Combined Chemoradiation Therapy for Limited-Stage Small-Cell Lung Cancer

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After nearly 4 decades of use in treating small-cell lung cancer (SCLC), thoracic radiation has become integral to the management of limited-stage disease. Many prospective randomized trials have demonstrated that adding

Introduction

Approximately 20% of new lung cancer cases are small-cell lung cancer,[1] composed of cells with small, round or spindle-shaped, darkly staining nuclei and scant cytoplasm. Small-cell lung cancer manifests as a central tumor with early dissemination to the regional lymph nodes and distant sites. It has a large growth fraction, grows rapidly, is associated with paraneoplastic syndromes (syndrome of inappropriate secretion of antidiuretic hormone, Cushing's syndrome, and Eaton-Lambert syndrome), develops almost exclusively in smokers, and is sensitive to chemotherapy.[2] Even when the disease is extensive, approximately 60% of patients will respond to intensive chemotherapy. The results of initial chemotherapy trials showed median survival of patients with limited-stage disease treated with combination chemotherapy to be approximately 12 months, compared with 3 months for those receiving best supportive care.[3] Long-term survival is rare, however, with fewer than 10% of patients alive at 10 years.

The American Joint Committee on Cancer’s TNM staging system has been used to stage non-small-cell lung cancer with reasonable prognostic predictive value. The system has not been universally adopted for small-cell lung cancer because the majority of small-cell lung cancer patients present with stages beyond IIIA, and because small-cell lung cancer is considered a systemic disease characterized by rapid proliferation and early distant dissemination. Thus, clinicians have adopted the simple two-stage system of the Veterans Administration Lung Cancer Study Group, limited and extensive disease. Limited stage is defined as tumor confined to one hemithorax and the regional nodes, and is based on whether all detectable disease can be encompassed by a tolerable, single continuous therapeutic radiation port. Extensive-stage disease encompasses demonstrable extra-thoracic disease. A better understanding of the biology of small-cell lung cancer and of its patterns of failure has provided the principles for its management.[2,4] Since small-cell lung cancer is a systemic disease, current treatment of limited disease consists of chemotherapy to manage undetected micrometastases present at diagnosis and thoracic radiation therapy to improve locoregional tumor control. The presence of pleural effusions or involved supraclavicular or contralateral hilar nodes has been considered limited disease in some trials and extensive disease in others; such differences must be kept in mind when results from different institutions and cooperative groups are compared.

Impact of Thoracic Radiation on Local Control and Survival

Thoracic radiation therapy has been used to treat small-cell lung cancer since the 1960s, but surgery was the treatment of choice for patients with all types of lung cancer until approximately 25 years ago. It was abandoned following the results of a randomized trial conducted in the United Kingdom by the Medical Research Council that compared radiation therapy alone with surgery alone in patients who had limited-stage disease.[5] None of the patients were alive at 10 years in the surgery group compared with 5% alive in the radiation group. Additionally, a review of the outcome of a large number of small-cell lung cancer patients treated in the United States whose disease was thought to be surgically resectable revealed absolutely no difference in survival whether or not surgery was performed.[6] Just as the discovery of the radiosensitivity of small-cell lung cancer shifted local management of
Limited disease from surgery to radiation,[5] realization of the propensity of small-cell lung cancer for early systemic metastases also led to the assessment of chemotherapy. The observation of high overall and complete response rates in limited-disease patients who received only chemotherapy initially led some to question the value of local therapy with thoracic radiation. In 1969, the Veterans Administration Lung Cancer Study Group demonstrated that cyclophosphamide (Cytoxan) treatment could double median survival in patients with extensive-stage disease.[7] However, the high frequency of locoregional recurrence (up to 80% of limited-stage patients) and the poor survival of patients who received only chemotherapy led to investigations of the role of thoracic radiation therapy in the management of small-cell lung cancer.

Several single-institution and cooperative group randomized trials were initiated in the United States to test the role of thoracic radiation therapy in the treatment of limited-stage small-cell lung cancer (Table 1).[8-20] The cooperative group randomized trials include those conducted by the Southeast Cancer Study Group (SECSG),[19] the National Cancer Institute,[10] the Cancer and Leukemia Group B (CALGB),[8] the Eastern Cooperative Oncology Group (ECOG),[13] and the Southwest Oncology Group (SWOG).[14] In each, patients with limited disease were randomized to chemotherapy with or without thoracic radiation. All results showed that chest radiation improved local control, and all but Osterlind,[11] LeBeau,[18] and the SWOG trial[14] reported borderline improvement or significantly improved survival with combined-modality treatment.

Two meta-analyses have also shown a small but significant improvement in survival for patients treated with chemotherapy and thoracic radiation vs those treated with chemotherapy alone.[21,22] Pignon et al obtained data on 1,862 individual patients from the American, European, and Japanese investigators who had conducted 13 randomized studies.[21] They then updated the survival rates and performed an intent-to-treat analysis that included all patients; they found that treatment with thoracic radiation was associated with a 14% reduction in the risk of death (P = .001). In addition, the 3-year survival rate improved for patients treated with chemotherapy and radiation therapy to 14.3% compared with 8.9% for patients who received chemotherapy alone. No significant survival differences emerged, however, when the timing of thoracic radiation (early vs late) and the schedule of chemotherapy and radiation (sequential vs concurrent) were evaluated.

Moreover, this intent-to-treat analysis may have underestimated the impact of radiation on improving survival. Warde and Payne analyzed 11 published trials and discovered significantly better survival for patients who received chemotherapy and radiation therapy.[22] The odds ratio was 1.56 for patients treated with chemoradiotherapy (P < .001). Comparison of the 2-year survival rates showed a 5.4% improvement for patients who received radiation therapy. The 5% increase in absolute survival in patients receiving thoracic radiation represents a more than 50% relative improvement in the survival rate observed with chemotherapy alone. Local control rates were doubled from approximately 25% with chemotherapy alone to approximately 50% with the addition of thoracic radiation. Neither study reported the "best" chemotherapy and radiation regimen. However, the use of cisplatin (Platinol) and etoposide (VePesid) (PE) and concurrent thoracic radiation has been associated with the best survival results observed thus far.

Despite these findings demonstrating the benefits of thoracic radiation on local control and survival in limited-stage small-cell lung cancer, the chest relapse rate remains unacceptably high, with a 60% actuarial risk of local recurrence by 3 years. Further enhancement of locoregional control may increase the proportion of long-term survivors. Issues like the optimal integration of thoracic radiation with chemotherapy (sequential vs concurrent vs alternating), the appropriate volume, and dose/fractionation need to be explored further.

Timing of Radiation and Chemotherapy

Because of small-cell lung cancer's propensity for distant metastasis, chemotherapy remains a cornerstone of therapy. However, cells resistant to chemotherapy may be killed by radiotherapy. Judicious timing of radiation treatment may eliminate resistant cells before they metastasize. The optimal timing of combined thoracic radiation and chemotherapy has not been identified, however. Available options in combining radiotherapy and chemotherapy include sequential, concurrent, and alternating administration.[23]

Sequential Administration

Sequential administration consists of a full course of chemotherapy and a full course of radiation given separately in time. One treatment is completed before the other begins, with either administered first. One of the major advantages of this regimen is that it avoids the excessive toxicities encountered when the two modalities are administered concomitantly, thus reducing host toxicity.
toxicity. Moreover, this approach potentially improves the ability to deliver the full chemotherapy dose. Nonetheless, the prolonged time needed to administer all of one modality followed by the other increases the possibility that therapeutic effectiveness will be diminished because the tumor cells repopulate during sequential treatment.

Carlson et al reported a phase III study evaluating the value of late consolidative involved-field radiation in the treatment of limited-stage small-cell lung cancer.[17] In this Northern California Oncology Group study, the 48 patients who responded to chemotherapy were randomized to more chemotherapy or to involved-field radiation therapy. Radiation at a total dose of 55 Gy delivered in daily fractions of 1.8 to 2.0 Gy over 5 to 7 weeks. Survival did not differ between the two groups. However, first disease relapse occurred in the thorax in 58% of patients randomized to chemotherapy vs 29% of patients who received radiation therapy (P = .042) (Table 1).

Lebeau et al reported a randomized study of delayed thoracic radiation therapy in 53 complete responders to chemotherapy.[18] Twenty-seven patients went on to receive a mean radiation dose of 46.5 Gy while the other 26 received no radiation until the disease relapsed. The median survival time was about 10.5 months in the immediate radiation group vs 16.5 months in the group that received no radiation until relapse. There was no difference in survival between the two groups (P = .66), and delayed radiation therapy seemed to worsen the outcome of complete responders. Although those who received immediate radiation in the study had a reduced rate of first relapse in the thorax (33% vs 58%), radiation did not improve their time to progression or their rates of survival (Table 1). The authors concluded that radiotherapy should not be delayed in this setting.

The development of chemotherapy-resistant tumor clones resulting in poor control of systemic disease was the most likely cause for this lack of survival benefit. Additionally, non–cisplatin-based chemotherapy was used, which resulted in relatively inferior survival results compared with those obtained in trials of cisplatin-based chemotherapy.

Alternating Administration

Recent clinical, experimental, and theoretical results with chemotherapy and radiotherapy to manage cancer emphasize the necessity for the greatest intensity possible in the initial phase of induction therapy.[23] Alternating administration is a strategy to give chemotherapy initially, maintain the chemotherapy schedules to avoid any reduction in effectiveness, and add radiation therapy as early as possible between chemotherapy courses to minimize the development of resistant clonogens.

Chemotherapy is given in the conventional way, every 3 to 4 weeks. Radiation is delivered between successive courses of chemotherapy. This strategy attempts to maximize the advantages of concomitant and sequential treatment by providing temporal separation of delivery of both modalities. Thus, both chemotherapy and radiation can be given at the initiation of induction therapy without compromising the intensity of the full therapeutic dose of either modality. This has the advantages of reducing toxicity, minimizing the build-up of tumor cells resistant to either treatment, and providing early chemotherapy to treat micrometastasis. This approach may also decrease the probability of developing cross-resistant tumor clonogens. The disadvantages of this approach are splitting the radiotherapy dose and the loss of concurrent administration of chemotherapy and radiation therapy.

Two large phase III trials have evaluated the role of alternating chemotherapy and thoracic radiation therapy. In the SECSG study, patients received non–cisplatin-based chemotherapy consisting of cyclophosphamide, doxorubicin (Adriamycin), and vincristine (Oncovin) (CAV), either alone or alternating with thoracic radiation therapy.[19] The addition of thoracic radiation improved both local control (64% vs 48%) and 2-year survival (24% vs 16%).

Lebeau et al compared alternating (20 Gy in eight fractions for the first two courses and 15 Gy in six fractions for the third course between chemotherapy cycles 2 and 5) and concurrent (50 Gy in 20 fractions starting with the second chemotherapy cycle) thoracic radiation therapy using non–cisplatin-based chemotherapy.[24] Three-year survival was poor in both arms (4% and 7%), with the slight difference favoring alternating chemoradiotherapy. These poor survival results might be due to the use of non–cisplatin-based chemotherapy.

Concurrent Administration

Concurrent administration administers both modalities together, with chemotherapy given in a conventional manner and thoracic radiation delivered simultaneously either up front (early) or delayed (late) in the treatment cycle. Using chemotherapy and radiation therapy at the beginning of induction therapy (early) permits both modalities to be administered with greater intensity. It also minimizes the build-up of cross-resistant tumor cells. Its disadvantage is increased toxicity. The mathematical model of Goldie and Coldman suggests that each modality is able to extinguish...
subpopulations of tumor cells that are resistant to the other mode of therapy.[25-27] The most effective regimen should be given early in the treatment course to prevent the emergence of resistant tumor clonogens. Additionally, tumor clonogens resistant to chemotherapy may be sensitive to ionizing radiation.

The CALGB conducted a three-arm trial in which patients were randomized to receive only chemotherapy or chemotherapy combined with thoracic radiation to 50 Gy over 6 weeks starting either on day 1 with cycle 1 (early) or on day 64 with cycle 4 (delayed).[8] Although local control was no different for early and delayed administration of thoracic radiation therapy, the median survival duration and the 2-year failure-free survival rate favored the delayed radiotherapy arm (14.6 months and 25%, respectively) over early radiotherapy (13.1 months and 15%, respectively). An update of this trial confirmed its initial findings. Survival at 5 years continues to favor delayed radiotherapy (13%) over early radiotherapy (6%) and chemotherapy only (3%).[28] Toxic effects in the early radiation groups caused the chemotherapy dose to be reduced slightly, which might explain the absence of benefit for early radiation therapy.

The National Cancer Institute of Canada conducted a trial in patients with limited-stage small-cell lung cancer who received three cycles of CAV alternating with three cycles of PE.[9] Thoracic radiation was given at a total dose of 40 Gy in 15 fractions over 3 weeks, concurrent with PE. Patients were randomized to either early (first PE cycle) or late (third PE cycle) administration of radiation. As in the CALGB study, local control was the same in the early and late radiotherapy arms, and no difference emerged in the overall rate of systemic metastases between the two arms. However, both 5-year progression-free survival and overall survival were significantly superior for patients who received early radiotherapy.

The median progression-free survival times were 15.4 and 11.8 months for early and late thoracic radiotherapy arms, respectively (P = .036). The median survival times were 21.2 and 16 months for the early and late thoracic radiotherapy arms, respectively (P = .008), and the 5-year survival rates were 20% and 11%, respectively (P = .006). The frequency of brain metastases was also lower in the early radiation arm (18% for early vs 28% for late [P = .042]). It is possible that the early use of radiotherapy eradicates subclones of drug-resistant cells before they have metastasized to extrathoracic sites, which otherwise may result in patient death.

A large CALGB study was reported by Jeremic et al in 1997, in which patients received small daily doses of carboplatin (Paraplatin) and etoposide given concurrently with early (weeks 1 through 4) or late (weeks 6 through 9) accelerated, hyperfractionated radiation therapy.[29] The median survival durations were 34 months and 26 months for early and late radiation therapy, respectively (P = .052). The results also showed a trend toward improved survival in patients who received early radiotherapy, with 5-year survival rates of 30% and 15%, respectively (multivariate analysis, P = .027). Patients who received the early radiotherapy also had a significantly higher rate of local control.

The question of early vs late concurrent administration of thoracic radiation remains unresolved. Either approach offers unique therapeutic advantages. The administration of early concurrent radiation reduces the risk of distant seeding, as in the case of brain metastases, possibly because radiation eradicates chemoresistant clonogens in the chest before micrometastases develop outside the radiation port. Late concurrent radiation therapy does not appear to compromise local control and has the advantage of permitting full chemotherapy doses to be delivered to patients. It also reduces treatment-related toxicities by treating only residual postchemotherapy tumor through a reduced radiation port.

Takada et al reported the results of a phase III trial by the Japanese Clinical Oncology Group. Patients with limited small-cell lung cancer received four cycles of PE, followed by thoracic radiation therapy 45 Gy over 3 weeks given either concurrently with day 2 of the first cycle or following the fourth chemotherapy cycle.[30] Concurrent thoracic radiotherapy produced superior survival (median survival duration, 31.3 months) compared with the same chemotherapy followed sequentially by thoracic radiotherapy (median survival, 20.8 months). The authors concluded that concurrent thoracic radiotherapy affords an excellent survival benefit to patients with limited-stage small-cell lung cancer.

Turrissi et al [31] recently published an intergroup trial with 5-year follow-up. Thoracic radiotherapy, given either once or twice daily, was initiated concurrently with the first cycle of chemotherapy. The median survival time and the 2-year survival rate were 19 months and 41%, respectively, for once-daily thoracic radiotherapy and 23 months and 47%, respectively, for twice-daily thoracic radiotherapy. Also noteworthy, the 5-year survival favored the twice-daily treatment group by 10% (26% vs 16%, P = .04). Patterns of failure showed a component of local
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failure after complete response occurring in 75% of patients on the once-daily regimen and in 42% of patients on the twice-daily regimen. Local failure alone was 52% vs 36%, and the incidence of brain metastasis was 14% vs 31% in the once-daily and twice-daily arms, respectively. This is the first study demonstrating that a significant (P = .04) percentage of patients with limited-stage small-cell lung cancer have been cured.

Numerous studies have failed to resolve the optimal timing of combined chemotherapy and thoracic radiation. In their meta-analysis, Pignon et al compared alternating and sequential combined-modality regimens.[21] They did not demonstrate a difference between the two regimens. However, all trials included in this analysis used cyclophosphamide- or doxorubicin-based regimens; none included cisplatin and etoposide as initial treatments. Some of the best survival results have been achieved by treating limited-stage small-cell lung cancer with early concurrent thoracic radiotherapy and cisplatin-based chemotherapy.[9,30] The 2-year survival in the intergroup study is about twice that reported in the trials using non-PE chemotherapy and delayed thoracic radiotherapy. Thus, early concurrent therapy is considered the standard when PE is used.

Radiation Dose

For the past 30 years, the radiation dose has remained between 40 and 50 Gy in continuous course treatment for limited-stage small-cell lung cancer. This dose is lower than that typically applied to non-small-cell lung cancer, most likely because small-cell lung cancer is more radioresponsive. With 40 to 50 Gy thoracic radiotherapy, however, the chest relapse rate remains unacceptably high (about 60% actuarial risk of local recurrence by 3 years). Since chest-only relapse is observed in about 40% of patients, further enhancing locoregional control may increase the proportion of long-term survivors.

To improve local control by increasing doses of radiation, a dose-response relationship must first exist. Table 2 presents dose-response data for limited-stage small-cell lung cancer.[32-36] Choi et al reported a dose-response relationship for thoracic radiotherapy in their CALGB trial.[34] In the dose range of 30 to 35 Gy, local control was only 20% to 25%, but when doses were escalated to a range of 45 to 50 Gy, local control increased to 60% to 70%. Doses beyond 50 Gy were not studied, however (Figure 1).

Arriagada et al increased the total thoracic dose from 45 to 65 Gy using a split course of radiotherapy sandwiched with chemotherapy.[36] The data demonstrated a trend toward better local control with higher doses. Choi et al reported a phase I/II CALGB study.[37] The primary end point of the trial was acute esophagitis. The maximum tolerated dose of hyperaccelerated twice-daily radiotherapy was determined to be 45 Gy in 30 fractions over 3 weeks, while the maximum tolerated daily dose was judged to be at least 70 Gy in 35 fractions over 7 weeks.

The limitations of the study were that fewer patients were entered at each dose level, acute esophagitis may have been related to the length of esophagus only, and acute esophagitis is transient and reversible. It does not lead to permanent injury. Patterns of failure did not differ significantly between patients who received the twice-daily and once-daily radiation schedules. Papac et al used 60 Gy thoracic radiotherapy, given in 3-Gy daily doses for 5 days a week for 10 treatments, followed by a 2-week rest and completion of the course in 2 weeks. The local failure rate was only 3%.[38] The duration of local control was not clearly defined in the report, and these results were never replicated by others. In summary, a study comparing the standard widely accepted 45 Gy to 50 Gy thoracic radiation therapy vs larger doses will be needed to assess the influence of high-dose radiation therapy on local control, survival, and tolerability.

Fractionation

The standard daily radiation dose in the United States to treat lung cancer ranges between 1.8 and 2.0 Gy. The apparent failure of conventional dose escalation in small-cell lung cancer led to the exploration of other means to improve the effectiveness of local radiation therapy. One such approach is to deliver the radiation in multiple fractions per day, with the radiation dose being reduced per fraction. Since small-cell lung cancer has a rapid proliferation and growth rate and lacks a shoulder on the radiation dose survival curve, hyperfractionated radiation may spare relatively fewer small-cell lung cancer tumor cells than normal tissues, thus increasing the therapeutic ratio. Turrisi et al first reported the administration of 45 Gy thoracic radiation in 30 fractions given twice daily concurrent with PE chemotherapy.[39,40] The local control rate was 91% and the 2-year survival was 56%. Several phase II studies using this regimen also have confirmed the efficacy of accelerated radiation therapy in conjunction with chemotherapy. A phase III North American
intergroup trial prospectively compared daily with twice-daily fractionation in patients with limited-stage small-cell lung cancer.[31] Patients were randomized to receive either 45 Gy over 3 weeks in twice-daily fractions or the conventional 45 Gy over 5 weeks in daily fractions, given concurrently with the first of four cycles of PE.

After a median follow-up of almost 8 years, the median survival was 19 months for the once-daily group and 23 months for the twice-daily group. The 2-year survival rates were 41% and 47% for those receiving once- and twice-daily radiation therapy, respectively. More significantly, the respective 5-year survival rates were 16% and 26% for once- and twice-daily radiotherapy (P = .04). The estimated hazard ratio for death with once-daily treatment compared with twice-daily treatment was 1.2. However, the acute toxicity, grade 3 esophagitis, was significantly more frequent in those who received twice-daily thoracic radiotherapy (27% vs 11%).

In summary, the current standard therapy for limited-stage small-cell lung cancer should be twice-daily radiation fractions of 1.8 to 2.0 Gy to a total dose of 45 to 50 Gy when PE chemotherapy is used.

**Volume**

Historically, large radiation portals have been used to treat limited-stage small-cell lung cancer for many reasons. One of the tenets of radiotherapy mandates coverage of the next echelon of uninvolved lymph nodes along with the primary tumor and involved lymphatic nodal chains. Confirmation of this tenet in the treatment of limited-stage small-cell lung cancer came from an analysis of the patterns of failure in the SECSG trial.[19] In this study, excluding the contralateral hilum or portions of the mediastinum increased the intrathoracic failure rate from 33% to 69% (P = .026). Additionally, tumor cells tend to spread locally via an infiltrative process where the exact full extent of disease is not always radiographically certain. Total clearance of local disease at the peripheral edges of the primary tumor by systemic therapy is always problematic. It is logical that the radiation portals should encompass prechemotherapy tumor volume.

In a study by Mira and Livingston, radiation ports encompassed only residual local chest disease following chemotherapy.[41] Five of seven intrathoracic failures occurred outside the radiation port, implying that initial chemotherapy did not totally eradicate microscopic disease at the edges of the primary tumor. Thus, coverage of prechemotherapy tumor volume within the radiation port should address both anatomic and chemotherapy response uncertainties.

In the combined-modality era, larger volumes include larger esophageal segments. Reducing the volume irradiated may avoid the likely increase in toxicity with combined-modality treatment when healthy surrounding tissue is exposed to both chemotherapy and radiation therapy. Liengswangwong et al reviewed patterns of locoregional failure at the Mayo Clinic in nonprotocol patients treated with radiation ports encompassing either prechemotherapy (31 patients) or postchemotherapy (28 patients) disease extent.[42] The rates of locoregional failure were similar for both groups of patients. Additionally, no marginal local failures were observed in the postchemotherapy radiation ports. In fact, all local failures occurred in the epicenter of the primary tumor. Further, in a SWOG study,[14] partial responders to initial chemotherapy were randomized to either a prechemotherapy or postchemotherapy radiation treatment volume. No difference in local chest control was observed between these two treatment groups.

In conclusion, larger volumes were no more effective than more conservative volumes. Only residual postchemotherapy thoracic sites need be included in the radiation port with combined-modality treatment.

**Conclusion**

To improve survival, the treatment of small-cell lung cancer depends on effective chemotherapy to control systemic disease and thoracic radiation to reduce local failure. The most effective treatment regimen remains contentious, particularly regarding which agents to use and how to blend the local therapy. A new drug that is active against small-cell lung cancer is paclitaxel (Taxol). In two phase II studies evaluating paclitaxel in previously untreated patients with extensive-stage small-cell lung cancer, the response rates were 34% and 41%.[43,44] Additionally, evidence suggests that paclitaxel acts as a radiation sensitizer.[45,46] Preliminary results suggest that adding paclitaxel to the PE regimen and radiation may significantly enhance therapeutic effect.[47,48] The Radiation Therapy Oncology Group has initiated a phase II study of paclitaxel, etoposide, and cisplatin combined with twice-daily thoracic radiotherapy for patients with limited-stage small-cell lung cancer. Thoracic radiotherapy is initiated on day 1 to a total of 45 Gy in 30 fractions twice-daily.
The ECOG has also activated a study using these three drugs with concurrent thoracic radiotherapy, which is given during chemotherapy cycles 3 and 4. The total radiation dose is 63 Gy in 35 daily fractions.

All patients in excellent overall health should be treated aggressively with both radiation and chemotherapy. The current standard therapy for limited-stage small-cell lung cancer is twice-daily radiation fractions of 1.8 Gy to a total dose of 45 Gy concurrently with PE or etoposide/carboplatin chemotherapy.

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