



Gary Ernest Smith. *Sorting Old Bales*. Oil on canvas, 18" × 24". Courtesy of Raymond E. Johnson's Overland Gallery of Fine Art, Scottsdale, Arizona.

The current management of limited-disease small-cell lung cancer is reviewed, and strategies to improve local control are discussed.

New Approaches for Small-Cell Lung Cancer: Local Treatments

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Background: Limited-disease small-cell lung cancer (LD-SCLC) can be cured with combinations of systemic chemotherapy and local treatments, predominantly radiation therapy. While systemic control inside the brain has been further improved with the inclusion of prophylactic cranial irradiation, long-term local control remains suboptimal, even with newer chemoradiation protocols.

Methods: The authors review the current management of LD-SCLC and discuss strategies to improve local control. They present their own experience with the inclusion of surgery in an aggressive combined-modality protocol for patients with LD-SCLC.

Results: Different approaches to improve local efficacy of treatment have been explored, including concurrent chemoradiation, administration of radiation as early as possible, newer fractionation schemas, and escalation of overall radiation doses. However, even following the currently most active chemoradiation protocols, local and locoregional relapse of LD-SCLC remains a problem. Surgery is feasible within this clinical setting and may add to long-term local control and possible cures.

Conclusions: Further investigation into the inclusion of surgery in LD-SCLC within carefully designed prospective clinical trials seems justified, although final evaluation would necessarily include prospective, randomized testing within a more "modernized" study design compared to the "old" and "historical" randomized Lung Cancer Study Group trial.

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Introduction

Lung cancer represents the leading cause of cancer-related deaths in industrialized countries.¹ While the majority of patients present with non-small-cell lung cancer (NSCLC) histopathologies, currently less than 20% are diagnosed with the small-cell carcinoma subtype.^{2,3} Although the relative number of cases with this subtype seems to be decreasing further, this represents approximately 18% of 171,900 new cases of lung cancer per year in the United States and thus is an important clinical problem.^{2,3}

Since the 1980s, systemic combination chemotherapy has emerged as the cornerstone of treatment for this disease, resulting in a significant improvement in overall survival prognosis.⁴ In patients with more advanced disease, called extensive-disease small-cell lung cancer, cure is rarely achieved. However, when cisplatin is included in the chemotherapy treatment protocols, median survival durations of between 7 and 11 months are reported, with only small improvements noted in the results from large clinical trials in recent years.⁴ Disease confined to the chest, called limited-disease small-cell lung cancer (LD-SCLC), can be cured by chemotherapy alone, achieving median survival durations of between 10 and 14 months.^{4,5} However, when optimizing systemic control (outside the brain) with the inclusion of combination chemotherapy, local treatment becomes crucial.

During the 1990s it became clear that radiation therapy for the primary tumor as well as the mediastinum improved local control and thus led to a significant long-term survival benefit for patients with SCLC.^{6,7} The 5-year survival rate increased from approximately 8% with chemotherapy alone to 15% with the addition of radiotherapy, as proven in a large meta-analysis of prospective randomized trials available at that time.⁷ Consequently, since then, different combinations of chemotherapy and radiotherapy have evolved as a standard of care for patients with LD-SCLC. Further promising developments of these combined modality protocols have found their way into the clinics and are reviewed later in this article. However, even with the most active current treatment approaches currently available, systemic failure inside the brain has developed into a major clinical problem.⁸ The cumulative relapse rate approaches between 30% and 40% at 5 years, especially in patients with prolonged survival duration achieved after initial combined modality treatment.⁹ These results have triggered a number of prospectively randomized investigations of prophylactic cranial irradiation (PCI) in this clinical setting, predominantly targeting patients in complete remission after initial therapy.^{8,9} When individual patient data from these randomized trials were combined in a meta-analysis, it was established that PCI adds

approximately 5% at 3 years to the long-term cure rates of these patients.⁹ Following these improvements in systemic control outside the brain, based on the systemic chemotherapy, as well as inside the brain, following administration of PCI, both local and locoregional control remain the major obstacles. Even the most active concurrent chemoradiation protocols for LD-SCLC, including those with intensified radiation fractionation schemas, still present with local and locoregional relapse rates of between 35% and 50%.¹⁰ Consequently, this has stimulated a renewed interest in strategies to further improve the local control for this disease that once was thought to be primarily systemic in nature. Keeping this in mind, we discuss in this article ways to increase local control for this lung cancer subtype.

Concurrent Chemoradiation Protocols

Experience involving other solid tumors showed that the efficacy of radiotherapy for local control was further improved by a simultaneous application of various chemotherapeutic agents with unique radiosensitizing properties. This identification of chemoradiation potentiation was also clinically established in the treatment of lung cancer. Thus, numerous trials with a concurrent application of chemotherapy and radiotherapy in lung cancer have been conducted.¹¹ A large, multicenter phase II trial by the Southwest Oncology Group in North America tested this strategy in the management of LD-SCLC.¹² When comparing the survival results of this trial with the historical data of the same group using a sequential application of chemotherapy and radiotherapy, the concurrent approach appeared to be superior.¹² However, this benefit for concurrent chemoradiation was seen only with chemotherapy regimens (eg, platinum and etoposide) that were given in full doses simultaneously with radiotherapy. Other regimens such as CAV (cyclophosphamide, doxorubicin [Adriamycin], and vincristine) produced survival results that were less promising when comparing concurrent approaches with radiotherapy, probably due to the need for treatment breaks and dose modification for these chemotherapy protocols.^{13,14} Within this clinical setting, the principal effect of concurrent application of chemotherapy and radiotherapy appeared to increase the local efficacy of radiation therapy, probably by adding further to local control. Therefore, it was concluded that the further benefit in survival outcome would predominantly be attributed to this increase in local control.

Accelerated Fractionation of Radiation

A further means to intensify the local efficacy of radiation was to escalate to a higher dosage in the radi-

ation application schema. Twice-daily fractionation as well as an increase in the daily dose of radiation — thus shortening the overall duration of the radiation course — was studied in different trials in patients with LD-SCLC. This so-called hyperfractionated and accelerated radiotherapy was typically given in 2 daily fractions. From a logistical perspective, this schedule is more convenient than the more-intensive CHART (continuous, hyperfractionated, accelerated radiotherapy) regimen consisting of 3 daily fractions at 6-hour intervals. The CHART regimen was introduced for patients with locally advanced NSCLC (LAD-NSCLC).¹⁵ A major pilot trial with this accelerated fractionation strategy was carried out in North America and showed promising clinical response rates and preliminary survival results.¹⁶ The twice-daily application was consequently investigated in a large Intergroup trial based on these pilot data. In this large, multicenter, randomized trial,¹⁰ the experimental arm included concurrent chemoradiation with platinum and etoposide concurrently given with 45 Gy of radiotherapy administered twice daily in 1.5-Gy fractions in the first 3 weeks. This regimen was compared to a more conventionally fractionated radiotherapy in the standard treatment arm, consisting of 45 Gy administered in 1.8-Gy fractions given once daily over 5 weeks. The long-term survival results of this large randomized phase III trial confirm the early experience of the pilot trial with improvement in long-term survival results with the twice-daily application vs the single fractionation comparative arm. The 5-year survival rate in the hyperfractionated, accelerated treatment arm was 26%, which is superior to the 16% 5-year survival rate in the once-daily radiotherapy arm ($P=.04$). Intrathoracic failure was 36% in the twice-daily arm and 52% in the once-daily arm ($P=.06$). Thus, the intensification of the local treatment in this study — radiation — directly translated into a substantial benefit for local control as well as survival of patients with LD-SCLC.

A second randomized trial by the North Central Cancer Treatment Group (NCCTG) did not repeat these promising results of the Intergroup trial. The split course in the radiation application may have negatively affected the overall outcome in this investigation and remains the major criticism toward this study.¹⁷ Furthermore, the design of the NCCTG trial differs strongly from that of the Intergroup trial in that the overall treatment time of radiation was not significantly shortened in the twice-daily arm.

Timing of Radiotherapy: Early vs Late

The timing of radiotherapy has been studied in several prospective randomized trials. While the Cancer and Leukemia Group B (CALGB) trial reported benefit

with a later, more conventional application of radiotherapy in combination with chemotherapy, the NCI-Canada Trial identified a substantial benefit for early vs late radiation therapy in the treatment of LD-SCLC.^{13,14,18} This tendency was recently confirmed by the Japan Clinical Oncology Group Study 9104.¹⁹ Early concurrent application vs late sequential application demonstrated a benefit in the long-term survival results, although this did not reach statistical significance. However, this trial did not directly compare early concurrent chemoradiation to late concurrent chemoradiation, which would have provided a more definite answer to the question of timing of radiation. Again, as with other protocols that include radiation therapy, this benefit was based mainly on a further increase in local control for this disease.^{20,21} Of note is the fact that the application of radiation in the Intergroup trial with twice-daily fractionated radiation therapy also included an early application of radiotherapy.¹⁰ The 5-year survival rate reported in that trial (26% in the superior twice-daily arm) is the highest of the large prospective, randomized multicenter investigations that have been performed in LD-SCLC. However, when reviewing the published data analysis, even in this most favorable treatment arm, the “clinical” local and locoregional relapse rate was 36%. This figure may underestimate the “real (pathological) local relapse rate,” as a postmortem examination in patients dying of distant failures (eg, brain) is no longer routinely performed. Also, this does not reflect the true cumulative

Table 1. — Major Studies of Surgery Followed by Adjuvant Chemotherapy in Limited-Disease Small-Cell Lung Cancer

Investigator	No. of Patients	Chemotherapy	5-Year Survival Stage	(%)
Hayata ²⁸ (1978)	72	NA	I	26
			II	17
			III	0
Osterlind ²⁹ (1986)	36	CAV	I	22 *
Karrer ³⁰ (1990, 1991)	157	CAV	I	61 **
			II	35 **
			III	35 **
Shepherd ³¹ (1988)	63	CAV	I	48
			II	24
			III	24
Hara ³² (1991)	37	NA	I	64
			II	42
			III	10.7
Wada ³³ (1995)	17	Various	I/II	80
			III	10
Suzuki ³⁴ (2000)	62	PE	I	64
			II	50
			IIIA	17

CAV = cyclophosphamide, doxorubicin (Adriamycin), vincristine

PE = cisplatin, etoposide NA = not available

* 3.5-year survival. ** 4-year survival.

Modified and updated from Shepherd.²⁷

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Table 2. — Selected Major Studies of Induction Chemotherapy Followed by Surgery in Limited-Disease Small-Cell Lung Cancer

Investigator	No. of Patients	Chemotherapy	Complete Resection (%)	Pathological Complete Response (%)	Survival (%)
Prager ³⁵ (1984)	39	CAVE	8 (21)	5	2-yr: 50
Johnson ³⁶ (1987)	24	CAV ± PE	15 (62)	37	5-yr: NA
Baker ³⁷ (1987)	37	CAE	20 (54)	5	3-yr: 65
Shepherd ³⁸ (1989)	72	CAV ± PE	33 (36)	10 *	5-yr: 36 *
Hara ³² (1991)	17	Various	17 (100)	NA	5-yr: 33

CAVE = cyclophosphamide, doxorubicin, vincristine, etoposide
 CAV ± PE = cyclophosphamide, doxorubicin, vincristine ± cisplatin, etoposide
 CAE = cyclophosphamide, doxorubicin, etoposide
 * of all 33 resected patients.
 Modified and updated from Shepherd.²⁷
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local/locoregional relapse rate. Within this context, it must be noted that a randomized trial reported by the Hellenic Group did not show a difference between concurrent and delayed concurrent chemoradiation.²² However, the number of patients in this randomized phase II trial is small (42 vs 39 patients), and therefore the statistical power of this result is not comparable to the large phase III North American trial.

Dose Escalation of Radiotherapy

So far, trials that included early concurrent chemoradiation for LD-SCLC limited the radiation doses to 45 Gy twice-daily radiotherapy to the primary tumor as well as the mediastinal nodes.^{10,16} With the new 3-dimensional conformal treatment planning techniques available, increasing the radiation doses is now possible. A recently reported phase I trial by the CALGB tested this concept of increased radiation dose, although this trial did not require 3-dimensional treatment planning and did not include twice-daily radiotherapy.²³ With conformal radiation application, doses of up to 70 Gy have been shown to be feasible in LAD-NSCLC and theoretically, even a further dose escalation seems possible. As trials for radiotherapy dose escalation in LAD-NSCLC are currently being performed, further investigation regarding dose escalation in LD-SCLC seems warranted.²⁴ Mature data are also being awaited on the inclusion of newer drugs with more active radiosensitizing properties (eg, the topoisomerase-I inhibitors and the taxanes) into combined modality protocols for SCLC, although preliminary results do not appear promising.^{25,26}

Surgery in the Treatment of SCLC

Based on the historical experience, surgery has been utilized only in early-stage disease. Most of the surgical cases during the 1980s and early 1990s included patients

with small pulmonary nodules, and the postoperative histopathology revealed an SCLC subtype.²⁷ The majority of these reports included adjuvant postoperative chemotherapy for these highly selected cases.^{28,33} Other investigations have studied surgery followed by adjuvant chemotherapy, but most of the published data sets were generated in the era of standard CAV chemotherapy (Table 1). To date, only one trial has studied the platinum and etoposide regimen in this setting.³⁴

Another treatment strategy involves a preoperative chemotherapy application followed by definitive surgery for local control.³⁵⁻³⁹ Table 2 shows selected major clinical investigations that have been performed. The majority of trials occurred in the 1980s and did not include a platinum-based chemotherapy regimen. Patients with more locally advanced SCLC (stages IIIA or IIIB) typically did not show promising outcomes in these clinical trials. In particular, long-term survival results of combinations of chemotherapy and surgery

Table 3. — Criticism and Comments Regarding the Lung Cancer Study Group Trial

<ul style="list-style-type: none"> • Data were never published as a full paper with mature long-term follow-up. • Chemotherapy regimen was not based on cisplatin. • Surgery was included late in the course of treatment. • No concurrent chemoradiation was included. • Trial included late timing of radiation after the fifth chemotherapy cycle. • Cross-over between both randomization arms was significant. • Trial statistics were not aimed at detecting small differences between both arms (5%-10%). • Trial was performed at the end of the 1980s when less valid staging methods were available. • This was the only randomized trial testing surgery in SCLC. <p>Data from Shepherd.²⁷</p>

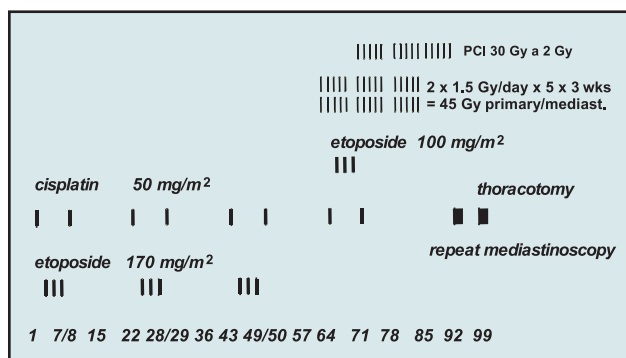


Fig 1. — Trimodality protocol for patients with proven mediastinal involvement (IIB, IIIA).

were not convincing for these subsets. Consequently, the results of the only randomized clinical trial that has been performed with this treatment strategy by the Lung Cancer Study Group testing the value of surgery for node-positive disease did not substantiate a significant benefit for surgery in this setting.³⁹ However, comments and criticism on the design and setting of this trial should be noted (Table 3).²⁷ The trial has not been published as a full paper or with a mature long-term survival analysis. More significantly, the trial was not based on a modern platinum-based chemotherapy regimen. Furthermore, surgery was included relatively late, and radiotherapy was also utilized late in the course of study treatment. No concurrent chemoradiotherapy was used at that time. Analysis of the data on induction chemotherapy alone followed by surgery indicates that patients with mediastinal disease always experienced inferior long-term results.⁴⁰

In 1990, with modern concurrent chemoradiation protocols available, our group decided to include such an approach early into the course of such a combined-modality protocol. Also, after gaining more experience with surgery after a bimodality induction treatment in LAD-NSCLC patients, it seemed appropriate to test an aggressive trimodality protocol in LD-SCLC patients. Our main goal with this inclusion of surgery in such an approach was to further increase the local control at the primary tumor site. We believed radiation therapy would not be as effective in bulky disease areas compared to the smaller mediastinal disease areas resembling tumor-positive mediastinal lymph nodes.

Surgery in a Combined-Modality Protocol

In 1991 we started to include surgery for further improvement of local control into a prognostically orientated multimodality treatment protocol at the West German Cancer Center in Essen. The preliminary results of this experience have already been published

in detail.⁴¹ While surgery was added directly after induction chemotherapy in 8 patients with earlier disease stages (IB, IIA), a group of 22 patients had already initially presented with either centrally located tumors or mediastinoscopically proven involvement of the mediastinum (stage IIB; n = 4) or predominantly to the mediastinal nodes (stage IIIA; n = 18). Following our experience with an aggressive trimodality program in LAD-NSCLC patients, we attempted to further optimize local and locoregional control in this group of patients with proven mediastinal involvement by sequentially adding a preoperative concurrent chemoradiotherapy based on hyperfractionated, accelerated radiotherapy to preoperative chemotherapy.⁴² Thus, in this prognostically unfavorable group with mediastinal disease, the induction protocol combined both the most active concurrent application of chemotherapy and radiotherapy with a twice-daily fractionation of radiotherapy (Fig 1). Patients with up to stage IIIA disease were then planned for an inclusion of thoracotomy, if possible, thus adding to a trimodality treatment design for this group (stage IIB/IIIA). Forty-six patients were included in this trial from 1991 to 1995. Patient selection for this study was typically based on eligibility criteria (other than histopathology and clinical stage) and a workup similar to the trimodality protocol in LAD-NSCLC (Table 4). Thirty-two patients of this group were primarily planned for an inclusion of surgery (stages IB to IIIA, and 2 selected patients with IIB). Overall, 24 patients (75%) were surgically treated, and in 23 of these (72%), tumor was completely resected at final thoracotomy.

We have updated the long-term survival outcome data of both the whole group of 46 patients and of those with proven mediastinal involvement (stage IIB/IIIA; n = 22 patients). With a median follow-up of

Table 4. — Patient Characteristics

	No. of Patients	%
Stage:		
IB/IIA	8	17
IIB (centrally located)	4	9
IIIA	18	39
IIIB	16	35
Sex:	32 M	70
	14 F	30
Age (yrs):		
Median	55	
Range	34-69	
Performance status:		
Median	0	
0	35	76
1	11	24

Modified from Eberhardt et al.⁴¹

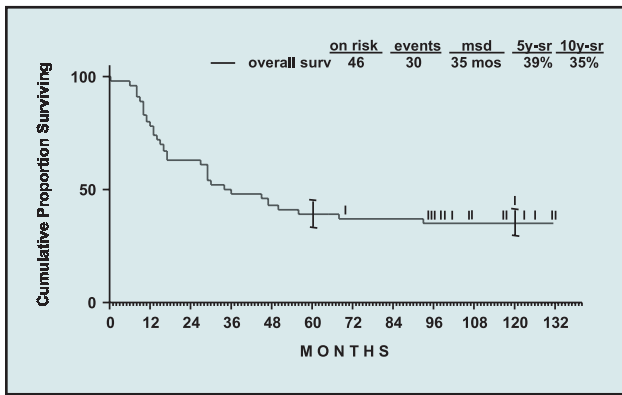


Fig 2. — Overall survival duration of all included patients (stages I-IIIb): long-term results.

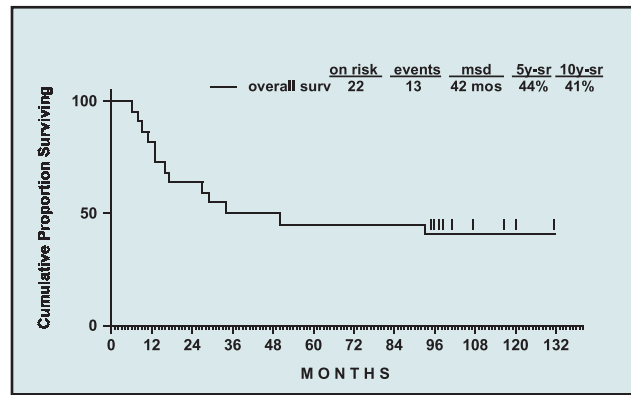


Fig 3. — Overall survival duration of patients with trimodality therapy (stages IIB, IIIA): long-term results.

the patients still alive at 107 months as of the writing of this report (January 2003), the actuarial 5- and 10-year survival rates are 39% and 35%, respectively, for the whole group of patients in this trial (Fig 2). The 22 patients who had initial disease involvement to the mediastinum (central T3 N2 disease) now have 5- and 10-year actuarial survival rates of 44% and 41%, respectively (Fig 3). It should be noted that local and locoregional tumor control was 100% in the group in whom a complete resection was achieved at surgery, even remaining stable in the long-term follow-up currently available. Of those patients who underwent surgery after chemotherapy and concurrent chemoradiation, a typical distribution of approximately half of the patients presented with a pathological complete response and half demonstrated remaining vital disease at the primary tumor site in the resected specimen. Interestingly, this exactly parallels the distribution of pathological response within our trimodality program in LAD-NSCLC (stages IIIA and IIIB).⁴² Most of the patients taken to surgery in our SCLC pilot also received PCI, either after surgery (few patients) or at the time of preoperative chemoradiation (the majority of patients). Surgery proved feasible and safe even after aggressive chemotherapy followed by concurrent accelerated chemoradiation. No perioperative or postoperative deaths were observed in this small patient group, which is in contrast to our in parallel reported experience with LAD-NSCLC.⁴² In addition, the overall toxicity profile of our trimodality approach in LD-SCLC resembled that of our LAD-NSCLC experience. An analysis of the long-term follow-up shows that within this whole patient group, all comorbidity and relapse events occurring beyond 4 years were associated with second malignancies (eg, 1 prostate cancer), with other organs of risk (eg, esophagus, trachea, bladder), or with the remaining contralateral lung (middle lobe, second lung primary). Another group of events resulted from the comorbidity profiles of the patients, such as myocardial infarction or respiratory insufficiency due to acute pneumonia.

We conclude from our experience that once systemic control outside the brain (with chemotherapy) or systemic control inside the brain (with PCI) is effectively controlled, local control is of crucial importance to the overall outcome.⁴³ By adding surgery, even after chemoradiation to the chest, complete local and locoregional control can be achieved; however, at the time of surgery, approximately half of the resected specimen still shows vital residual tumor. During recent years, we have extended the inclusion of surgery after bimodality induction treatment to more locally advanced SCLC stages, including selected stage IIIB patients. Table 5 summarizes the selection of patients with stage IIIB disease in whom we have already successfully performed such an aggressive trimodality approach.

Although patient accrual in these selected stages of LD-SCLC is generally slow due to the decreasing number of patients presenting with SCLC, we have considered moving forward to a randomized phase II trial design as a result of our encouraging phase II long-term survival data (Table 6). Following induction chemotherapy and concurrent chemoradiation, we will randomize patients considered to be operable within the last week of chemoradiation to receive either definitive surgery or a small-volume chemoradiation boost to the primary tumor. Target parameter of this trial will be a comparison of locoregional relapse-free survival at 4 years between the 2 arms, keeping in mind the reduced

Table 5. — Stages of IIIB Small-Cell Lung Cancer Considered for “Trimodality Treatment”

T4	Involvement of:
	- carina
	- 1 vertebral body
	- pulmonary artery
	- right atrium
	- vena cava
	Diffuse involvement of:
	- mediastinal organs
N3	Contralateral mediastinal nodes

Table 6. — Ongoing Randomized Trials Evaluating Surgery in Limited-Disease Small-Cell Lung Cancer

Trial	Chemotherapy	Design
Essen Thoracic Oncology Group randomized phase II trial	cisplatin, etoposide	CT → CT → CT → CT/Hf-RT (45 Gy; twice daily) → Arm A: surgery → Arm B: boost CT/RT (20/26 Gy daily)
West Japan Lung Cancer Study Group randomized trial	cisplatin, etoposide	Arm A: CT → CT → CT → CT/Hf-RT (45 Gy; twice daily) + surgery (trimodality arm) Arm B: CT × 2/Hf-RT (45 Gy; twice daily) → CT → CT (bimodality arm)
German multicenter randomized trial	paclitaxel, etoposide, carboplatin	Arm A: CT → CT → CT → CT → CT → surgery ± RT (50 Gy; once daily) Arm B: CT → CT → CT → CT → CT → RT (50 Gy; once daily)

CT = chemotherapy
Hf-RT = hyperfractionated accelerated radiation therapy

number of patients currently presenting with SCLC at our institute and the difficulties of extending this into a large multicenter phase III trial. The West Japan Lung Cancer Group is also performing a prospective randomized evaluation of trimodality treatment in LD-SCLC. This group has recently started a randomized comparison of concurrent chemoradiation vs trimodality, including surgery in patients with mainly stage IIIA (M. Fukuoka, MD, and H. Tada, MD, unpublished data, 2002). However, this trial has two differences between the randomization arms — the inclusion or exclusion of surgery and the timing of radiotherapy — that will complicate its final analysis. Another multicenter randomized trial in Germany is evaluating surgery in a more conservative trial design with delayed sequential radiotherapy that does not include any complex chemoradiation protocol and therefore may not be the optimal choice of comparison, given the recent superior results obtained with concurrent chemoradiation in LD-SCLC (M. Thomas, MD, and B. Passlick, MD, unpublished data, 2002).

Conclusions

In recent years, we have seen small but definitive progress in the combined modality treatment of LD-SCLC.⁴⁴ These curative treatment approaches must consider the different concurrent risks for this well-defined patient population. Following aggressive systemic approaches with platinum-based chemotherapy and a reduction in the rate of brain relapse with the inclusion of PCI, local control becomes of major importance. While the standard of care for these patients currently consists of concurrent chemoradiation protocols with a significant increase in the long-term survival rates, further improvements of radiation therapy techniques in this setting have been reported, such as the hyperfractionated, accelerated (twice daily) radiotherapy.

Planned radiation doses that are higher and more conformally planned have already been investigated, but

further testing is needed. Surgery remains the treatment of choice for achieving local control at the primary tumor site. While prospective data on the inclusion of surgery into the combined modality treatment of SCLC are limited, carefully planned investigations with surgically/mediastinoscopically staged patients and inclusion of selected patients groups with stage IIIB disease should be encouraged. Comparable to LAD-NSCLC, “trimodality protocols” currently represent the most complex treatment approach to LD-SCLC. The data generated from prospective, randomized trials studying this strategy may result in a comparable impact as that of the Intergroup 0139 trial in LAD-NSCLC.

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