Incorporation of Radiotherapy Fractionation in the Combined-Modality Treatment of Limited Small-Cell Lung Cancer*

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Although systemic failure continues to plague patients receiving combined-modality treatment for limited small-cell lung cancer (SCLC), improvements in chemotherapy, including use of cisplatin/etoposide-based regimens, and radiotherapy have produced increases in median, 2-year, and 5-year survival over the last decade. Employing more conservative volumes of radiotherapy in more aggressive ways, today about 50% of SCLC patients will survive 2 years and 30%, 5 years. Moreover, integrating radiotherapy with chemotherapy early in the course of treatment can potentially eliminate resistant clones. The various factors in radiotherapy, including dose, volume, fractionation, and timing, therefore deserve scrutiny in the reporting and design of clinical trials. (Chest 1993; 103:418S-22S)

Over the last decade, progress has been made in the treatment of limited small-cell lung cancer (SCLC). Despite persistent difficulty with systemic failures, refinements in systemic chemotherapy and improvements in methods of administering external-beam radiotherapy have been associated with increases in median survival, 2-year survival, and, indeed, 5-year survival. Although some have attributed this principally to better patient selection and stage migration, it appears that recent therapeutic advances have improved local control despite adverse prognostic factors in many of these patients.

Radiotherapy Factors of Note

Dose

The following factors deserve scrutiny and attention in the reporting and design of clinical trials employing thoracic radiotherapy: total physical dose now is generally reported in centigray, which is the equivalent of the former unit, rad. The physical dose is a measure of how much radiation is actually absorbed by the tissue. The biologic effectiveness of a dose comprises both its antitumor effects and its acute and late effects on normal tissues. Choi and Carey, analyzing physical dose as it influences local control, reported that doses of 3,000 to 3,500 cGy were associated with only 50% local control. When doses were increased from 4,000 to 5,000 cGy, the local control rate increased to 70%. Interestingly, the Cancer and Leukemia Group B (CALGB) showed a significant improvement in survival with the addition of thoracic radiotherapy to chemotherapy. Local failure occurred in nearly 90% of patients given chemotherapy alone, but, even with the addition of low-dose radiotherapy, the local failure rate was still approximately 50%.

Volume

The volume of radiation also may influence tumor effects and normal tissue complications. Radiation oncologists have designed their portals based on radiographic observations but also on anatomic knowledge of the distribution of lymphatics and frequency of tumor involvement. Over the years, radiotherapeutic volumes in lung cancer have been expanded to include supraclavicular and contralateral hilar and lymph nodes, and sometimes, the lymph nodes to the level of the diaphragm, largely based on knowledge of the lymphatic distribution and postulated frequency of involvement. In addition, nearly a century ago, Halsted devised the concept of en bloc resections for breast cancer. In an attempt to model radiotherapy ports after en bloc surgical approaches to treat these lymphatics, the ports were expanded. In the 1950s and 1960s, the understanding of this spread by contiguity and the use of total lymphoid irradiation improved outcomes for patients treated for Hodgkin's disease. In response to these successes, lung cancer ports were increased in size. However, it has never been demonstrated that expanding the size of the lung cancer ports to cover these lymphatics leads to improved survival or even local control. In the present era of combined-modality therapy, the price of expanded nodal volumes is increased normal tissue dose. The merit of such increases must be balanced against the augmented risk of normal tissue toxicity.

The tolerance of the lung to radiotherapy has been reported to be in the range of 2,000 to 2,500 cGy with radiation alone; when chemotherapy is used, that dose is reduced to 1,500 cGy. However, these commonly quoted tolerances were derived mainly from whole lung doses achieved in animal models or from studies in children using total body irradiation. The partial organ tolerance of portions of the lung is, in essence, unknown, but it is extrapolated and estimated by experts without definitive data. Because lung cancer patients are commonly heavy smokers with diseased lungs, the precise influence of radiation damages is assumed to be important, but few, if any, studies have addressed this issue. This is primarily because methods for measuring irradiated volumes as a proportion of total lung volume and measuring toxic events have not been available until recently. A few studies have looked at pulmonary function tests and nuclear medicine assessments of air and blood flow, but these have not been able to accurately assess volume.

One lingering question in SCLC is whether it is important to treat the prechemotherapy initial volume of disease vs the reduced volume of disease found after treatment with chemotherapy. This is not an issue in concurrent strategies, because chemotherapy and radiation therapies begin simul-

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taneously in such an approach. When radiation is administered following chemotherapy, the volume to be irradiated may be reduced, thereby sparing exposure of adjacent normal tissue. On the other hand, a larger volume insures adequate coverage, but leaves the normal tissue of the lung and other organs susceptible to toxicity. To resolve this issue, the benefits and risks of larger and smaller volumes of radiotherapy will have to be weighed and compared in clinical trials.

Measures have been employed to protect other critical organs in the chest, including the esophagus, heart, and the spinal cord, from excessive radiation exposure. To protect the spinal cord, direct posterior spinal blocks have been used in the past. Unfortunately, these blocks have also shielded the mediastinum, particularly the central subcardinal spaces, resulting in underdosing of that region. Alternate strategies using oblique fields can spare the spinal cord, but at the price of increasing the volume and dose of radiation to normal lungs. Many have adopted these strategies, but critical analysis and studies of lung tolerances and functional changes are needed.

If smaller targets are chosen for radiation treatment, new sophisticated imaging techniques are now available, such as computed tomography (CT), positron emission tomography, and magnetic resonance imaging (MRI), that allow us to define these targets more precisely. Treatment planning capabilities, which include accurate display of dose to these targets and adjacent normal tissues, also use these same imaging techniques. Nevertheless, despite this sophistication in imaging, radiotherapists regularly add margins to account for: physical dose build-up at the edges of fields, uncertainty about tumor extent beyond radiographic abnormalities, variations in day-to-day patient set-up, and inadvertent patient movements that occur due to both physiological events like respiration and the cardiac rhythm and fidgeting.

**Fractionation**

Fractionation is the method by which the total physical dose is divided into daily portions. Standard fractionation is approximately 200 cGy ± 10% administered 5 days a week with weekends off. Two to three decades ago, it was popular to use a split-course technique. This allowed for treatment of an initially larger volume of disease for a period of 1 to 2 weeks, and then intentionally provided a 2- to 3-week break, allowing normal tissue reactions to subside and tumor shrinkage. This strategy also enabled physicians to identify and exclude patients who had an early aggressive course of disease. For those who did progress early in the course of radiation or during the break, therapy was terminated early, and thus, patients were spared unnecessary toxicity and expensive treatments.

The 2 new strategies that have been developed are hyperfractionation and accelerated fractionation. Hypertreatment uses multiple doses of radiation twice a day or more, and each individual dose is approximately 100 to 120 cGy. This allows the total radiation dose to be increased, but keeps the total time of treatment relatively constant in comparison with standard fractionation schemes. Since the fraction size is small, this strategy decreases the prospect of late effects. Therefore, if late effects limit the dose, this strategy may be effective. The tumor, however, must respond to the relatively low fraction size.

Accelerated fraction schemes use a somewhat different strategy. The daily fraction size is two thirds to three quarters that of standard daily fraction schemes. In a twice- or three-times-daily accelerated schedule, an intense amount of radiation is given in a relatively brief period of time. The total physical dose in this strategy is generally less than that given in standard fraction schemes, but the time is also shorter, providing an intense, biologically effective dose. Applying such intense radiation may actually increase activity against a rapidly growing tumor population. Theoretically, however, rapidly growing normal cells will also be more severely affected by this strategy. Both strategies rely on the fact that there are relatively resistant (S) and relatively sensitive (G and M) phases of the cell cycle. Recent trials using radiotherapy without chemotherapy in non-small-cell lung cancer offer the clearest evaluation of accelerated treatment.

Table 1 compares the relative effects, both acute and late, for a standard 6,000-cGy dose given in 30 200-cGy fractions

<table>
<thead>
<tr>
<th>Total Dose, Gy</th>
<th>No. Fractions</th>
<th>Dose per Fraction, Gy</th>
<th>Time, d</th>
<th>Acute Effects</th>
<th>Late Effects</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NSD (RET)</td>
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<tr>
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</table>

*NSD = nominal standard dose; RET = radiation equivalent therapy; NRET = neurologic RET; BED = biologic effective dose.
†Multiple daily fractions.

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\text{NSD} = \text{Dose} \times \text{Gy(N)} \quad \text{(T)} \quad \text{Gy-10} = \text{BED}, \quad \frac{\text{BED} = \text{Dose}_{\text{cGy}}(1 + \frac{\text{Fx Size}}{\alpha/\beta})}{= 10} \]

| \( \frac{\text{NSD} = \text{Dose} \times \text{Gy(N)} \quad \text{(T)} \quad \text{Gy-3} = \text{BED}, \quad \frac{\text{BED} = \text{Dose}_{\text{cGy}}(1 + \frac{\text{Fx Size}}{\alpha/\beta})}{= 3} \) |

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over the course of 40 days. The Radiation Therapy Oncology Group (RTOG) conducted a hyperfractionation trial using 120-cGy fractions twice daily to a variety of total doses, but they considered 6,960 cGy to be the best dose. Recently, Saunders and Dische at Mount Vernon Hospital in the United Kingdom have used the CHART (continuous hyperfractionated accelerated radiotherapy) schedule employing 140- to 150-cGy fractions to a total dose of 5,000 to 5,400 cGy. Table 1 uses measures of relative scales based on the nominal standard dose (NSD) method of Ellis (NSD reported in radiation equivalent therapy [RET] for acute effects), and the neurologic-radiation equivalent therapy (NRET) method of Sheline et al for late effects. Also tabulated are the alpha-beta models, which use Gy-10 as a measure of acute effects and Gy-3 as a measure of late effects. Despite differences in total dose, Table 1 shows that, measured in the RET or Gy-10 scales, there are no dramatic differences in acute effects among the 3 fractionation methods: 60-Gy standard, 54-Gy accelerated, or 69.6-Gy hyperfractionated. The alpha-beta techniques, which rely heavily on the daily fraction size, do not have a parameter for time. Looking at relative late effects, as measured in NRET or in Gy-3, one can arrive at divergent conclusions, but in fact, there is very little difference among the 3 methods despite a rather broad difference in the total physical dose. Thus, the biologic effectiveness of radiation may be influenced profoundly by the way it is administered. Looking only at the total doses ignores some of these important factors.

Timing

There are 3 basic strategies by which one can combine radiotherapy with systemic therapy. Clearly, systemic chemotherapy is the cornerstone of management of SCLC. One of the prime advantages of the development of the cisplatin and etoposide (PE) regimen is that PE does not damage intrathoracic organs directly. Many of the older regimens employed subliminal pulmonary toxins like nitrosoureas, other alkylators, or antimetabolites, all of which have low frequencies of hypersensitivity or pulmonary toxicity. Nevertheless, when combined with radiotherapy to the chest, they sometimes cause unacceptable adverse effects. Doxorubicin causes cardiac toxicity by itself, and when combined with radiotherapy, intensifies the latter's adverse effects on the esophagus. Although pneumonitis, cardiitis, and esophagitis are frequently attributed to radiation therapy, they are in fact combined-modality effects.

The relative antitumor efficacy of a combined modality must be weighed against its effects on normal tissues. Leliaveld et al, in a series of experiments, compared the effects of a combined modality in mice on tumors and a variety of normal tissues. The investigators used a number of chemotherapeutic agents and administered them at various times prior to, concurrent with, or hours after administration of radiotherapy. These elegant laboratory experiments have provided an inkling about radiotherapy and chemotherapy interactions, as well as the time intervals between administration of each modality, and the influence of these factors on outcomes in combined-modality trials in humans.

Thus, the timing of delivery of chemotherapy with radiation may also have a profound influence. Furthermore, the choice of chemotherapeutic agent, its intrinsic toxicity, and the additive or synergistic toxicity when used with radiotherapy need to be considered in the design of clinical trials.

The three timing strategies—concurrent, alternating, and sequential—point to the different ways of combining chemotherapy with radiation therapy in clinical trials. Most trials delivering therapy concurrently show improved survival when compared to older retrospective series employing either a concurrent or an alternating technique. The alternating strategy, in which chemotherapy is given during week 1 and radiotherapy during week 2 or 3, was an attempt to combine both modalities at full doses in a close temporal sequence. The clinical goal was to avoid toxicities while maintaining an intense amount of radiotherapy. The group most associated with the alternating strategy is the Institut Gustave Roussy in Villejeuf, France. Whenever alternating techniques are used, by definition a split course must be administered. Arriagada et al have employed the alternating technique in dose-escalation studies using radiotherapeutic doses of 4,500, 5,500, and 6,500 cGy. Interestingly, for local control, little dose response was noted despite dose escalation. Even with the use of high doses, the local failure rate remained uniformly 30% at 3 years.

Using chemotherapy and radiotherapy concurrently has a number of rationales. Chemotherapy may alter the radiation sensitivity of the cells and may influence repair of radiation damage. Administering both modalities in close proximity may provide the mutual benefits of better access of chemotherapy to the tumor and fewer hypoxic cells, which are usually more radioresistant.

Timing: Early vs Late. Two trials using concurrent therapy, but at different times during the total course of treatment, are worthy of note. The first is the CALGB study. This study randomized patients to receive chemotherapy alone, immediate radiotherapy with cycle 1 of chemotherapy, or delayed radiotherapy with cycle 4. The trial employed a cyclophosphamide-based regimen and did not incorporate PE. It was designed in the early 1980s, and its median and 2-year survivals were similar to those of other cyclophosphamide-based trials. Results showed a statistically significant improvement in outcome when concurrent radiotherapy was delayed to cycle 4. A review of the chemotherapy intensity in this trial showed that patients randomized to immediate chemoradiotherapy required profound reductions of systemic chemotherapy doses. The local failure rate was nearly 50% in both radiotherapy arms. Many have interpreted this trial to show that delaying radiotherapy to cycle 4 is an excellent strategy, and in fact, better than giving immediate radiotherapy. One should be mindful, however, that alternative explanations exist as to why variations in outcome occurred. The results of this trial show that the combination chemotherapy used and dose and sequence of radiotherapy produced less than optimal local control and 2-year survival, particularly in comparison with current cisplatin-based studies.

In a trial by the National Cancer Institute of Canada, 6 cycles of cyclophosphamide, doxorubicin, and vincristine (CAV) alternating with PE were given to patients with limited SCLC. Additionally, patients were randomized to receive radiotherapy concurrent with either cycle 2 or cycle 6, both of which were PE cycles. This trial showed a
significant improvement in survival when radiotherapy was administered at cycle 2 rather than delayed to cycle 6. The investigators theorized that this was due to a resistant clone of cells at the primary site which, when attacked early, was eliminated before it had the opportunity to emigrate from the primary site. Delaying radiotherapy may provide resistant cells the opportunity to leave the primary site and metastasize distantly, causing patient demise. Once cells that are resistant to chemotherapy leave the primary site, patient demise is assured.

**Trials of PE Combined With Radiotherapy**

In the mid-1980s, combined-modality trials began to use PE as their base chemotherapy; PE has an advantage in combined-modality treatment, because cisplatin appears to sensitize tumors more than normal tissues, and neither cisplatin nor etoposide has intrinsic pulmonary or cardiac toxicity. Table 2 displays outcomes of trials employing thoracic radiotherapy with PE. These trials show median survivals in the 18- to 24-month range and 2-year survivals of about 40% to 60%. The rationale for using accelerated, twice-daily radiotherapy in SCLC is founded on biologic observations. The SCLC, from in vitro data concerning single cell radiation survival responsiveness, shows no radiobiologic shoulder. Radiobiologic shoulder is generally the initial part of the radiation survival curve and usually indicates a need for accumulation of damage prior to exponential cell killing. Cells without a shoulder are killed exponentially with small fractions of radiotherapy. Thus, a 2- or 3-times-daily schedule would allow the opportunity to expose normal tissues to a lower, less injurious dose of radiotherapy that at the same time can exponentially kill SCLC. Additionally, when multiple fields are used, some normal tissues receive radiation only once a day, whereas the tumor receives doses twice a day. Since SCLC has one of the largest growth fractions of any tumor, cells could also migrate from relatively resistant phases of the cell cycle (S phase) into more radiosensitive phases (G2 or M).

Importantly, when it has been reported, most of these trials showed excellent local control. In the study from the University of Pennsylvania, which now has a minimum 54-month follow-up, only patients in whom treatment failed locally also had tumors with the biologic characteristic of variant histologic findings. Unlike most small cells, those with variant histologic condition have a radiobiologic shoulder. In this series of 32 patients, all 4 patients initially diagnosed with variant histologic condition failed treatment locally and died by 24 months. Of the remaining 28 patients with classic histologic condition, only 1 failed treatment locally, and that patient could not complete radiotherapy. Interestingly, at failure, cancer cells showed variant histologic findings. None of the other 27 patients with pure small-cell histologic finding failed locally during the 5 years of follow-up.

**Conclusions**

Radiotherapy factors may play an important role in both the response and local control of patients with limited SCLC. Even with older techniques, a recently reported retrospective meta-analysis showed that long-term survival was significantly improved with the addition of thoracic radiotherapy. Today, with PE regimens and more conservative volumes of radiotherapy administered in more aggressive ways, long-term survival is now attainable in patients with SCLC; 2-year survival rates approach 50% and 5-year survival is in the range of 30%.

Presently, the Eastern Cooperative Oncology Group is testing fractionation in patients with limited SCLC given 4 cycles of PE. Patients are randomized to receive twice-daily radiotherapy providing 4,500 cGy administered either in 25 fractions over 33 days or in 30 fractions over 19 days, respectively. More than 400 patients have been entered into this trial, which closed in August 1992. Integrating radiotherapy with chemotherapy early in the course of treatment has the advantage of potentially eliminating resistant clones; however, results from the CALGB study imply that early radiotherapy may compromise systemic therapy. The dose-reduction rules were very cautious, though. Since the majority of SCLC deaths and failures continue to be systemic, development of new agents and new strategies for systemic therapy is certainly warranted. However, analysis of the French alternating-modality experience suggests local relapse is also a major cause of failure. Therefore, improved local management remains a worthy goal.

**References**

1 Choi NC, Carey RC. Locoregional failure rate in relation with


