent chemoradiotherapy to be a significant favorable predictor for survival.\(^9\)

Unfortunately, the apparent benefits of combined-modality treatment regimens are realized at the cost of increased treatment-related toxic reactions, including myelosuppression, esophagitis, and pneumonitis. The meta-analysis of Warde and Payne\(^2\) reported a 1.2% excess death rate for patients who received combined chemotherapy and radiotherapy compared with those who received chemotherapy alone. Furthermore, the toxic reactions of treatment appear to be higher for the concurrent or alternating regimens than for the sequential regimens.

The concurrent and alternating approaches are intuitively appealing because they enable delivery of multiple chemotherapy cycles without interruption. Insofar as SCLC is a systemic disease, the delivery of optimal systemic treatment is paramount. However, further evaluation of such intense treatment regimens must consider toxic reactions and quality of life issues as well as treatment efficacy.

**When Used With Chemotherapy, Should Thoracic Radiotherapy Be Given Early or Late?**

Treatment for SCLC generally will begin with chemotherapy for several reasons: there may be a theoretical advantage to early treatment of micrometastatic disease outside the chest; initial treatment with chemotherapy enables evaluation of disease response to chemotherapy; and treatment often can be initiated faster with chemotherapy than with thoracic radiotherapy. The data are conflicting with respect to the question of early vs late delivery of thoracic radiotherapy. The Cancer and Leukemia Group B (CALGB) trial reported by Perry et al\(^7\) slightly favored delayed delivery of thoracic radiotherapy. This trial was a randomization of three treatment approaches for patients with limited-stage SCLC: (1) thoracic radiotherapy delivered concurrently with cycle 1 of chemotherapy (early radiation); (2) thoracic radiotherapy delivered concurrently with cycle 4 of chemotherapy (late radiation); and (3) chemotherapy given alone. Chemotherapy was identical for all groups, consisting of cyclophosphamide, etoposide, and vincristine, with doxorubicin substituted for etoposide in alternate cycles during cycles 7 through 18. Thoracic radiotherapy con-
sisted of 40 Gy given in 4 weeks, with a 10-Gy boost to residual disease. All patients received PCI. Survival for patients treated with chemotherapy alone was significantly inferior to the two concurrent approaches. Although there was no statistically significant survival difference between the two concurrent arms, there was a trend favoring the regimen with late delivery of thoracic radiation ($p=0.08$). However, the reason for this potential survival difference may be related to the overall chemotherapy dose delivered rather than to the timing of radiotherapy. The authors pointed out that early delivery of thoracic radiotherapy with chemotherapy (ie, during cycle 1) was associated with significant toxic reactions (primarily neutropenia), which may have been instrumental in subsequent chemotherapy dose reductions and, therefore, reduced treatment efficacy for the early radiation treatment arm.

A more recent randomized trial from the National Cancer Institute (NCI) of Canada compared two concurrent chemotherapy and thoracic radiation regimens in patients with limited-stage SCLC. In one arm, radiotherapy was delivered early (with cycle 2) and in the other arm it was delivered late (with cycle 6). In both treatment arms, patients received six cycles of chemotherapy consisting of CAV (cyclophosphamide/doxorubicin/vincristine) alternating with EP (etoposide/cisplatin) every 3 weeks. The radiation dose consisted of 40 Gy given in 15 fractions over 3 weeks. Both 3-year progression-free survival and 3-year overall survival rates were statistically significantly higher for the early radiotherapy group than for the late radiotherapy group (26 vs 19% and 29.7 vs 21.5%, respectively). Unlike the CALGB study in which patients in the early radiotherapy group received lower total doses of chemotherapy, patients in both treatment arms of the NCI-Canada study received similar chemotherapy doses. However, the dose of thoracic radiation was significantly lower than that conventionally used in the United States.

Thus, based on limited data, early delivery of thoracic radiotherapy may be preferable. Murray et al postulated the following biologic explanation for this observation: early delivery of thoracic radiotherapy may help reduce the total tumor burden as well as prevent the formation and dissemination of chemoresistant clones, thereby rendering subsequent chemotherapy more effective.

**Thoracic Radiotherapy: Total Dose, Treatment Volume, and Dose Schedule**

**Dose**

Several studies using conventional thoracic radiotherapy for SCLC have provided evidence of a dose-response effect. A randomized study by Coy et al compared the efficacy of 2.5-Gy fraction sizes delivered to a total dose of 25 Gy vs 37.5 Gy. Actuarial local progression at 2 years was 80% for those receiving 25-Gy, compared with 69% for those in the higher-dose arm ($p=0.04$). In a retrospective analysis of patients with SCLC treated with standard fractionation, Choi and Carey showed an improvement in local control rates as the total dose delivered increased from 30 to 50 Gy. Reported 2.5-year local control rates were 16% for patients who received 30 Gy vs 68% for patients who received 50 Gy. In a third study, Papac et al showed a local control rate of 96% for 26 patients with limited-stage SCLC who received 60 Gy. Most standard thoracic radiation regimens attempt to deliver dosages in the range of 50 to 60 Gy, using daily fractions of 1.8 to 2.0 Gy. In the concurrent setting, the total dose is often reduced.

**Treatment Volume**

Whether the appropriate thoracic radiation treatment fields should cover the original prechemotherapy tumor volume or postchemotherapy tumor volume is an unresolved issue. SWOG performed a randomized trial in which 191 patients with limited-stage SCLC who had a partial response or stable disease following induction chemotherapy were randomized to thoracic radiation fields that included prechemotherapy vs postchemotherapy tumor volumes. This study failed to demonstrate a significant difference in failure patterns or median survival between the two thoracic radiation groups. The study is flawed, however, due to a high patient dropout rate and inclusion of patients who did not respond to chemotherapy (for these patients there was no difference in the prechemotherapy vs postchemotherapy tumor volumes). There were no apparent differences between the thoracic radiation groups in terms of severe drug-related toxic reactions or severe radiation pneumonitis. However, severe complications related to myelosuppression were higher for patients treated with wide-field radiation (17/93, 18%) than for those receiving reduced-field radiation (8/98, 8%). A retrospective review of 59 patients with limited-stage SCLC treated at the Mayo Clinic with thoracic radiation fields that covered either prechemotherapy or postchemotherapy tumor volumes also failed to show a significant difference in local recurrence, progression-free survival, and overall survival rates. All local failures occurred within the radiation fields; there were no failures at the margin of a field, which would imply the treated volume was too small. Thus, although the data are limited, the use of limited thoracic radiation fields appears to be a reasonable approach for the treatment of limited-stage SCLC. Such an approach may reduce the rate
and severity of combined-modality therapy toxic reactions without jeopardizing local control rates. As chemotherapy doses are intensified and agents with potential lung toxicity are added to chemotherapy regimens, such considerations may have increasing importance.

Fractionation Schedule

Standard radiation fractionation schedules for SCLC employ once-daily treatments five times a week over a continuous course for 5 to 6 weeks with dosages of 1.8 to 2.0 Gy/d. Accelerated hyperfractionation refers to delivery of a radiation course over a shorter total treatment time (acceleration) and with a greater number of treatment fractions (hyperfractionation). Radiation is delivered two or three times daily, and often the individual fraction sizes are reduced (ie, 1.5 Gy rather than 2.0 Gy per treatment).

There has been recent interest in the investigation of accelerated hyperfractionated radiotherapy schedules in the treatment of SCLC. The theoretical advantage for such schedules is that the delivery of smaller, more frequent radiation doses may enable greater normal tissue repair and, therefore, less long-term toxic reactions without compromising tumor cell kill. Acute toxic reactions, however, may be increased owing to reduced repair of sublethal damage between treatment fractions.

Turrisi et al\textsuperscript{15} pioneered a concurrent chemotherapy/thoracic radiotherapy trial in which the radiation was delivered twice daily and concurrently with cycle 1 of EP chemotherapy. The radiation regimen consisted of 1.5 Gy delivered twice a day over 3 weeks to a total dosage of 45 Gy. Results showed no local failures among 21 patients with limited-stage SCLC, and the actuarial 2-year survival was 57%. Johnson et al\textsuperscript{16} reported a 2-year survival rate of 65% for 41 patients treated at the NCI with a similar thoracic radiation regimen. In a third study, which also employed a twice-daily thoracic radiation schedule, Armstrong et al\textsuperscript{17} showed a 2-year survival rate of only 19%. This less favorable outcome may be related to the fact that the accelerated hyperfractionated radiation regimen was delivered late in the treatment course: radiation was administered sequentially following four cycles of alternating CAV/EP chemotherapy.

Hyperfractionated radiation has also been delivered as a split course in alternating chemotherapy/thoracic radiotherapy regimens. In the pilot study by the Eastern Cooperative Oncology Group,\textsuperscript{18} radiotherapy consisted of 1.5 Gy delivered twice daily over 5 continuous days after cycles 1, 2, and 3 of EP chemotherapy. The 2-year progression-free survival rate for this series was 47%. The Groupe Lyonnais d’Oncologique Thoracique employed a similar hyperfractionated radiation schedule alternating with chemotherapy in the treatment of 76 patients.\textsuperscript{19} For this group, the median survival rate was 14 months, and the 1-year disease-free survival rate was 42%.

With the caveats of potential patient selection bias in mind, the results from these studies appear to demonstrate an advantage in local control and survival favoring hyperfractionation regimens over regimens incorporating standard once-daily fractionation schedules. To test this hypothesis, the North Central Cancer Treatment Group (NCCTG) has commenced a randomized trial for patients with limited-stage SCLC consisting of treatment with three cycles of EP followed by either standard fractionated thoracic radiotherapy or accelerated hyperfractionated split-course (alternating) thoracic radiotherapy.\textsuperscript{20} This study should provide useful information with respect to the relative efficacy and toxic reactions of the two radiation fractionation schedules.

The toxic reactions for the five described hyperfractionated trials were primarily hematologic, pulmonary, and esophageal.\textsuperscript{15-19} There were 7 treatment-related fatalities among the total of 201 patients (3.5%) treated in the 5 trials. Four patients died of acute pulmonary toxicity reactions following completion of thoracic radiotherapy, and 3 patients died of sepsis. Nonfatal toxicity rates varied from trial to trial but ranged from 9 to 28% for pulmonary toxicity, 12 to 69% for esophageal toxicity, and 13 to 100% for hematologic toxicity. These toxic reactions, although significant, appeared to be tolerable; future trials should continue to assess treatment-related toxicities. Such treatment is considerably more complex, increases patient survival time, and may be more expensive than standard fractionation. The ultimate role for alternative fractionation remains undefined.

Is There a Role for PCI in Patients With Limited-Stage SCLC?

Following systemic treatment for SCLC, a significant number of patients suffer relapse with brain metastases. Rosen et al\textsuperscript{21} reported a 38% crude rate of cerebral metastases among 48 patients who achieved a complete response (CR) to systemic therapy but who received no PCI; the central nervous system (CNS) was a first and isolated site of failure for 17% of such patients. Furthermore, the investigators noted that the rate of CNS failure approached 100% for patients who survived 2 years. The significant CNS failure rate demonstrated in patients with SCLC is attributed to the fact that most chemotherapeutic agents do not adequately penetrate the blood-brain barrier, and, as in leukemia, the brain is a “sanctuary site.”

Based on the above-described natural history of...
SCLC, PCI has been proposed as a potential means to improve CNS control and patient survival. Nine randomized trials have been performed to assess the role of PCI.22-30 Eligibility criteria (ie, limited vs extensive disease, CR vs no response to chemotherapy) and treatments varied considerably among these studies. The radiation dosages delivered ranged from 20 to 40 Gy with fraction sizes of 2.0 to 4.0 Gy/d. Six of the nine trials showed a statistically significant decrease in the frequency of brain metastases for patients who received PCI.23-28 In an overview of these trials, Pederson et al31 demonstrated that 22% of patients who did not receive PCI experienced clinically detected brain metastases compared with 6% of patients who did receive PCI.

To our knowledge, no prospective randomized trial has demonstrated a significant survival advantage for patients treated with PCI. However, the subgroup of patients most likely to benefit from PCI includes patients with limited-stage disease who achieve a CR to systemic therapy (since those patients with extensive disease at presentation or who do not achieve CR are not likely to have an isolated CNS failure),21 and no randomized trial has targeted this favorable patient subset. Therefore, it is possible that PCI confers a survival benefit for these patients, but this has yet to be demonstrated.

Since the benefit of PCI is still in question, the toxicity of this therapy is an important factor that must be considered when making a treatment recommendation. Acute toxic reactions of PCI include scalp erythema, fatigue, and alopecia, all of which are usually self-limited. Long-term toxic reactions are difficult to quantify and assess but include potentially devastating neurologic and intellectual disabilities. Such deficits appear to be increased with the use of concurrent chemotherapy or large fraction sizes (3.0 to 4.0 Gy).32-34 Therefore, if PCI is given, we recommend (1) that it be given sequentially (not concomitantly) with chemotherapy, (2) that the total dose be in the range of 30 to 36 Gy, and (3) that daily fraction sizes not exceed 2.0 Gy.

We believe that the use of PCI should be individualized. For patients who present with limited-stage disease and achieve a CR or near CR to chemotherapy, it is reasonable to offer the option of PCI after a discussion of the risk and benefits of treatment.

Conclusion

In conclusion, we recommend thoracic radiotherapy be part of the treatment strategy for most patients with limited-stage SCLC who achieve a complete or partial response to chemotherapy. However, owing to the modest survival benefit and increased toxic reactions of combined-modality treatment, it may be prudent to consider withholding such treatment for certain patients deemed to be at high risk for treatment-related complications. The optimal timing of chemotherapy and thoracic radiotherapy is still uncertain, but concurrent or alternating regimens are appealing because (1) the efficacy of thoracic radiotherapy may be enhanced by the use of radiosensitizing chemotherapeutic agents, and (2) these delivery schedules do not interrupt the delivery of chemotherapy. Hyperfractionated thoracic radiotherapy appears promising in single-arm trials and is worthy of further investigation such as is being done in the ongoing NCCTG randomized trial. Outside of a protocol setting, we recommend conventional thoracic radiotherapy using standard fractionation (1.8 to 2.0 Gy) to a total dose of about 56 Gy. Limited treatment fields that include sites of known gross disease are probably sufficient. The role of PCI is controversial, but it is worth considering for patients with limited-stage disease who have achieved a CR to chemotherapy and thoracic radiotherapy. If the patient and physician agree to proceed with PCI, we recommend treatment to a total dose of 30 to 36 Gy in 2.0-Gy fractions. Prophylactic cranial irradiation should not be given concurrently with chemotherapy.

References

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