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Management of Small Cell Lung Cancer*

ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

George R. Simon, MD, FCCP; and Andrew Turrisi, MD

Purpose: **This guideline is for the management of patients with small cell lung cancer (SCLC) and is based on currently available information. As part of the guideline, an evidence-based review of the literature was commissioned that enables the reader to assess the evidence as we have attempted to put the clinical implications into perspective.**

Methods: **We conducted a comprehensive review of the available literature and the previous American College of Chest Physicians guidelines of SCLC. Controversial and less understood areas of the management of SCLC were then subject to an exhaustive review of the literature and detail analyses. Experts in evidence-based analyses compiled the accompanying systematic review titled "Evidence for Management of SCLC." The evidence was then assessed by a panel of experts to incorporate "clinical relevance." The resultant guidelines were then scored according to the grading system outlined by the American College of Chest Physicians grading system task force.**

Results: **SCLC accounts for 13 to 20% of all lung cancers. Highly smoking related and initially responsive to treatment, it leads to death rapidly in 2 to 4 months without treatment. SCLC is staged as limited-stage and extensive-stage disease. Limited-stage disease is treated with curative intent with chemotherapy and radiation therapy, with approximately 20% of patients achieving a cure. For all patients with limited-stage disease, median survival is 16 to 22 months. Extensive-stage disease is primarily treated with chemotherapy with a high initial response rate of 60 to 70% but with a median survival of 10 months. All patients achieving a complete remission should be offered prophylactic cranial irradiation. Relapsed or refractory SCLC has a uniformly poor prognosis.**

Conclusion: **In this section, evidence-based guidelines for the staging and treatment of SCLC are outlined. Limited-stage SCLC is treated with curative intent. Extensive-stage SCLC has high initial responses to chemotherapy but with an ultimately dismal prognosis with few survivors beyond 2 years.** ***(CHEST 2007; 132:324S–339S)***

Key words: chemotherapy; guideline; radiation therapy; review; small cell lung cancer; staging

Abbreviations: BSC = best supportive care; CAV = cyclophosphamide, adriamycin, vincristine; CEV = cyclophosphamide, etoposide and vincristine; CI = confidence interval; CPT-11 = camptothecin-11; CR = complete response; ECOG = Eastern Cooperative Oncology Group; EP = cisplatin and etoposide; NSCLC = non-small cell lung cancer; PCI = prophylactic cranial radiation; PE = etoposide/cisplatin; PET = positron emission tomography; PS = performance status; SCLC = small cell lung cancer; TC = oral topotecan/IV cisplatin; TRTx = thoracic radiation therapy

This document presents an evidence-based guideline based on the current literature on the staging and optimal treatment of patients with small cell lung cancer (SCLC). The quality of the recommendation and the evidence on which it is based is graded as outlined by the American College of Chest Physicians grading system task force.[1] Accompanying this guide-

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line is an evidence report titled "Evidence for Management of SCLC." Nine key questions were addressed by the technical report and are the following (see chapter "SCLC Evidence").

Key Questions

1. What are the relative benefits or harms of combining thoracic radiotherapy (TRTx) with chemotherapy in alternating, concurrent, or sequential fashion?

2. Does early vs late administration of TRTx influence outcome?

3. Does the duration of administration of TRTx affect survival or toxicity?

4. In responding patients with extensive disease, does the administration of consolidative TRTx affect outcome?

5. What is the role of prophylactic cranial irradiation (PCI) in the treatment of SCLC?

6. Is there a role for positron emission tomography (PET) scanning in SCLC staging?

7. Do the pathologic subtypes of SCLC influence treatment outcome?

8. What is the role of surgery in the management of patients with SCLC, and how are patients selected for surgery?

9. What is the role and what are the relative benefits of second-line/salvage therapy?

Clinical research has slowed in this disease, and there are few contemporary studies that directly address many of these questions. Evidence-based guidelines rely on timely, contemporary, pertinent evidence that is largely lacking in many of these areas. Decreased disease frequency and difficulty in conducting large trials are oft-cited reasons for this lack of activity. With the exception of question 7 regarding pathology subtypes, all of these questions posed to the systematic review are discussed in the context of these guidelines.

Materials and Methods

We organized a systematic review of the published SCLC literature to update the previous American College of Chest Physicians guideline. Supplemental material appropriate to this topic was obtained by literature search of a computerized database (MEDLINE) and review of the Thoracic Oncology NetWork reference lists of relevant articles. Recommendations were developed by the writing committee, graded by a standardized method (see "Methodology for Lung Cancer Evidence Review and Guideline Development" chapter) and reviewed by all members of the lung cancer panel before approval by the Thoracic Oncology Network, Health and Science Policy Committee, and the Board of Regents of the American College of Chest Physicians.

Accompanying this guideline is an "Evidence for Management of SCLC' chapter, comprehensive research of some of the most controversial but not infrequently encountered questions in SCLC. In relevant sections of this guideline, the reader will be referred to this evidence report (see "SCLC Evidence" chapter).

Guideline

SCLC constitutes approximately 13 to 20% of all lung cancers[2]; therefore, the estimated annual incidence of SCLC ranges from 22,000 to 34,000. If there are 170,000 annual lung cancer cases, this suggests approximately 22,000 cases at a minimum. With non-small cell lung cancer (NSCLC), SCLC shares a strong association with tobacco use, and without treatment it tends to lead an aggressive course.

Staging of SCLC

SCLC is staged according to a two-stage system developed by the Veteran's Administration Lung Cancer study group as limited disease or extensive disease. Patients with limited disease have involvement restricted to the ipsilateral hemithorax that can be encompassed within a safe radiation treatment plan. Extensive disease is defined as the presence of overt metastatic disease by imaging or physical examination. Patients with otherwise limited-stage disease with the presence of contralateral hilar or supraclavicular nodes or malignant pleural or pericardial effusions are excluded from clinical trials for limited-stage SCLC.

Complete evaluation of a patient with newly diagnosed SCLC consists of a history and physical examination, pathology confirmation or review, CT of the chest and abdomen to include the whole liver and adrenal glands, bone scan, and a CT with contrast or MRI examination of the brain. While the prevalence of brain metastases at diagnosis varies, the brain is a common site of treatment failure; therefore, evaluation of the brain prior to treatment remains mandatory. Scanning the asymptomatic brain is likely to lead to the diagnosis of more previously unsuspected brain metastases, but there is no evidence yet that it improves survival.[3] However, because it has a direct impact on the correct staging of the disease and consequently on developing a treatment plan, it is the opinion of the authors of this guideline that brain imaging should be performed for all patients currently undergoing staging for SCLC. Additionally, CBCs, electrolytes, BUN, creatinine, and liver function tests should be performed in all patients at baseline. The utility of PET in SCLC has been reported in several small prospective studies.[2,4–10] These studies are small, with varying reference stan-

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dards and with uncertainty about the execution and interpretation of the results. Even though the cumulative evidence suggests that PET added to conventional staging improves the sensitivity in detecting extracranial disease, the frequency of changes in stage attributable to PET are still unknown and is plagued by wide confidence intervals (CIs) in the estimates of diagnostic and staging accuracy. Randomized prospective studies need to be conducted before the routine use of PET scan for staging SCLC can be recommended. Therefore, outside of a clinical trial, the routine use of PET in SCLC cannot be recommended. (Please refer to question 6 of the evidence report. (See "Evidence for Management of Small Cell Lung Cancer" chapter)

The routine use of bone marrow aspiration has been abandoned because it was rare to have disease detected in the bone marrow in the absence of obvious bony disease in the bone scan. In one study,[11] of 403 patients with SCLC, only 7 patients (1.7%) had extensive disease based on marrow involvement alone. Because bone marrow examination rarely changes the stage of cancer in noninvasively assessed patients, and because all patients with SCLC receive chemotherapy as part of their overall treatment strategy, routine use of this procedure is not recommend in the staging of SCLC. Other investigators[12,13] have also reached similar conclusions. Therefore, bone marrow examination, formerly standard, is rarely indicated and has been abandoned as a routine procedure for the staging of SCLC.

Recommendations

1. Routine staging of SCLC includes history and physical examination, CBCs and comprehensive chemistry panel, CT of the chest and abdomen or CT of the chest with cuts going through the entire liver and adrenal glands, CT or MRI of the brain, and bone scan. Grade of recommendation, 1B

2. PET is not recommended in the routine staging of SCLC. Grade of recommendation, 2B

Treatment for Extensive-Stage SCLC

First-Line Treatment

Platinum-based chemotherapy remains the mainstay of treatment for extensive SCLC. In a metaanalysis[14] of randomized trials (19 trials with 4054 evaluable patients) comparing cisplatin-based regimen with a noncisplatin-based regimen, patients randomized to regimens containing cisplatin had significantly increased response and survival rates without an increase in toxicity. Detailed analyses of the role of etoposide and cisplatin in SCLC have been performed by Berghmans et al[15] and reported in abstract form in September 1999. Thirty-six eligible trials[15] conducted between 1980 and 1998 were classified into four groups: (1) cisplatin vs noncisplatin (n = 1); (2) etoposide (without cisplatin) vs no etoposide (n = 17); (3) cisplatin/etoposide vs no cisplatin/etoposide (n = 9); and (4) cisplatin/etoposide vs etoposide (n = 1). The authors concluded that the use of cisplatin and/or etoposide offered a significant survival advantage in patients with SCLC.

A metaanalysis performed by Chute et al[16] evaluated 21 cooperative group trials performed in North America from 1972 to 1993. Patients with extensive-stage SCLC treated during a similar time interval listed in the Surveillance, Epidemiology, and End Results database were also examined. Trends were tested in the number of trials and the survival time of patients over time. In this analysis, a 2-month prolongation in median survival was demonstrated in extensive-stage SCLC. This improvement in survival was independently associated with both cisplatin-based therapy and in the improvement of best supportive care (BSC) and general medical management. This metaanalysis further strengthens the evidence in favor of cisplatin-based chemotherapy for the first-line treatment of extensive stage SCLC.

The issue of carboplatin vs cisplatin was reviewed by Brahmer et al,[17] who concluded that carboplatin plus etoposide seems to be as effective but less toxic (except for increased myelosuppression) than cisplatin plus etoposide. The Hellenic Oncology Group conducted a randomized phase II trial[18] comparing cisplatin and etoposide with carboplatin and etoposide. In this study, consisting of patients with limited-stage and extensive-stage disease, median survival times were 11.8 months for the cisplatin group and 12.5 months for the carboplatin group. The difference was not statistically significant, although the study did not have enough power to show a survival difference.

A Japanese trial[19] compared cisplatin and irinotecan (camptothecin-11 [CPT-11]) with cisplatin and etoposide. Patients randomized to the cisplatin/CPT-11 arm fared statistically significantly better than the patient cohort randomized to the cisplatin/etoposide arm (median survival, 420 days vs 300 days). Confirmatory trials were then launched in the United States. One of these trials using a different dosing schedule for cisplatin/irinotecan failed to show a survival advantage over cisplatin/etoposide. Fewer patients receiving cisplatin/irinotecan had hematologic toxicities (*ie*, grade 3/4 anemia, thrombocytopenia, neutropenia, and febrile neutropenia) compared with patients receiving cisplatin/etoposide. However, more patients receiving cisplatin/CPT-11 had nonhematologic toxicities in the form of

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Table 1—*SCLC Combination Chemotherapy for Untreated Patients, Phase II Trials*

Treatment	Patients, No.	Responders, No.			Response Rate		Median Survival			Comments	Reference
		CR	Partial	Total	%	95% CI	Mo	1 yr, %	2 yr, %		
Cisplatin + etoposide + carboplatin	46	10	32	42	91	79–98	18, stage IIIB; 14, stage IV	22	15	Age ≤ 72 yr	21
Cisplatin + etoposide + paclitaxel	38	6	28	34	90	75–97	12		10		22
Cisplatin + etoposide + paclitaxel	23	5	14	19	83	61–95	11	46	14		23
Cisplatin + irinotecan	35	10	20	30	86	70–95	13	21.7			24
Cisplatin + vinblastine + mitomycin-C	30	1	21	22	73	66–96	6				25
Cisplatin + etoposide + all-trans-retinoic acid	22	1	9	10	45	24–68	11	41		13 patients discontinued retinoic acid prematurely because of toxicity	26
Cisplatin + paclitaxel + granulocyte colony-stimulating factor	34	3	20	23	61	53–8	8			Abstract	27
Topotecan + paclitaxel	28	6	11	17	60	41–79	14			Abstract	28
Etoposide + irinotecan	50			33	66	51–79	12			Abstract	29
Paclitaxel + carboplatin	69	5	37	42	61	48–72	12			Abstract	30
Paclitaxel + irinotecan	11	4	1	5	45	17–77				Abstract	31
Paclitaxel + doxorubicin	16	1	3	4	25	7–52				Abstract	32
Cisplatin + docetaxel	20	0	11	11	55	32–77				Abstract	33
Topotecan + paclitaxel	13			8	69	39–91	14			Abstract	34
Topotecan + paclitaxel	15	10	5	15	100	78–100				Abstract	35
Cisplatin + paclitaxel + topotecan	18	3	10	13	72	47–90					36
Etoposide + paclitaxel + epirubicin	12	6	6	12	100	74–100					37

grade 3/4 diarrhea and vomiting.[20] Several phase II trials with irinotecan, topotecan, paclitaxel, in combination with either cisplatin or etoposide, have been reported. These have been summarized in Table 1.[21–37]

An open-label, randomized, multicenter phase III study[38] compared oral topotecan/IV cisplatin (TC) with IV etoposide/cisplatin (PE) in patients with untreated extensive-disease SCLC. A total of 784 patients were randomly assigned to either oral topotecan at 1.7 mg/m^2/d for 5 days with IV cisplatin at 60 mg/m^2 on day 5 (n = 389), or IV etoposide at 100 mg/ m^2/d for 3 days with IV cisplatin at 80 mg/ m^2 on day 1 (n = 395) every 21 days. Overall survival rate (primary end point) was similar between groups. One-year survival rate was 31% (95% CI, 27 to 36%) in both groups. Response rates were similar between groups (TC vs PE, 63% vs 69%). Time to progression was slightly but statistically longer with PE (log rank p = 0.02; median TC vs median PE, 24 weeks vs 25 weeks). The regimens were similarly tolerable. Grade 3/4 neutropenia occurred more frequently with PE (84% vs 59%), whereas grade 3/4 anemia and thrombocytopenia occurred more frequently with TC (38% vs 21% and 38 vs 23%, respectively). Lung Cancer Symptom Scale scores were statistically better with PE, but the differences were small and of debatable clinical significance. Even though the TC arm may have a more convenient schedule, there was no demonstrable improvement in several of the key survival, toxicity, or quality of life parameters when compared to PE.[38]

Pemetrexed/platinum combinations have been investigated in extensive-stage SCLC. A randomized phase II trial[39] evaluated the use of cisplatin or carboplatin plus pemetrexed in previously untreated patients. Patients were randomly assigned to receive pemetrexed at 500 mg/m^2 plus cisplatin at 75 mg/m^2 or carboplatin (area under the concentration curve of 5). Treatment was administered once every 21 days for a maximum of six cycles. Seventy-eight patients were enrolled into this multicenter trial. Median survival time for cisplatin/pemetrexed was 7.6 months, with a 1-year survivorship of 33.4% and a response rate of 35% (95% CI, 20.6 to 51.7%). Median survival time for carboplatin/pemetrexed was 10.4 months, with a 1-year survivorship of 39.0% and a response rate of 39.5% (95% CI, 24.0 to 56.6%). Median time to progression for cisplatin/pemetrexed was 4.9 months and for carboplatin/pemetrexed was 4.5 months. Grade 3/4 hematologic toxicities included neutropenia (15.8% vs 20.0%) and

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thrombocytopenia (13.2% vs 22.9%) in the cisplatin/pemetrexed and carboplatin/pemetrexed treatment groups, respectively. Pemetrexed/platinum doublets had activity and appeared to be well tolerated in first-line extensive-stage SCLC. This randomized phase II trial suggests that pemetrexed/platinum combinations may be comparable in efficacy in extensive-stage SCLC to the more traditional cisplatin-etoposide or cisplatin-irinotecan regimens.[39]

The issue of adding a third drug to cisplatin and etoposide has been investigated. The Hoosier Oncology Group[40] evaluated the addition of ifosfamide to cisplatin and etoposide in a phase III trial of 171 extensive-disease patients. At the expense of increased toxicity, 2-year survival increased from 5 to 13% with addition of ifosfamide. Mavroudis et al[41] compared paclitaxel, etoposide, and platinum with etoposide and platinum. The study was terminated early secondary to higher number of toxic deaths in the paclitaxel, etoposide, and platinum arm. Despite a statistically significant improvement in the time to progression for paclitaxel, etoposide, and platinum, there was no difference in overall survival.

The issue of adding TRTx to chemotherapy in the treatment of extensive-stage SCLC has also been evaluated. This has been discussed in the accompanying evidence report and technological assessment and to which the reader is referred to for a more detailed analysis. One randomized controlled trial[42] (n = 99) suggests that adding concurrent TRTx improves survival of patients with extensive-stage disease that responds to an initial three cycles of platinum/etoposide chemotherapy with a complete response (CR) outside the thorax and at least a partial response in the thorax. Uncontrolled data from the same trial[42] suggest little to no benefit for other patients. Grades 3/4 esophagitis was more common with TRTx.

In summary, for extensive-stage SCLC, a combination of cisplatin combined with either etoposide or CPT-11 or carboplatin combined with etoposide are currently considered standard regimens. The standard treatment arm for a comparative prospective study remains cisplatin (60 to 80 mg/m^2), and etoposide delivered in three to five divided doses between 250 and 360 mg/m^2. There is no evidence to support continuing treatment beyond six cycles. It is reasonable to administer consolidative TRTx in patients achieving a CR outside the chest and at least a CR or partial response in the chest, although the evidence for this is weak. This issue needs to be further addressed in phase III randomized trials.

Recommendations

3. Patients with extensive-stage disease should receive four to not more than six cycles of cisplatin or carboplatin-based combination chemotherapy. Cisplatin could be combined with either etoposide or CPT-11. Grade of recommendation, 1B

4. After chemotherapy, patients achieving a CR outside the chest and complete or partial response in the chest can be offered consolidative TRTx in the chest. Grade of recommendation, 2C

Maintenance Treatment

The topic of maintenance therapy in SCLC has been extensively reviewed in the European Journal of Cancer in 1998.[43] Several randomized trials have demonstrated that 4 to 6 months of treatment is equal to prolonged treatment when survival is considered as the end point. In the metaanalyses reported by Sculier et al,[43] 13 published randomized trials were included. One showed a statistically significant difference in survival in favor of maintenance, five studies showed survival advantage in subgroups of patients, one study showed significantly shorter survival with maintenance therapy, and six studies showed no difference. The Eastern Cooperative Oncology Group (ECOG) conducted a phase III trial in which patients showing response or stable disease after four cycles of cisplatin and etoposide were randomized to observation alone or four cycles of topotecan.[44] Despite an improvement in progression-free survival, the addition of topotecan did not improve overall survival results.

Treatments other than chemotherapy for maintenance were also tested in randomized clinical trials. A phase III randomized trial[45] evaluated the efficacy of anti-GD3 immunization as maintenance treatment. There was no benefit in overall survival. Metalloproteinase inhibitors and inhibitors of angiogenesis including thalidomide are currently being investigated in the maintenance setting.

Recommendation

5. Outside of a clinical trial, maintenance treatment for patients with extensive-stage or limited-stage disease achieving a partial or complete remission is not recommended. Grade of recommendation, 1B

Treatment of Relapsed or Refractory SCLC (Systematic Review Question 9)

Despite high initial response rates to chemotherapy (45 to 75% CRs) reported in limited disease and

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20 to 30% CRs in extensive disease, response duration is usually short, with a median progression-free survival of approximately 4 months for extensive-stage disease. Most patients are destined to relapse, and the prognosis for this group of patients who relapse is poor. Patients who relapse < 3 months after first-line therapy are commonly called *refractory*, and patients who relapse 3 months after therapy are labeled as *sensitive*.

In a randomized multicenter study, von Pawel et al[46] compared cyclophosphamide, adriamycin, and vincristine (CAV) with topotecan as a single agent in patients who had relapse at least 60 days after completion of initial therapy. Patients received either topotecan as a 30-min/d infusion for 5 days every 21 days, or CAV infused on day 1 every 21 days. A total of 211 patients were enrolled. The response rates were 24.3% in patients treated with topotecan and 18.3% in patients treated with CAV ($p = 0.285$). Median times to progression were 13.3 weeks for the topotecan arm and 12.3 weeks for the CAV arm. Median survival times were 25 weeks for topotecan and 24.7 weeks for CAV. The proportion of patients with symptom improvement was greater in the topotecan arm than in the CAV group for four of the eight symptoms evaluated. The authors[46] concluded that topotecan was at least as effective as CAV in the treatment of patients with recurrent SCLC and resulted in improved symptom control. However, toxicity rates were high in both arms and alternative dose schedules of topotecan are currently favored.

Another study[47] randomly assigned patients with relapsed SCLC not considered as candidates for standard IV therapy to BSC alone (n = 70) or oral topotecan (2.3 mg/m/d, days 1 through 5, every 21 days) plus BSC (topotecan; n = 71). In an intent-to-treat analysis, survival (primary end point) was prolonged in the topotecan group (log rank $p = 0.0104$). Median survival time with BSC was 13.9 weeks (95% CI, 11.1 to 18.6), and with topotecan it was 25.9 weeks (95% CI, 18.3 to 31.6). Partial responses were seen in 7% of patients receiving topotecan, with an additional 44% of patients achieving stable disease. Patients receiving topotecan had slower quality of life deterioration and greater symptom control. Principal toxicities with topotecan were hematologic: grade 4 neutropenia, 33%; grade 4 thrombocytopenia, 7%; and grade 3/4 anemia, 25%. Toxic deaths occurred in four patients (6%) in the topotecan arm. All-cause mortality rates within 30 days of random assignment were 13% with BSC and 7% with topotecan. Hence, in patients unable to tolerate IV chemotherapy, treatment with oral topotecan is an option.[47] Several reported phase II trials in relapsed/refractory SCLC are summarized in Table 2.[31,48–51]

In the chapter "Evidence for Management of SCLC," nine randomized trials comparing various second-line chemotherapy regimens are discussed. Two randomized trials compared chemotherapy to BSC. It is wise to be cautioned about the potential for toxicity outweighing survival in many trials. Patients who achieve CRs to front-line therapy and then experience relapse appear to benefit most from second-line therapy.

Recommendation

6. Patients who experience relapse or have refractory disease with SCLC should be offered further chemotherapy. Grade of recommendation, 1B

Treatment of Elderly (or Poor Performance Status) Patients With SCLC

Performance status (PS) and the physiologic status of the patient should guide treatment decision rather than the patient's chronologic age. It is clear that elderly patients with good PS (ECOG 0 or 1) and normal organ function should be treated with optimal chemotherapy (and radiotherapy if indicated) as in their younger counterparts. Simi-

Table 2—*SCLC Combination Chemotherapy for Refractory or Relapsed Disease in Patients, Phase II Trials*

Treatment	Patients, No.	Responders, No.			Relative Risk		Median Survival		Comments	Reference
		CR	Partial	Total	%	95% CI	Mo	1 yr (%)		
Etoposide + irinotecan	24	3	14	17	71	53–89	9			48
Cisplatin + topotecan	28	1	7	8	29	13–49			Abstract; all patients had responded to previous chemotherapy	49
Etoposide + hexmethylmelamine	30	1	5	6	22	8–39	5	21	Abstract	50
Irinotecan + paclitaxel	11	1	4	5	45	17–77			Abstract	31
Carboplatin + paclitaxel	18	0	3	3	17	4–41			Abstract	51

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lar outcomes for elderly patients (in comparison to their younger counterparts) with limited-stage SCLC have been shown in the Intergroup trial 0096 in which cisplatin, etoposide, and thoracic radiotherapy was administered once per day or twice daily.[52] The National Cancer Institute of Canada performed a retrospective review of their BR3 and BR6 trials and also concluded that age did not appear to impact the delivery, tolerance, or efficacy of thoracic irradiation in the combined modality management of limited-stage SCLC.[53] Greater myelosuppression is to be expected because equivalent exposure to drug will lead to more myelosuppression in the elderly. This has been shown to be the case with etoposide.[54] Greater ancillary support therefore will be required in the elderly. However, despite treatment delays, elderly patients with good PS derive the same level of benefit relative to younger patients.

Elderly patients with poor PS or with compromised organ function may be offered single-agent chemotherapy or polychemotherapy in attenuated doses. However, several randomized studies[55,56] have indicated that such "gentler" chemotherapy is inferior to optimal combination chemotherapy. Options available to these patients include oral etoposide for 14 days combined with carboplatin on day 1 every 28 days[57]; abbreviated chemotherapy with CAV in full doses followed up 3 weeks later by cisplatin and etoposide in optimal doses[58]; or chemotherapy with platinum, adriamycin, vincristine, and etoposide, with all four drugs in reduced doses.[59] A phase III trial[60] compared carboplatin/gemcitabine with cisplatin/etoposide in patients with poor-prognosis SCLC, with carboplatin and gemcitabine exhibiting a more favorable overall toxicity profile at the expense of increased myelotoxicity but with equivalent efficacy. Another phase III trial[61] compared single-agent carboplatin with CAV, with carboplatin producing response rates, relief of tumor-related symptoms, and survival similar to that seen with CAV. There was a lower risk of life-threatening sepsis and less need for hospitalization in the group that received carboplatin.

Recommendations

7. Elderly patients with good PS (ECOG PS 0 or 1) with intact organ function should be treated with platinum-based chemotherapy. Grade of recommendation, 1A

8. Elderly patients with poor prognostic factors such as poor PS or medically significant concomitant comorbid disease may still be considered for chemotherapy. Grade of recommendation, 2C

Studies with SCLC cell lines have shown that they have greater radiosensitivity than human adenocarcinomas or squamous cell lung cancer cell lines. Because of these observations, many early trials of combining radiation with chemotherapy in SCLC used lower total radiation doses. It has become increasingly clear that higher doses than those of the old regimens of 30 Gy in 10 fractions or 45 Gy in 25 fractions are needed to provide durable local control because lower doses are associated with local relapse rates in excess of 50%.

A number of trials conducted in the 1970s and 1980s compared chemotherapy alone to chemotherapy plus TRTx in patients with limited SCLC. There were differences in radiation dose, timing, and choice of chemotherapeutic agents, but most were performed with alkylating agent and doxorubicin-based therapy rather than cisplatin and etoposide. The analysis by Warde and Payne[62] showed improved local control and survival with the addition of TRTx, particularly in patients $\leq$ 60 years old. Pignon et al[63] obtained individual patient data from these trials and was able to update analyses from the time of original publication. They found that the addition of TRTx resulted in an increase in 3-year survival from 8.9 to 14.3%, an absolute improvement of 5%, and a relative improvement of nearly 50%. With the publication of these two metaanalyses, the debate shifted from whether to use TRTx to how best to integrate it with chemotherapy.

In limited disease, the ability to use concurrent therapy is predicated on avoiding drugs with intrathoracic organ toxicity that compound with radiotherapy. The optimal chemotherapy to utilize with radiation therapy has been a subject of investigation as well. A prospective randomized trial[64] comparing cisplatin and etoposide (PE) to cyclophosphamide, etoposide and vincristine (CEV) was reported by Sundstrom et al. A total of 436 eligible patients were randomized to chemotherapy with PE (n = 218) or CEV (n = 218). Patients were stratified according to extent of disease (limited disease, n = 214; extensive disease, n = 222). The PE group received five courses of etoposide at 100 mg/m^2 IV and cisplatin at 75 mg/m^2 IV on day 1, followed up by oral etoposide 200 mg/m^2/d on days 2 to 4. The CEV group received five courses of epirubicin at 50 mg/m^2, cyclophosphamide at 1,000 mg/m^2, and vincristine at 2 mg, all IV, on day 1. In addition, patients with limited disease received TRTx concurrent with chemotherapy cycle 3, and those achieving CR during the treatment period received PCI. The 2-year and

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5-year survival rates in the PE arm (14% and 5%; p = 0.0004) were significantly higher compared with those in the CEV arm (6% and 2%). Among patients with limited disease, median survival time was 14.5 months vs 9.7 months in the PE and CEV arms, respectively (p = 0.001). The 2-year and 5-year survival rates of 25% and 10% in the PE arm compared with 8% and 3% in the CEV arm (p = 0.0001). Quality-of-life assessments revealed no major differences between the randomized groups. The authors concluded that PE is superior to CEV in patients with limited-disease SCLC. Therefore, PE is the recommended chemotherapy regimen to combine with TRTx in the treatment of limited-stage SCLC.

Sequencing and Timing of Radiation and Chemotherapy

Whether to administer radiation and chemotherapy concurrently, sequentially, or in an alternating fashion, and whether radiation should be administered early or late in the overall course of treatment continue to be a matter of debate. In many trials, these issues have been confounded by a lack of clarity in the clinical trial design and the resulting ambiguous interpretation of results. "Alternating therapy," interdigitating weeks of radiotherapy with weeks of chemotherapy in lower doses of each, is a tacit acknowledgment of the fact that certain chemotherapy-radiotherapy combinations were quite toxic. This term is a quaint reference to trials in the late 1980s and has no currency or application in the cisplatin/etoposide era.

Murray et al[65] performed a metaanalysis of trials that combined chemotherapy and TRTx, using progression-free survival at 3 years as a surrogate end point for long-term survival, and favored the earlier initiation of concurrent TRTx with chemotherapy. If initiation of radiation was delayed beyond 5 weeks of initiation of chemotherapy, the benefit decreased and survival approached that seen with chemotherapy alone. However, this analysis did not separate issues of timing from those of concurrency.

There have been at least nine randomized trials that have addressed the issue of the timing of radiation in limited SCLC (Table 2 in the evidence report and technical assessment; see chapter "SCLC Evidence"). There are major differences in trial design, choice of chemotherapeutic agents, and radiation dose and fractionation schedules.

De Ruysscher et al[66] undertook a systematic review and literature-based metaanalysis to determine whether the timing of chest radiotherapy may influence the survival of patients with limited-stage SCLC. Eligible randomized controlled clinical trials were identified according to the Cochrane Collaboration Guidelines, comparing different timing of chest radiotherapy. Early chest irradiation was defined as beginning within 30 days after the start of chemotherapy. Considering all seven eligible trials, the overall survival at 2 years or 5 years was not significantly different between early or late chest radiotherapy. When only trials were considered that used platinum chemotherapy concurrent with chest radiotherapy, a significantly higher 5-year survival was observed when chest radiotherapy was started within 30 days after the start of chemotherapy (2-year survival: odds ratio, 0.73; 95% CI, 0.51 to 1.03; p = 0.07; 5-year survival: OR, 0.64; 95% CI, 0.44 to 0.92; p = 0.02). This was even more pronounced when the overall treatment time of chest radiotherapy was < 30 days. These data seem to indicate that 5-year survival rates of patients with limited-stage SCLC are in favor of early chest radiotherapy, with a significant difference if the overall treatment time of chest radiation is < 30 days and if a platinum-based chemotherapy is used concurrently.

In another report, Spiro et al[67] examined the effect on survival of the timing of TRTx in patients with limited-disease SCLC. Patients received three cycles of cyclophosphamide, doxorubicin, and vincristine, alternating with three cycles of EP. Three hundred twenty-five chemotherapy- and radiotherapy-naive patients were randomly assigned to either early TRTx administered concurrently in the second cycle or late TRTx administered concurrently with the sixth cycle. The dose was 40 Gy in 15 fractions over 3 weeks. TRTx was received by 92% and 82% of patients in the early and late arms, respectively (p = 0.01). Sixty-nine percent of patients in the early arm received all six courses of chemotherapy, compared with 80% in the late arm (p = 0.003). There was no evidence of a survival difference; median overall survival times were 13.7 months and 15.1 months in the early and late arms, respectively (p = 0.23). This study suggests that it may be essential to ensure optimal delivery of platinum-based chemotherapy with early TRTx to see a survival advantage.

The reader is again referred to the accompanying evidence report and technical assessment for an exhaustive review and analyses of the literature. Several reasonable conclusions emerge from these data.

1. Trials that used alkylating agents and doxorubicin-based chemotherapy showed little effect of radiation timing and sequencing. They also reported significant difficulty delivering planned treatment (both chemotherapy and radiation) when radiation was administered given concur-

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rently with or alternating between cycles of chemotherapy. Long-term survival in most of these trials was in the range of 10%, which is minimally different from that seen with chemotherapy alone.

2. When platinum/etoposide regimens are used, concurrent TRTx is superior to sequential TRTx.
3. When EP and concurrent TRTx are used, the data are inconclusive concerning early vs late treatment. Table 2 in the evidence chapter deals with the issue (see chapter "SCLC Evidence"). Inadequate underpowered trials make a categoric recommendation inappropriate; however, the existing data suggest that there may be a survival advantage for early initiation of TRTx with cisplatin-based chemotherapy.

Radiation Dose

Please see question 3 of the evidence report and technical assessment for a detailed analysis of the literature on this issue. No trial has asked a direct question to establish optimal dose in any schedule, and relatively few trials have addressed the issue of optimizing TRTx dose at all. Retrospective analysis[68] of patients treated at the Massachusetts General Hospital report improved local control as radiation dose has increased from 30 to 70 Gy delivered with one daily fraction. The Cancer and Leukemia Group-B[69] has tried to define the maximal tolerated dose for concurrent TRTx and cisplatin/etoposide chemotherapy when these were administered after three courses of induction chemotherapy with cyclophosphamide/cisplatin/etoposide. They examined both daily radiation therapy schedules with 2-Gy fractions and twice-daily schedules with 1.5-Gy fractions. They defined dose-limiting toxicity as acute esophagitis, and the maximum tolerated dose was reported to be 45 Gy in 3 weeks for twice-daily fractionation and 70 Gy in 7 weeks for daily fractionation. Because all grades of esophagitis recover and stricture formation is rare, using esophagitis as a dose-limiting toxicity seems inappropriate. Because the best local control rates certainly may not be optimal, exploration of dose escalation seems warranted. Studies in NSCLC have clearly shown the feasibility of administering higher radiation doses to conformal planned fields with concurrent chemotherapy, and this approach may also be necessary in limited-stage SCLC. Though success of using doses in the range of 60 to 70 Gy has never been established as safer or better by any measure, there has been a tendency to use higher doses in the single-fractionation schedule.

Radiation Fractionation

Fractionation refers to the dose per treatment, number of treatments per day, and overall time of treatment. Ordinarily one expects to deliver 10 Gy/wk. Using more than one treatment per day is commonly called *hyperfractionation*. Delivering more than the anticipated 10 Gy/wk in standard daily fractions is called *accelerated fractionation*. Cancer cell kill and tumor control, as well as acute and late radiation effects, change with method of treatment delivery. Protracting total time of treatment may provide an ability to tolerate larger doses, but the excess time may be detrimental to tumor control. Shortening time may add to acute toxicity but may be more efficient at killing rapidly proliferating tumor cells before resistance develops or they metastasize.

The rapid growth rate of SCLC both *in vitro* and *in vivo* and the radiobiologically small shoulder on the *in vitro* survival curve seen on many SCLC cell lines encouraged the exploration of treatment acceleration by administering two fractions per day with a modest reduction in fraction size from the usual 1.8 to 2.0 Gy to 1.5 Gy. Two prospective trials have compared this approach to conventional daily fractionation. The North American Intergroup Trial 0096[70] compared 45 Gy in 25 fractions over 5 weeks to the investigational arm of 45 Gy in 30 fractions over 3 weeks. Chemotherapy consisted of four cycles of PE. The accelerated regimen resulted in improved local control (intrathoracic failure reported in 36% on the accelerated arm and 52% on the standard arm) and long-term survival, which was 26% for the twice-daily regimen and 16% for the standard regimen. There was an increased rate of grade 3 esophagitis (26% vs 11%) but no other significant differences in toxicity.[70] Unfortunately, intrathoracic failure included "not achieving a CR." The partial response patients survived identically to the completely responding ones in the accelerated fractionated group, but as expected poorly in the 45-Gy single-fraction group. We lack local controlled data for the mostly phase II trials using doses > 50 Gy. For the commonly used 60 to 70 Gy doses, we have only reliable safety data. Reliable local control or patterns of failure data are lacking with the higher dose studies.

The North Central Cancer Treatment Group also compared a twice-daily fractionation to daily fractionation, but with a significantly different twice-daily scheme and overall study design[71] than that used in the Intergroup trial reported by Turrisi et al.[72] In both arms, radiation was administered concurrent with the fourth and fifth cycles of chemotherapy. The once-daily radiation regimen was 50.4 Gy in 28 fractions over 5 weeks. The twice-daily arm used 48 Gy, with a 2.5-

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week split after the initial 24 Gy, and the total treatment time was > 5 weeks. Thus, unlike the Intergroup trial,[70] there was no overall acceleration of the radiation delivery. In this trial, there were no differences in local control or survival between the two arms. The trial did not replicate the accelerated treatment outcome, and it mildly ameliorated toxicity.

Radiation Target Volume

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

1. Radiation to normal-appearing lymph nodes has become an important issue for toxicity and local control. This issue has not been studied prospectively. However, the North American Intergroup trial,[72] which produced the best 5-year survival reported by a cooperative group, limited elective radiation, with no intentional radiation to the contralateral hilum or to supraclavicular nodes unless there was bulky superior mediastinal adenopathy.
2. Regarding radiation therapy after induction chemotherapy, retrospective review of data from the Mayo Clinic[71] and North Central Cancer Treatment Group[73] suggests that this can be performed without compromise in local control or survival because recurrences tended to be at the center of the tumor rather than at the periphery.[74] An earlier trial by the Southwest Oncology Group[75] that randomized patients having partial responses to chemotherapy to radiation to before or after chemotherapy volumes also reported no difference in recurrence rates.

In summary, the standard therapy "control treatment" for future randomized studies of limited SCLC remains four cycles of PE concurrently combined with day-1, cycle-1 45 Gy delivered in 3 weeks (in twice-daily fraction, as administered in the Intergroup trial[70]). Induction chemotherapy commonly used is not evidence based in the PE treatment era and protracts "start to end of radiotherapy." When induction therapy is used to reduce radiotherapy target size, the postchemotherapy residual may be used as a reasonable target without evidence that this compromises local control or survival. The use of protracted once-daily radiation scheduled to 60 to 70 Gy has established safety from phase I and II trials, but there is no evidence outside of these clinical trials that these schedules are superior to 45 Gy delivered in 3 weeks in an accelerated hyperfractionated manner.[70]

Recommendations

10. Patients with limited-stage SCLC should be treated with combined concurrent chemoradiotherapy. Patients require referral to a radiation oncologist and a medical oncologist for the consideration of combined modality treatment. Grade of recommendation, 1A

11. If the PS and comorbid illnesses allow, patients with limited-stage disease should be treated with chemotherapy and radiation therapy concurrently. Grade of recommendation, 1C

12. In patients eligible to receive early concurrent chemoradiotherapy, patients should be treated with accelerated hyperfractionated radiation therapy concurrently with platinum-based chemotherapy. Grade of recommendation, 1B

PCI

Brain metastases are common in SCLC. In patients who achieve a CR to induction therapy, CNS metastases will emerge over the next 2 years in approximately 50 to 60% of patients; and in 20 to 30% of patients, the brain will be the only apparent site of disease.[76] Overt metastatic disease in the brain, while often responding temporarily to radiation or chemotherapy, is rarely if ever cured. The hypothesis that lower doses of radiation administered to patients without detectable CNS involvement might eradicate occult metastatic disease has been entertained for > 20 years,[77] but data have emerged to allow a reasonable consensus that the PCI can reduce the risk of CNS failure, improve survival, and do so without excessive toxicity.[78–80] A metaanalysis of randomized trials of PCI in patients with CR (predominately with limited disease) concluded that it significantly reduced CNS failure by approximately 50% and produced a modest (approximately 5%) but significant improvement in median survival. There was a trend to better results with higher doses (30 to 36 Gy using 2-Gy fractions) than with 20 Gy, but this was not protected by randomization. An Intergroup trial is currently comparing 25 Gy in 10 fractions to 36 Gy in 18 fractions.

Earlier trials of PCI had variably reported late neurotoxicity, with deterioration in memory, ability to calculate, and quality of life. The relation of these toxicities to treatment was unclear. In several trials in which cognitive function has been assessed prospectively, significant differences between SCLC patients and age- and gender-matched control subjects have been observed before any treatment, with up to 40% of patients showing significant impairment.[81] Significant further deterioration after PCI was not seen in a large trial[82] in the United Kingdom. Van

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Oosterhout et al[83] performed careful neurologic and neurophysiologic examinations of 59 survivors who are alive > 2 years after diagnosis and who underwent cranial CT or MRI. Groups were neurophysiologically compared with matched control subjects. The authors[83] concluded that although more intensively treated patients showed more neurologic impairment, there was no statistical evidence for additional neurotoxicity caused by the administration of PCI.

In summary, the evidence report and technological assessment was most solid for the robust evidence in favor of PCI for patients achieving a CR to therapy. There was no group singled out (*ie*, elderly, continued smokers) that did not benefit. PCI for documented patients with CR is standard therapy. The dose and schedule remain less clear. In practice, 25 Gy in 10 fractions has been a cooperative group standard that currently is being compared to higher or accelerated doses of 36 Gy. Late neurocognitive effects are reported in the population and are not different in those who have survived 2 years, regardless of whether they have been treated with PCI. The frequency of neurocognitive defects at 2 years is < 10%, and it is approximately 7% for those receiving PCI and 5% for those observed. Neurocognitive defects are much more likely in patients relapsing with brain metastasis, and salvage therapeutic radiation is less effective at restoring symptoms, PS, and quality of life.

Recommendations

13. Patients with limited-stage SCLC achieving a CR or resected patients with stage I disease should be offered PCI. Grade of recommendation, 1B

14. Patients with extensive-stage SCLC achieving a CR should be offered PCI. Grade of recommendation, 1C

Role of Surgery in Early Stage SCLC

The role of surgery in early stage SCLC has been reviewed.[84] Surgery as a primary modality of treatment was abandoned after the British Medical Council published the results of their study[85] comparing primary radiation therapy with surgery in patients with resectable SCLC with a 10-year follow-up. The overall survival was better for the radiation therapy-alone arm, and there were no long-term survivors in the surgery arm. However, subsequent reports published in the 1970s and early 1980s showed long-term survival in patients treated with surgery alone in very early disease. The most favorable subset of patients had T1N0 tumors identified either at the time of surgery or at the time of postoperative pathology examination.[86–89] Even though the role of adjuvant therapy has not been evaluated in prospective randomized trials, there are several reports[88,90–96] suggesting benefit for adjuvant chemotherapy even in the earliest stages of the disease.

The role of surgery in patients with node-positive disease was evaluated prospectively by the Lung Cancer Study Group.[97] Patients with stage I were excluded from this trial. Patients were initially treated with five cycles of CAV. Responding patients were randomized to undergo surgery or no surgery. All patients received radiation therapy to the chest and brain. There was no difference in survival between the arms. For all patients, median survival time was 15 months, and 2-year survival rate was 20%.

All patients who are to undergo surgery require mediastinoscopy before resection. Its usefulness in SCLC has been validated in a small prospective Japanese trial.[98] The evidence review and technological evidence researching this issue in question 8 found two randomized controlled studies and eight nonrandomized comparative observational studies. There was inadequate objective evidence to support any categorical recommendation regarding surgery in these patients. However, the authors favor surgery in patients with node-negative disease with small tumor size (< 3 cm) because of the lower likelihood of metastasis with small tumor sizes.

Recommendations

15. In patients with SCLC and stage I disease who are being considered for curative-intent surgical resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI, abdominal CT plus bone scan) performed in all patients should be offered. Grade of recommendation, 1A

16. In patients with stage I SCLC who have undergone curative intent surgical resection, platinum-based adjuvant chemotherapy is recommended. Grade of recommendation, 2C

Management of Tumors With Mixed SCLC/NSCLC Histology

The evidence report and technological assessment researched this issue and found few studies of any design that included patients with mixed histology. No conclusions can be drawn from the evidence available in the literature. Before a biopsy result is labeled as a mixed histology, it is imperative to obtain

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a detailed pathologic consultation. Large-cell tumors with neuroendocrine features are now classified as NSCLC and should be treated as such.

If, however, after a detailed pathologic review it is clear that the patient has mixed SCLC/NSCLC, then it is the bias of the authors of this article that the natural history of such a mixed-histology disease would be defined by the natural history of the more rapidly growing small cell component. Hence, we treat these patients like patients with SCLC. Again, as noted, evidence for this is scant. Implicit in this statement is the fact that most chemotherapeutic regimens and combined chemotherapy and radiation therapy strategies used for the treatment of SCLC should work effectively for NSCLC as well. PE and TRTx is commonly used for NSCLC,[99] albeit in a different schedule. The most commonly used treatment regimen for patients with stage IV NSCLC had been cisplatin or carboplatin and etoposide, and is a reasonable, though some would argue, not optimal chemotherapy for NSCLC.[100]

Recommendation

17. Patients with mixed SCLC/NSCLC histology should be treated like patients with SCLC. All the treatment recommendations made for SCLC should apply to this category of patients. Grade of recommendation, 2C

Summary of Recommendations

1. Routine staging of SCLC includes history and physical examination, CBCs and comprehensive chemistry panel, CT of the chest and abdomen or CT of the chest with cuts going through the entire liver and adrenal glands, CT or MRI of the brain, and bone scan. Grade of recommendation, 1B

2. PET is not recommended in the routine staging of SCLC. Grade of recommendation, 2B

3. Patients with extensive-stage disease should receive four to not more than six cycles of cisplatin or carboplatin-based combination chemotherapy. Cisplatin could be combined with either etoposide or CPT-11. Grade of recommendation, 1B

4. After chemotherapy, patients achieving a CR outside the chest and complete or partial response in the chest could be offered consolidative TRTx in the chest. Grade of recommendation, 2C

5. Outside of a clinical trial, maintenance treatment for patients with extensive-stage or limited-stage disease achieving a partial remission or CR is not recommended. Grade of recommendation, 1B

6. Patients with SCLC with relapsed or refractory disease should be offered further chemotherapy. Grade of recommendation, 1B

7. Elderly patients with good PS (ECOG PS 0 or 1) with intact organ function should be treated with platinum-based chemotherapy. Grade of recommendation, 1A

8. Elderly patients with poor prognostic factors such as poor PS or medically significant concomitant comorbid disease may still be considered for chemotherapy. Grade of recommendation, 2C

9. Outside of a clinical trial, there is no role of either dose dense/intense initial/induction or maintenance treatment for extensive-stage or limited-stage SCLC. Grade of recommendation, 1A

10. Patients with limited-stage SCLC should be treated with combined concurrent chemoradiotherapy. Patients require referral to a radiation oncologist and a medical oncologist for the consideration of combined modality treatment. Grade of recommendation, 1A

11. If the PS and comorbid illnesses allow, patients with limited-stage disease should be treated with chemotherapy and radiation therapy administered concurrently. Grade of recommendation, 1C

12. In patients eligible to receive early concurrent chemoradiotherapy, patients should be treated with accelerated hyperfractionated radiation therapy concurrently with platinum-based chemotherapy. Grade of recommendation, 1B

13. Patients with limited-stage SCLC achieving a complete remission or patients with stage I disease who have had resection should be offered PCI. Grade of recommendation, 1B

14. Patients with extensive-stage SCLC achieving a complete remission should be offered PCI. Grade of recommendation, 1C

15. In patients with SCLC and stage I disease who are being considered for curative intent surgical resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI, abdominal CT plus bone scan) performed in all patients should be offered. Grade of recommendation, 1A

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16. In patients with stage I SCLC who have undergone curative intent surgical resection, platinum-based adjuvant chemotherapy is recommended. Grade of recommendation, 2C

17. Patients with mixed SCLC/NSCLC histology should be treated like patients with SCLC. All the treatment recommendations made for SCLC should apply to this category of patients. Grade of recommendation, 2C

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