Radiation Therapy for Small-Cell Lung Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin* 2010; 60(5):277-300.	15	N/A	American Cancer Society's compilation of the most recent data regarding cancer incidence, mortality, and survival based on incidence data from the National Cancer Institute, the Centers for Disease Control and Prevention, and the North American Association of Central Cancer Registries and mortality data from the National Center for Health Statistics.	A total of 1,529,560 new cancer cases and 569,490 deaths from cancer are projected to occur in the United States in 2010. Overall cancer incidence rates decreased in the most recent time period in both men (1.3% per year from 2000 to 2006) and women (0.5% per year from 1998 to 2006), largely due to decreases in the 3 major cancer sites in men (lung, prostate, and colon and rectum [colorectum]) and 2 major cancer sites in women (breast and colorectum). Among men, death rates for all races combined decreased by 21.0% between 1990 and 2006, with decreases in lung, prostate, and colorectal cancer rates accounting for nearly 80% of the total decrease. Further progress can be accelerated by applying existing cancer control knowledge across all segments of the population and by supporting new discoveries in cancer prevention, early detection, and treatment.	4
2. Zelen M. Keynote address on biostatistics and data retrieval. *Cancer Chemother Rep 3* 1973; 4(2):31-42.	15	N/A	Summary of workshop on how to gather data to provide recommendations to decrease instances of bronchogenic carcinoma.	N/A	4
3. Einhorn LH, Bond WH, Hornback N, Joe BT. Long-term results in combined-modality treatment of small cell carcinoma of the lung. *Semin Oncol* 1978; 5(3):309-313.	4	58 patients	To evaluate the long-term results in combined-modality treatment of small cell carcinoma of the lung.	There were 27 (48%) partial remissions and 23 (41%) complete remissions, and median survival was 51 weeks. Initial performance status and extent of disease had a definite effect on survival. 5/19 patients (26%) with limited disease remain alive and in complete remission at 26-45+ months. It is becoming clear from this and other recent studies that we can significantly prolong median survival in small cell lung cancer. However, even more important is the fact that limited-extent small cell lung cancer may be a potentially curable disease.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
4. Miller AB, Fox W, Tall R. Five-year follow-up of the Medical Research Council comparative trial of surgery and radiotherapy for the primary treatment of small-celled or oat-celled carcinoma of the bronchus. *Lancet* 1969; 2(7619):501-505.	1	144 patients: 71 allocated to surgery series; 73 to the radical-RT series	Randomized trial to compare surgery and RT for the primary treatment of small-celled or oat-celled carcinoma of the bronchus.	The survival-rates for the 71 patients in the surgery series and the 73 patients in the radical-RT series were 4% and 10% at 24 months, 3% and 7% at 48 months, and 1% and 4% at 60 months, respectively. The one 5-year survivor in the surgery series was a patient too breathless for surgery who was treated by RT. The three 5-year survivors in the RT series had all received radical RT. They remain alive and well with no evidence of recurrence after more than 6 years. The mean survival for the surgery series was 199 days and for the radical-RT series 284 days, a statistically significant difference (P=0.05). It is concluded that in this trial radical RT has given, in terms of survival, a somewhat better result than surgery in the treatment of patients with small-celled or oat-celled carcinoma of the bronchus diagnosed preoperatively on bronchial biopsy and judged to be operable.	1
5. Fox W, Scadding JG. Medical Research Council comparative trial of surgery and radiotherapy for primary treatment of small-celled or oat-celled carcinoma of bronchus. Ten-year follow-up. *Lancet* 1973; 2(7820):63-65.	3a	144 total patients	10 year results of previously randomized trial to compare surgery and RT for the primary treatment of small-celled or oat-celled carcinoma of the bronchus.	There were no 10-year survivors in the surgery series, but in the RT series 3 remained alive and well. The mean survival for the surgery series was 199 days and for the radical-RT series 300 days — a statistically significant difference (P=0·04). This reinforces the conclusion of the 5-year report that in this trial radical-RT has given, in terms of survival, a somewhat better result than surgery in the treatment of patients with small-celled or oat-celled carcinoma of the bronchus diagnosed preoperatively on bronchial biopsy and judged to be operable.	3

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
6. Cohen MH, Ihde DC, Bunn PA, Jr., et al. Cyclic alternating combination chemotherapy for small cell bronchogenic carcinoma. *Cancer Treat Rep* 1979; 63(2):163-170.	1	61 patients	Randomized trial to evaluate cyclic alternating combination chemotherapy for small cell bronchogenic carcinoma.	The addition of VAP increased the CR rate from 42% to 74% in limited-disease patients and from 24% to 36% in extensive-disease patients. Half of the patients were randomized to a third combination of VO-16-213 and ifosfamide. These patients were cycled at 6-week intervals through the three drug regimens while the remaining patients were cycled between cyclophosphamide, methotrexate, and CCNU and VAP. The addition of VP-16-213 and ifosfamide did not increase the CR rate or prolong survival. Only complete responders survived beyond 24 months. Sequential use of non-cross-resistant drug combinations represents one method for increasing the CR rate.	1
7. Gaspar LE, Gay EG, Crawford J, Putnam JB, Herbst RS, Bonner JA. Limited-stage small-cell lung cancer (stages I-III): observations from the National Cancer Data Base. *Clin Lung Cancer* 2005; 6(6):355-360.	3a	22,969 total patients; 4 cohorts	To describe demographic and treatment pattern changes as well as 5-year survival rates across cohorts.	The 5-year survival rates and 95% CI for the 1985, 1990, and 1995 cohorts of all ages of patients treated with chemoradiation therapy are as follows: 10.5% (CI, 6.75%-14.25%), 11.88% (CI, 9.63%-14.13%), and 13.3% (CI, 11.2%-15.4%). Between 1985 and 2000 there was a significant increase in the percentage of women diagnosed with LS-SCLC. The use of combined chemotherapy and RT also increased during this period. This increase in chemoradiation therapy was associated with a decreased use of chemotherapy alone. Despite changes in demographics and treatment during these time intervals, the 5-year survival for patients with LS-SCLC treated with chemoradiation therapy did not increase significantly. These results demonstrate the continued need for the evaluation of new treatments in this group of patients.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
8. Green RA, Humphrey E, Close H, Patno ME. Alkylating agents in bronchogenic carcinoma. *Am J Med* 1969; 46(4):516-525.	1	1,239 total patients; 16 VA hospitals	To evaluate chemotherapeutic agents in the randomized treatment of patients with bronchogenic carcinoma.	Intravenous cyclophosphamide, and possibly nitrogen mustard, had a slight favorable influence upon survival for all patients. A difference between the two agents was seen: patients with squamous cell carcinoma appeared to respond best to nitrogen mustard therapy and patients with small cell undifferentiated carcinoma to cyclophosphamide therapy, in fairly striking fashion. Over-all influences upon survival, however, were not remarkable.	1
9. Weiss RB. Small-cell carcinoma of the lung: therapeutic management. *Ann Intern Med* 1978; 88(4):522-531.	7	N/A	To review the therapeutic management of SCLC.	Although bronchogenic carcinoma generally remains a tumor resistant to treatment, marked progress in the therapy of the small-cell undifferentiated subtype has occurred in the past 5 years. Many aspects of its growth and metastatic spread are such that it is not satisfactorily treated surgically. However, it is sensitive to both radiation and a variety of chemotherapeutic agents. Use of these agents in combination seems to produce a greater antitumor effect than single drugs. The combination of radiation and chemotherapy results in marked tumor regressions. Untreated, this carcinoma has a very short median survival (2 months). Administration of current “aggressive” combination therapy regimens has resulted in median survivals of nearly 1 year with some patients still living 3 years after therapy.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
10. Pignon JP, Arriagada R, Ihde DC, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *N Engl J Med* 1992; 327(23):1618-1624.	7	2,140 total patients from 13 trials	Meta-analysis of randomized trials to evaluate the hypothesis that TRT contributes to a moderate increase in OS in limited SCLC.	Median follow-up period for the surviving patients was 43 months. The RR of death in the combined-therapy group as compared with the chemotherapy group was 0.86 (95% CI, 0.78-0.94; P=0.001), corresponding to a 14% reduction in the mortality rate. The benefit in terms of OS at 3 years (+/- SD) was 5.4 +/- 1.4%. Indirect comparison of early with late RT and of sequential with non-sequential RT did not reveal any optimal time for treatment. There was a trend toward a larger reduction in mortality among younger patients: the RR of death in the combined-therapy as compared with the chemotherapy group ranged from 0.72 for patients <55 years old (95% CI, 0.56-0.93) to 1.07 (0.70-1.64) for patients over 70. TRT moderately improves survival in patients with limited SCLC who are treated with combination chemotherapy. Identification of the optimal combination of chemotherapy and RT will require further trials.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
11. Warde P, Payne D. Does thoracic irradiation improve survival and local control in limited-stage small-cell carcinoma of the lung? A meta-analysis. *J Clin Oncol* 1992; 10(6):890-895.	7 (meta-analysis)	11 randomized trials	To determine whether the addition of TRT to systemic chemotherapy improves 2-year survival, improves local (intrathoracic) tumor control, and affects treatment-related mortality in patients with LS-SCLC.	The overall OR for benefit of TRT on 2-year survival (ie, the odds of surviving 2 years among patients allocated to radiation compared with the odds of surviving 2 years among patients allocated to control) is 1.53 (95% CI, 1.30-1.76; chi 2 = 12.76; P<.001). The risk difference method showed that RT improved 2-year survival by 5.4% (95% CI, 1.1%-9.7%). Local control results were available for only 9 studies, the OR for treatment benefit is 3.02 (95% CI, 2.80-3.24; chi 2 = 101.48; P<.0001), and intrathoracic tumor control was improved by 25.3% (95% CI, 16.5%-34.1%). The OR for excess treatment-related deaths in the thoracic radiation-treated patients was 2.54 (95% CI, 1.90-3.18; chi 2 = 8.24; P<.01). The risk difference for treatment-related deaths was 1.2% (95% CI, –0.6%-3.0%). This meta-analysis shows a small but significant improvement in survival and a major improvement in tumor control in the thorax in patients receiving TRT. However, this is achieved at the cost of a small increase in treatment-related mortality.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
12. Janne PA, Freidlin B, Saxman S, et al. Twenty-five years of clinical research for patients with limited-stage small cell lung carcinoma in North America. *Cancer* 2002; 95(7):1528-1538.	7	6,564 patients; 30 trials	To determine the changes in clinical trials and outcomes of patients with LS-SCLC treated on Phase III randomized trials initiated in North America between 1972 and 1992.	Median of median survival times of all patients treated on the control arms of the Phase III trials initiated between 1972 and 1981 and between 1982 and 1992 were 12.0 months (range, 10-16 months) and 17.0 months (range, 11-20 months), respectively (P<0.001). Of 26 studies available for survival analysis, 5 (19%) showed a statistically significant survival prolongation in the experimental arm compared with the control arm with a median prolongation of 3.4 months (range, 1-5.2 months). All 5 evaluated some aspect of TRT. Over a similar time period, there was a 6.4-month increase in the median survival of LS-SCLC patients listed in the SEER database (P<0.0001) and a more than doubling of the 5-year survival from 5.2% to 12.1% (P=0.0001). Analyses of the patients with LS-SCLC treated on Phase III trials in North America initiated between 1972 and 1992 and those listed in the SEER database show significant improvements in median survivals. Furthermore, the 5-year survival of patients with LS-SCLC listed in the SEER database has more than doubled over the last 25 years. Further research will be needed to determine the relative contribution of improved therapy, supportive care, and stage migration to this prolongation in survival.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
13. Lally BE, Geiger AM, Urbanic JJ, et al. Trends in the outcomes for patients with limited stage small cell lung cancer: An analysis of the Surveillance, Epidemiology, and End Results database. *Lung Cancer* 2009; 64(2):226-231.	3a	6,271 patients	To examine the outcomes of patients with LS-SCLC over time and to determine if any trends were present with respect to the publication of significant clinical trials.	When compared to patients diagnosed in 1983-1987 who did not receive RT, the hazard for mortality was significantly reduced for patients diagnosed in 1988-1992 regardless of whether they received RT (HR=0.59; CI 0.52-0.65; P<0.0001) or not (HR=0.67; CI 0.60-0.75; P<0.0001). Patients who were diagnosed in 1993-1998 and received RT had similarly improved survival (HR=0.53; CI 0.47-0.58; P<0.0001), which was better than patients from the same time era who did not receive RT (HR=0.77; CI 0.69-0.85; P<0.0001). In conclusion, the survival for patients with LS-SCLC has improved over time. Many factors are likely involved, however we believe that part of this improvement was the result of clinical trials which investigated and subsequently defined chemoradiotherapy as the standard of care. In order to continue to improve clinical outcomes, clinical trials investigating new treatment paradigms are needed.	2
14. Langer CJ, Swann S, Werner-Wasik M, et al. Phase I study of irinotecan (Ir) and cisplatin (DDP) in combination with thoracic radiotherapy (RT), either twice daily (45 Gy) or once daily (70 Gy), in patients with limited (Ltd) small cell lung carcinoma (SCLC): Early analysis of RTOG 0241. *ASCO Meeting Abstracts* 2006; 24(18_suppl):7058.	3a	36 patients	To determine if irinotecan can be safely and effectively integrated with concurrent RT and irinotecan in LS-SCLC.	Attributable DLT was not seen in seq A, but was observed in seq B (70 Gy) at 50 mg/m^2 with 1 episode each of Grade 4 diarrhea and esophagitis, necessitating hospitalization. In addition, 1 patient in seq B had non-attributable Grade 4 cardiovascular adverse events. There has been no acute Grade 5 toxicity. 1 patient experienced late Grade 3 pulmonary toxicity, another Grade 3 constitutional toxicity, including weight loss. The overall incidence of Grade 3 esophagitis was 34%. In LS-SCLC, irinotecan at 60 mg/m^2 d 1 and 8 is safe and feasible in combination with cisplatin 60 mg/m^2 q 3 weeks and twice-daily RT (45 Gy). The maximum tolerated dose for irinotecan in combination with RT (70 Gy) and irinotecan 60 mg/m^2 is 40 mg/m^2 d 1 and 8. Response, progression, survival data remain immature.	3

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15. Movsas B, Moughan J, Komaki R, et al. Radiotherapy patterns of care study in lung carcinoma. *J Clin Oncol* 2003; 21(24):4553-4559.	3a	42,335 patient records from 58 institutions	To determine the national patterns of RT practice in patients treated for nonmetastatic lung cancer in 1998 to 1999.	Regarding treatment strategies, for SCLC and CS III NSCLC, chemotherapy plus RT was used significantly more than RT alone (P<.05); in CS I NSCLC, RT alone was the primary treatment (P<.05). Overall, 58% of patients received systemic therapy. On multivariate analysis, factors correlating with increased use of chemotherapy included younger age, histology (SCLC > NSCLC), increasing CS, increasing Karnofsky performance score, and lack of comorbidities. Only 3% of all patients were treated on prospective clinical trials. This study establishes the general patterns of care for lung carcinoma in RT facilities within the United States. As supported by clinical trials, patients with LS-SCLC and CS III NSCLC received chemotherapy plus RT more than they received RT alone. Further improvements in staging, smoking cessation, and increased accrual to clinical trials must be encouraged.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
16. Miller KL, Marks LB, Sibley GS, et al. Routine use of approximately 60 Gy once-daily thoracic irradiation for patients with limited-stage small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2003; 56(2):355-359.	3a	65 total patients: 32 concurrent RT/chemotherapy; 33 sequential chemotherapy and then RT	To review the outcome of patients with LS-SCLC receiving daily TRT to approximately 60 Gy.	The median follow-up for all patients was 16.7 months and for surviving patients was 29.6 months. The median age was 64 years (range 36-83), and the median Karnofsky performance status was 80 (range 50-100). The 3-year actuarial rate of local failure, PFS, and OS was 40%, 25%, and 23%, respectively. One case of acute Grade 3 esophagitis developed. Ten late complications occurred: four pulmonary, two esophageal, two infectious, one leukemia, and one retinal toxicity with PCI. Six were mild and resolved with treatment. Chemotherapy plus approximately 60 Gy of once-daily RT for LS-SCLC was generally well tolerated. The survival rates were less than have been reported using 45 Gy in 1.5-Gy twice-daily fractions (2-year OS rate 47% compared with 30% in this study), but may be comparable because fewer than one-half our patients received concurrent chemotherapy/RT and only 26% received PCI. The relatively low rate of normal tissue morbidity in our patients supports the use of conventional once-daily fractionation to ≥60 Gy. A randomized trial would be required to compare the outcomes after maximally tolerated dose twice-daily RT vs maximally tolerated dose daily RT.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
17. Bogart JA, Herndon JE, 2nd, Lyss AP, et al. 70 Gy thoracic radiotherapy is feasible concurrent with chemotherapy for limited-stage small-cell lung cancer: analysis of Cancer and Leukemia Group B study 39808. *Int J Radiat Oncol Biol Phys* 2004; 59(2):460-468.	4	63 total patients	To prospectively evaluate the feasibility of delivering 70 Gy once-daily TRT, concurrent with chemotherapy, in the treatment LS-SCLC.	90% of patients (57/63) proceeded to protocol TRT. There was one treatment-related fatality. Nonhematologic Grade 3/4 toxicities affecting more than 10% of patients, during or after TRT, were dysphagia (16%/5%) and febrile neutropenia (12%/4%). The response rate to all therapy was 92% and the median OS is 22.4 months (95% CI, 16.1, infinity). 28 patients remain alive with a median follow-up of 24.7 months. 70 Gy once-daily TRT can be delivered safely in the cooperative group setting for patients with LS-SCLC. Initial efficacy data are encouraging. The hypothesis that high-dose once-daily TRT results in comparable or improved survival compared with twice-daily accelerated TRT warrants testing in a phase III trial.	3
18. Miller AA, Wang XF, Bogart JA, et al. Phase II trial of paclitaxel-topotecan-etoposide followed by consolidation chemoradiotherapy for limited-stage small cell lung cancer: CALGB 30002. *J Thorac Oncol* 2007; 2(7):645-651.	4	63 total patients	To evaluate the activity and tolerance of the rationally designed sequence of paclitaxel-topotecan-etoposide, a nonplatinum regimen, as induction therapy for LS-SCLC before combined chemotherapy and RT.	Induction chemotherapy resulted in six (10%) CRs and 35 (56%) PRs. Overall response to chemoradiotherapy included 27 (43%; 95% CI, 30%-56%) CRs and 24 (38%) PRs. Median PFS is 12 months (95% CI, 9-15 months). Median OS is 20 months (95% CI, 16-24 months). Frequent (>20%) Grade 3/4 toxicities during all therapy included neutropenia, febrile neutropenia, anemia, thrombocytopenia, fatigue, and dysphagia. This treatment regimen has significant activity in LS-SCLC but did not meet our prospectively defined criteria for further investigation in this setting. The addition of etoposide and the use of a sequenced administration schedule did not seem to improve overall activity beyond our prior experience with a topotecan-paclitaxel doublet.	2

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19. Roof KS, Fidias P, Lynch TJ, Ancukiewicz M, Choi NC. Radiation dose escalation in limited-stage small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2003; 57(3):701-708.	4	84 patients reviewed	To review the treatment outcomes of LS-SCLC patients treated with ≥50 Gy of radiation at Massachusetts General Hospital between 1987 and 2000 and to assess for evidence of a continuation of a radiation dose response.	54 (64%) met the inclusion criteria; 30 patients (56%) in this study died, and 4 (7%) were lost to follow-up. The median follow-up of the surviving patients was 42 months. The median OS was 29 months. The 2- and 5-year survival rate was 64% and 47%, respectively. The local control rate at 3 years was 78%. The OS, local control, and DFS rates for LS-SCLC patients treated with ≥50 Gy of radiation compare favorably with historical data. These findings suggest a continuation of the radiation dose-response curve in LS-SCLC. This further supports the need for appropriately powered, phase III, prospective randomized trials in radiation dose escalation or radiation dose intensification for LS-SCLC.	4
20. The NCCN Clinical Practice Guidelines in Oncology™ Small Cell Lung Cancer V.1.201 National Comprehensive Cancer Network, Inc. http://www.24hmb.com/UpLoad/Editor/2010/1/4/2010010471447841.pdf.	15	N/A	Practice Guidelines for Small Cell Lung Cancer.	N/A	4
21. Turrisi AT, 3rd, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med* 1999; 340(4):265-271.	1	417 patients	Randomized trial to compare twice-daily with once-daily TRT in limited SCLC treated concurrently with EP.	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 survival rates for patients receiving once-daily RT were 41% at 2 years and 16% at 5 years. For patients receiving twice-daily RT, the survival rates were 47% at 2 years and 26% at 5 years. Grade 3 esophagitis was significantly more frequent with twice-daily TRT, occurring in 27% of patients, as compared with 11% in the once-daily group (P<0.001). 4 cycles of cisplatin plus etoposide and a course of RT (45 Gy, given either once or twice daily) beginning with cycle 1 of the chemotherapy resulted in overall 2- and 5-year survival rates of 44% and 23%, a considerable improvement in survival rates over previous results in patients with limited SCLC.	1

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22. Willers H, Held KD. Introduction to clinical radiation biology. *Hematology/oncology clinics of North America* 2006; 20(1):1-24.	7	N/A	To review some of the most important and established factors that determine the effectiveness of radiation biology in a wide variety of tumor types and normal tissues: the significance of increasing the dose of radiation, the importance of altered fractionation schemes, such as accelerated fractionation or hyperfractionation, and the need to address tumor hypoxia.	Although the field of radiation biology is rapidly evolving as a result of advances in molecular biology and genetics and the availability of new technologies, a thorough understanding of the established factors that determine radiation responses will remain an important prerequisite for the successful application of multimodal cancer therapies and molecularly targeted approaches in the future.	4
23. Bonner JA, Sloan JA, Shanahan TG, et al. Phase III comparison of twice-daily split-course irradiation versus once-daily irradiation for patients with limited stage small-cell lung carcinoma. *J Clin Oncol* 1999; 17(9):2681-2691.	1	262 total patients	Randomized trial to evaluate TRT given twice-daily in SCLC.	There were no differences between the two treatments with respect to local-only progression rates, overall progression rates, or OS. The patients who received twice daily TRT had greater esophagitis (≥Grade 3) than those who received once daily TRT (12.3% vs 5.3%; P=.05). Although patients received TRT encompassing the postchemotherapy volumes, only 7/90 local failures were out of the portal of irradiation. When TRT is delayed until the 4 cycle of chemotherapy, twice daily TRT does not result in improvement in local control or survival compared with once daily TRT.	1

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24. Schild SE, Bonner JA, Shanahan TG, et al. Long-term results of a phase III trial comparing once-daily radiotherapy with twice-daily radiotherapy in limited-stage small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2004; 59(4):943-951.	1	310 patients	Phase III study to determine whether twice-daily RT resulted in better survival than once-daily RT for patients with LS-SCLC.	Follow-up ranged from 4.6 to 11.9 years (median, 7.4 years). The median survival and 5-year survival rate from randomization was 20.6 months and 21% for patients who received once-daily. RT compared with 20.6 months and 22% for those who received twice-daily RT (P=0.68), respectively. No statistically significant differences were found in the rates of progression (P=0.68), intrathoracic failure (P=0.45), in-field failure (P=0.62), or distant failure (P=0.82) between the two treatment arms. No statistically significant difference was found in the overall rate of Grade 3 or worse (P=0.83) or Grade 4 or worse toxicity (P=0.95). Grade 3 or worse esophagitis (P=0.05) was more common in the twice-daily arm. Grade 5 toxicity occurred in 4 (3%) of 130 patients who received twice-daily RT compared with 0 (0%) of 131 who received once-daily RT (P=0.04). Although this study did not demonstrate an advantage to split-course twice-daily RT, the long-term survival was favorable, likely reflecting the positive influences of concurrent combined modality therapy and PCI.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
25. De Ruysscher D, Pijls-Johannesma M, Bentzen SM, et al. Time between the first day of chemotherapy and the last day of chest radiation is the most important predictor of survival in limited-disease small-cell lung cancer. *J Clin Oncol* 2006; 24(7):1057-1063.	7 (systematic review)	N/A	To identify time factors for combined chemotherapy and RT predictive for long-term survival of patients with limited-disease SCLC.	The start of any treatment until the end of RT was the most important predictor of outcome. There was a significantly higher 5-year survival rate in the shorter start of any treatment until the end of RT arms (RR = 0.62; 95% CI, 0.49 to 0.80; P=.0003), which was more than 20% when the start of any treatment until the end of RT was <30 days (upper bound of 95% CI, 90 days). A low start of any treatment until the end of RT was associated with a higher incidence of severe esophagitis (RR = 0.55; 95% CI, 0.42 to 073; P<.0001). Each week of extension of the start of any treatment until the end of RT beyond that of the study arm with the shortest start of any treatment until the end of RT resulted in an overall absolute decrease in the 5-year survival rate of 1.83% +/- 0.18% (95% CI). A low time between the first day of chemotherapy and the last day of chest RT is associated with improved survival in limited-disease SCLC patients. The novel parameter start of any treatment until the end of RT, which takes into account accelerated proliferation of tumor clonogens during both RT and chemotherapy, may facilitate a more rational design of combined-modality treatment in rapidly proliferating tumors.	3

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26. Fried DB, Morris DE, Poole C, et al. Systematic review evaluating the timing of thoracic radiation therapy in combined modality therapy for limited-stage small-cell lung cancer. *J Clin Oncol* 2004; 22(23):4837-4845.	7 (meta-analysis)	N/A	To evaluate early vs late timing of TRT in LS-SCLC, and to assess the impact of radiation fractionation and chemotherapeutic regimen on timing.	OS RRs for all studies were 1.17 at 2 years (95% CI, 1.02 to 1.35; P=.03) and 1.13 at 3 years (95% CI, 0.92 to 1.39; P=.2), indicating a significantly increased 2-year survival for early RT vs late RT patients and suggestive of a similar trend at 3 years. Subset analysis of studies using hyperfractionated RT revealed OS RR for early RT vs late RT of 1.44 (95% CI, 1.17 to 1.77; P=.001) and 1.39 (95% CI, 1.02 to 1.90; P=.04) at 2 and 3 years, respectively, indicating a survival benefit of early RT vs late RT. Studies using once-daily fractionation showed no difference in 2- and 3-year OS RRs for early RT compared with late RT. Studies using platinum-based chemotherapy had OS RRs of 1.30 (95% CI, 1.10 to 1.53; P=.002) and 1.35 (95% CI, 1.07 to 1.70; P=.01) at 2 and 3 years, respectively, favoring early RT. Studies using nonplatinum-based chemotherapy regimens had nonsignificant differences in OS. Small but significant improvement in 2-year OS for early RT vs late RT in LS-SCLC was observed, similar to the benefit of adding RT to chemotherapy or PCI. A greater difference was evident for hyperfractionated RT and platinum-based chemotherapy.	3

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
27. Pijls-Johannesma MC, De Ruysscher D, Lambin P, Rutten I, Vansteenkiste JF. Early versus late chest radiotherapy for limited stage small cell lung cancer. *Cochrane Database Syst Rev* 2005; (1):CD004700.	7 (meta-analysis)	7 randomized trials	To establish the most effective way of combining chest RT with chemotherapy for patients with LS-SCLC in order to improve long-term survival.	When the only study that delivered chest RT during cycles of nonplatinum chemotherapy was excluded, a trend for the 5-year survival was observed (RR: 0.93, P=0.07) in favor of early radiation, but not for the 2-year survival. Survival at 5 years, but not at 2 years, was significantly better for those having early chest RT delivered in an overall treatment time of <30 days compared with a longer treatment time (RR: 0.90, P=0.006). These results, however, should be interpreted with caution because the largest trial has follow-up data at 3 years, but not later. A trend for a higher chance to develop pneumonitis when early chest RT was delivered during nonplatinum based chemotherapy was observed. At present, it is uncertain whether the timing of chest RT as such is important for survival. The optimal integration of chemotherapy and chest RT in patients with LS-SCLC is unknown. Therefore, further research is needed to establish the most effective combination of RT and chemotherapy in this disease.	2
28. Murray N, Coy P, Pater JL, et al. Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. The National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 1993; 11(2):336-344.	1	308 patients	Randomized trial to assess the importance of the timing of TRT in the combined modality therapy of LS-SCLC.	Although complete remission rates were not significantly different between the two arms, PFS (P=.036) and OS (P=.008) were superior in the early TRT arm. Patients in the late TRT arm had a higher risk of brain metastases (P=.006). The early administration of TRT in the combined modality therapy of LS-SCLC is superior to late or consolidative TRT.	1

Radiation Therapy for Small-Cell Lung Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
29. Takada M, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. *J Clin Oncol* 2002; 20(14):3054-3060.	1	231 total patients	Phase III study to evaluate the optimal timing for TRT in LS-SCLC.	Concurrent RT yielded better survival than sequential RT (P=.097 by log-rank test). The median survival time was 19.7 months in the sequential arm vs 27.2 months in the concurrent arm. The 2-, 3-, and 5-year survival rates for patients who received sequential RT were 35.1%, 20.2%, and 18.3%, respectively, as opposed to 54.4%, 29.8% and 23.7%, respectively, for the patients who received concurrent RT. Hematologic toxicity was more severe in the concurrent arm. However, severe esophagitis was infrequent in both arms, occurring in 9% of the patients in the concurrent arm and 4% in the sequential arm. This study strongly suggests that cisplatin plus etoposide and concurrent RT is more effective for the treatment of LS-SCLC than cisplatin plus etoposide and sequential RT.	1
30. Jeremic B, Shibamoto Y, Acimovic L, Milisavljevic S. Initial versus delayed accelerated hyperfractionated radiation therapy and concurrent chemotherapy in limited small-cell lung cancer: a randomized study. *J Clin Oncol* 1997; 15(3):893-900.	1	103 patients: 52 - Group I patients received concurrent chemoradiation at weeks 1 to 4; 51 - Group II patients at weeks 6 to 9	To perform a randomized study of the optimal timing of TRT as accelerated hyperfractionated RT in combination with concurrent chemotherapy in LS-SCLC.	The median survival time was 34 months in group I and 26 months in group II, and the Kaplan-Meier 5-year survival rates were 30% and 15%, respectively. The difference was almost significant on univariate analysis (P=.052) and was significant on multivariate analysis (P=.027). Group I patients had a significantly higher local control rate than group II patients, but there was no difference between the two groups in distant metastasis rate. There was no difference in the incidence of acute or late Grade 3 to 4 toxicity. Initial administration of thoracic accelerated hyperfractionated RT with concurrent chemotherapy seems to produce better local control and survival rates than delayed administration.	1

Radiation Therapy for Small-Cell Lung Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
31. Videtic GM, Fung K, Tomiak AT, et al. Using treatment interruptions to palliate the toxicity from concurrent chemoradiation for limited small cell lung cancer decreases survival and disease control. *Lung Cancer* 2001; 33(2-3):249-258.	3a	215 patients	To analyze the impact on survival outcomes of treatment interruptions due to toxicity arising during the concurrent phase of chemotherapy/RT for the LS-SCLC population over the past 10 years.	2-year and 5-year OS and disease-specific survival were 22.7% and 7.2%, 27.6% and 9.3%, respectively; OS and disease-specific median survival were 14.7 months each. A total of 56 patients (26%) had treatment breaks due to toxicity. Hematologic depression caused the majority of breaks (88%). The median duration of breaks was 5 days (range 1-18). Patients with and without interruptions were compared for a range of prognostic factors and were not found to have any significant differences. Comparing interrupted/uninterrupted courses, median survivals were 13.8 vs 15.6 months, respectively, and 5-year OS were 4.2% vs 8.3%, respectively. There was a statistical difference between OS curves which favored the uninterrupted group (P=0.01). When comparing a series of prognostic variables, multivariable analysis found that the most significant factor influencing survival in the present study was the presence of treatment breaks (P=0.006). There was a trend for development of any recurrence in the patients with breaks (P=0.08). When controlling for the use of PCI in the two groups, the rate of failure in the chest was higher in the patients with RT breaks (58% vs 33%). The rate of failure in the brain was dependent on the use of PCI only.	2

Radiation Therapy for Small-Cell Lung Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
32. Gregor A, Drings P, Burghouts J, et al. Randomized trial of alternating versus sequential radiotherapy/chemotherapy in limited-disease patients with small-cell lung cancer: a European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group Study. *J Clin Oncol* 1997; 15(8):2840-2849.	1	335 patients	To evaluate the effectiveness of alternating or sequential schedules of cyclophosphamide, doxorubicin, and etoposide chemotherapy and irradiation in patients with previously untreated SCLC.	The overall median survival duration was 15 months, with 62% (95% CI, 57% to 67%) 1-year, 25% (95% CI, 20% to 30%) 2-year, and 14% (95% CI, 10% to 18%) 3-year survival rates. There was no significant difference between the arms. The median survival time was 14 months in A and 15 months in S. 1-year survival was 60% in A (95% CI, 53% to 67%) and 64% in S (95% CI, 57% to 71%); 2-year survival was 26% in A (95% CI, 19% to 33%) and 23% in S (95% CI, 16% to 30%); and 3-year survival was 12% in A (95% CI, 6% to 18%) and 15% in S (95% CI, 9% to 21%). World Health Organization (WHO) Grade 3 and 4 neutropenia occurred in 90% of A and 77% of S patients (P<.001) and WHO Grade 3 and 4 thrombocytopenia in 33% of A and 20% of S patients (P<.001). Rates of other acute and late toxicities were similar in both arms. Hematologic toxicity compromised treatment dose delivery; <50% of A patients received >95% of prescribed chemotherapy and 77% their full radiation course, compared with 60% and 93% for arm S (P<.009). Local relapse was the site of first failure in 60% of all patients and 75% of these suffered an in-field relapse; no difference could be seen between the two arms. This trial failed to confirm the superiority of an alternating schedule of delivery. For this combination of chemotherapy and irradiation, hematologic toxicity compromised treatment delivery and could have contributed to the overall result. The poor rates of local control are disappointing and require intensification of the RT strategy.	1

Radiation Therapy for Small-Cell Lung Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
33. Perry MC, Eaton WL, Propert KJ, et al. Chemotherapy with or without radiation therapy in limited small-cell carcinoma of the lung. *N Engl J Med* 1987; 316(15):912-918.	1	399 patients	A prospective, randomized study to clarify the role of RT of the primary tumor in limited small-cell cancer of the lung.	There was a statistically significant difference in the frequency of CRs in favor of the two RT regimens (P=0.0013). Failure-free survival was also longer with these two regimens (P<0.001), as was the interval before treatment failure in the chest (P<0.001) and OS (P=0.0099). As expected, toxic effects—chiefly eutropenia—were also increased. The addition of RT of the primary tumor to combination chemotherapy improved both CR rates and survival, with increased but acceptable toxicity.	1
34. Perry MC, Herndon JE, 3rd, Eaton WL, Green MR. Thoracic radiation therapy added to chemotherapy for small-cell lung cancer: an update of Cancer and Leukemia Group B Study 8083. *J Clin Oncol* 1998; 16(7):2466-2467.	1	399 patients	Randomized trial to provide a 10-year update of the experience of the Cancer and Leukemia Group B (CALGB) in the addition of TRT to chemotherapy in LS-SCLC.	Arm I patients had a median survival of 13.04 months, arm II patients 14.54 months, and arm III patients 13.58 months (log-rank test, P=.0072). Median time to clinical failure was 11 months in arm I, 11.21 months in arm II, and 8.7 months in arm III (log-rank test, P=.0004). With 10 years of follow-up, the two arms that included TRT remain superior to chemotherapy alone. The addition of TRT to combination chemotherapy improved both CR rates and survival, with increased but acceptable toxicity.	1
35. Spiro SG, James LE, Rudd RM, et al. Early compared with late radiotherapy in combined modality treatment for limited disease small-cell lung cancer: a London Lung Cancer Group multicenter randomized clinical trial and meta-analysis. *J Clin Oncol* 2006; 24(24):3823-3830.	1	325 patients	Randomized trial to replicate an earlier National Cancer Institute of Canada (NCIC) trial that examined the effect on survival of the timing of TRT in patients with limited disease SCLC.	There was no evidence of a survival difference; median OS time was 13.7 and 15.1 months in the early and late arms, respectively (P=.23). In a meta-analysis of all 8 trials that compared early and late TRT, there were 3 in which the proportion of patients who completed their planned chemotherapy was similar between the TRT arms (HR = 0.73; 95% CI, 0.62 to 0.86) and 5 in which proportionally fewer patients in the early TRT arm completed their chemotherapy (HR = 1.06; 95% CI, 0.97 to 1.17). This study failed to show a survival advantage for early TRT with chemotherapy in LS-SCLC, unlike the NCIC trial. However, the results of a meta-analysis suggest that it is essential to ensure that the delivery of chemotherapy is optimal when administered with early TRT.	1

Radiation Therapy for Small-Cell Lung Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
36. Work E, Nielsen OS, Bentzen SM, Fode K, Palshof T. Randomized study of initial versus late chest irradiation combined with chemotherapy in limited-stage small-cell lung cancer. Aarhus Lung Cancer Group. *J Clin Oncol* 1997; 15(9):3030-3037.	1	199 consecutive patients	To evaluate if the timing of chest RT with respect to chemotherapy would influence survival and local and distant control in patients with LS-SCLC.	The timing of RT had no significant effect on the 2-year OS rate (20% after initial chest RT vs 19% after late chest RT, P=.4) or the 2-year in-field recurrence rate (72% after initial chest RT vs 68% after late chest RT, P=.2). Median survival durations were 10.5 (initial chest RT) and 12.0 (late chest RT) months. Similarly, no difference in the 2-year incidence of central nervous system recurrences was found between the 2 arms in patients who received PCI (19% after initial chest RT vs 13% after late chest RT, P=.24). Bone marrow toxicity was acceptable, as 15% developed WHO Grade 4 leukocytopenia and 4% Grade 4 thrombocytopenia. Grade 4 leukocytopenia was more pronounced in the initial chest RT group. There was no difference in the frequency and severity of other toxicities between the 2 groups. Timing of chest RT did not significantly influence the incidence of in-field recurrences, central nervous system recurrences, or OS.	1
37. Murray N, Grafton C, Shah A, et al. Abbreviated treatment for elderly, infirm, or noncompliant patients with limited-stage small-cell lung cancer. *J Clin Oncol* 1998; 16(10):3323-3328.	4	55 patients	To evaluate the efficacy of an abbreviated treatment plan consisting of 2 cycles of chemotherapy plus TRT in a population of LS-SCLC patients who were elderly, infirm, or noncompliant with standard-duration therapy.	CR occurred in 28 patients (51%) and PR in 21 (38%). The median survival time was 54 weeks; the 2-year survival rate was 28% and the actual 5-year survival rate was 18%. Three patients died of toxicity. Elderly, infirm, or noncompliant LSCLC patients who are unable to receive standard-duration chemotherapy may have useful palliation and potential for long-term survival with abbreviated chemotherapy (2 cycles) and TRT.	2

Radiation Therapy for Small-Cell Lung Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
38. Videtic GM, Belderbos JS, Spring Kong FM, Kepka L, Martel MK, Jeremic B. Report from the International Atomic Energy Agency (IAEA) consultants' meeting on elective nodal irradiation in lung cancer: small-cell lung cancer (SCLC). *Int J Radiat Oncol Biol Phys* 2008; 72(2):327-334.	7	N/A	To address the concepts underlying elective or selective nodal irradiation as it applies to SCLC, looking at clinical, imaging, and RT reports to help define the parameters appropriate to treating individual patients.	This review revealed how limited the scope is for high level evidence in deciding on the place of elective or selective nodal irradiation in SCLC. Therefore the most appropriate setting for answering the controversial question on the place of elective or selective nodal irradiation in SCLC should be within the framework of a prospective clinical trial. To date, a single phase II study using CT-based imaging for tumor identification suggests increased a risk of increased locoregional nodal failure for patients with restricted nodal fields. PET series suggest that it is a very appropriate tool for enhanced definition of tumor, but there are no prospective data that correlate PET findings and pathologic findings to long-term clinical outcomes. Surgical assessment of the mediastinum in SCLC patients is rarely done, but the available studies suggest that it optimized identification of tumor compared with clinical imaging. In the absence of strong evidence supporting omission of elective or selective nodal irradiation, clinicians must use thoughtful clinical judgment, integrating a number of factors with appropriate interpretation of the evidence to guide their treatment planning, with an emphasis on a balance between increase of failure risk and maximal reduction of treatment-related toxicities to support improvements in outcomes.	4

Radiation Therapy for Small-Cell Lung Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
39. Bradley JD, Dehdashti F, Mintun MA, Govindan R, Trinkaus K, Siegel BA. Positron emission tomography in limited-stage small-cell lung cancer: a prospective study. *J Clin Oncol* 2004; 22(16):3248-3254.	10	24 patients	To determine how often FDG-PET detects extensive-stage SCLC in patients considered to have limited-stage disease based on conventional staging procedures, and to determine the impact of PET on treatment planning for presumed LS-SCLC.	FDG-PET demonstrated findings consistent with extensive-stage SCLC in 3/24 patients. FDG-PET correctly upstaged two (8.3%) of 24 patients to extensive-stage disease (95% CI, 1.03% to 27.0%). PET correctly identified tumor in each SCLC mass (primary or nodal) that was suspected on CT imaging, thus giving a lesion-based sensitivity relative to CT of 100%. PET identified unsuspected regional nodal metastasis in 6 (25%) of 24 patients, and the RT plan was significantly altered to include the PET-positive/CT-negative nodes within the high-dose region in each of these patients. Brain PET images in 23 patients disclosed no evidence of brain metastasis. FDG-PET has high sensitivity for SCLC and appears to be of value for initial staging and treatment planning of patients with presumed limited-stage disease.	2
40. van Loon J, De Ruysscher D, Wanders R, et al. Selective nodal irradiation on basis of (18)FDG-PET scans in limited-disease small-cell lung cancer: a prospective study. *Int J Radiat Oncol Biol Phys* 2010; 77(2):329-336.	4	60 patients	To evaluate the results of selective nodal irradiation on basis of FDG-PET scans in patients with limited-disease-SCLC on isolated nodal failure.	A difference was seen in the involved nodal stations between the pretreatment FDG-PET scans and CT scans in 30% of patients (95% CI, 20%-43%). Of the 60 patients, 39 (65%; 95% CI, 52%-76%) developed a recurrence; 2 patients (3%, 95% CI, 1%-11%) experienced isolated regional failure. The median actuarial OS was 19 months (95% CI, 17-21). The median actuarial PFS was 14 months (95% CI, 12-16). 12% (95% CI, 6%-22%) of patients experienced acute Grade 3 (Common Terminology Criteria for Adverse Events, version 3.0) esophagitis. PET-based selective nodal irradiation for limited-disease-SCLC resulted in a low rate of isolated nodal failures (3%), with a low percentage of acute esophagitis. These findings are in contrast to those from our prospective study of CT-based selective nodal irradiation, which resulted in an unexpectedly high percentage of isolated nodal failures (11%).	2

Radiation Therapy for Small-Cell Lung Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
41. Arriagada R, Le Chevalier T, Borie F, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. *J Natl Cancer Inst* 1995; 87(3):183-190.	1	294 patients	Randomized trial to prospectively evaluate the effects of PCI on brain metastasis, OS, and late-occurring toxic effects in patients with SCLC in complete remission.	The 2-year cumulative rate of brain metastasis as an isolated first site of relapse was 45% in the control group and 19% in the treatment group (P<10(-6)). The total 2-year rate of brain metastasis was 67% and 40%, respectively (RR = 0.35; P<10(-13)). The 2-year OS rate was 21.5% in the control group and 29% in the treatment group (RR = 0.83; P=.14). There were no significant differences between the two groups in terms of neuropsychological function or abnormalities indicated by computed tomography brain scans. PCI given to patients with SCLC in complete remission decreases the risk of brain metastasis threefold without a significant increase in complications. A possible beneficial effect on OS should be tested with a higher statistical power. The results of the trial favor, at present, the indication of PCI for patients who are in complete remission. Longer follow-up and confirmatory trials are needed to fully assess late-occurring toxic effects. The possible effect on OS needs to be evaluated with a larger number of patients in complete remission, and a meta-analysis of similar trials is recommended.	1

Radiation Therapy for Small-Cell Lung Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
42. Gregor A, Cull A, Stephens RJ, et al. Prophylactic cranial irradiation is indicated following complete response to induction therapy in small cell lung cancer: results of a multicentre randomised trial. United Kingdom Coordinating Committee for Cancer Research (UKCCCR) and the European Organization for Research and Treatment of Cancer (EORTC). *Eur J Cancer* 1997; 33(11):1752-1758.	1	314 patients	Randomized trial to evaluate the effects of PCI.	With PCI, there was a large and highly significant reduction in brain metastases (HR = 0.44, 95% CI, 0.29-0.67), a significant advantage in brain-metastasis-free survival (HR = 0.75, 95% CI, 0.58-0.96) and a non-significant OS advantage (HR = 0.86, 95% CI, 0.66-1.12). In both groups, there was impairment of cognitive function and quality-of-life before PCI and additional impairment at 6 months and 1 year, but no consistent difference between the two groups and thus no evidence over 1 year of major impairment attributable to PCI. PCI can safely reduce the risk of brain metastases. Further research is needed to define optimal dose and fractionation and to clarify the effect on survival. Patients with SCLC achieving a CR to induction therapy should be offered PCI.	1
43. Auperin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med* 1999; 341(7):476-484.	7 (meta-analysis)	987 patients	A meta-analysis to determine whether PCI prolongs survival.	The RR of death in the treatment group as compared with the control group was 0.84 (95% CI, 0.73 to 0.97; P=0.01), which corresponds to a 5.4% increase in the rate of survival at 3 years (15.3% in the control group vs 20.7% in the treatment group). PCI also increased the rate of DFS (RR of recurrence or death, 0.75; 95 % CI, 0.65 to 0.86; P<0.001) and decreased the cumulative incidence of brain metastasis (RR, 0.46; 95% CI, 0.38 to 0.57; P<0.001). Larger doses of radiation led to greater decreases in the risk of brain metastasis, according to an analysis of 4 total doses (8 Gy, 24 to 25 Gy, 30 Gy, and 36 to 40 Gy) (P for trend=0.02), but the effect on survival did not differ significantly according to the dose. We also identified a trend (P=0.01) toward a decrease in the risk of brain metastasis with earlier administration of cranial RT after the initiation of induction chemotherapy. PCI improves both OS and DFS among patients with SCLC in complete remission.	2

Radiation Therapy for Small-Cell Lung Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
44. Komaki R, Byhardt RW, Anderson T, et al. What is the lowest effective biologic dose for prophylactic cranial irradiation? *Am J Clin Oncol* 1985; 8(6):523-527.	4	327 consecutive patients	To determine the lowest effective biologic dose for PCI.	The cumulative (time corrected) probability of brain metastasis was approximately 10% at 1 year and was similar for patients who received 25 Gy and those who received 30 Gy. Although detailed neuropsychological testing has not been performed, clinically apparent late sequelae that might be attributed to PCI have not been seen. Nonetheless, the dose fractionation regimen of 25 Gy in 10 fractions with combination chemotherapy, cyclophosphamide, doxorubicin (or methotrexate), and vincristine is as effective in eliminating subclinical metastasis to the brain. It can be recommended for future trials until more data become available about late sequelae of treatment of SCCL and the patient characteristics and treatment factors that may contribute.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
45. Sorensen JB. The role of prophylactic brain irradiation in small cell lung cancer treatment. *Monaldi Arch Chest Dis* 2003; 59(2):128-133.	7 (meta-analysis)	7,793 total patients; 68 total trials	To review the effectiveness and safety of PCI in patients with SCLC.	The 5-year cumulative rate of brain metastases as isolated first site of relapse was 37% among 260 patients without PCI compared to 20% among 245 with PCI in two randomized trials (P<0.001). A meta-analysis on 7 randomized trials of PCI vs no PCI including 987 patients in complete remission without brain metastases or prior brain RT showed statistically significant effect in favor of PCI on survival, DFS, and risk of brain metastases (RRs being 0.84, 0.75, and 0.46, and p-values being 0.01, <0.001, and <0.001, respectively). 2 randomized trials evaluated neurotoxicity in totally 350 patients before PCI and found abnormalities in 24%-60%. Repeated examination during the following years revealed no differences on cerebral CT-scans or neuropsychological testing between PCI patients or controls. A review including 42 PCI trials with 4,749 patients revealed the optimal total RT dose to be 30-35 Gy given as 2 Gy fractions. Also 24 Gy in 3 Gy fractions appear safe based on data from a large randomized study. Both the former study and the meta-analysis suggested early PCI to be better than late.	2

Radiation Therapy for Small-Cell Lung Cancer
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
46. Le Pechoux C, Dunant A, Senan S, et al. Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial. *Lancet Oncol* 2009; 10(5):467-474.	1	720 patients from 157 centers	To compare the effect of standard vs higher PCI doses on the incidence of brain metastases.	After a median follow-up of 39 months (range 0-89 months), 145 patients had brain metastases; 82 in the standard-dose group and 63 in the higher-dose group. 226 patients in the standard-dose group and 252 in the higher-dose group died; 2-year OS was 42% (95% CI, 37-48) in the standard-dose group and 37% (32-42) in the higher-dose group (HR 1.20 [1.00-1.44]; P=0.05). The lower OS in the higher-dose group is probably due to increased cancer-related mortality: 189 patients in the standard group vs 218 in the higher-dose group died of progressive disease. The most common acute toxic events were fatigue (106 [30%] patients in the standard-dose group vs 121 [34%] in the higher-dose group), headache (85 [24%] vs 99 [28%]), and nausea or vomiting (80 [23%] vs 101 [28%]). No significant reduction in the total incidence of brain metastases was observed after higher-dose PCI, but there was a significant increase in mortality. PCI at 25 Gy should remain the standard of care in LS-SCLC.	1
47. Spira A, Ettinger DS. Extensive-stage small-cell lung cancer. *Semin Surg Oncol* 2003; 21(3):164-175.	7	N/A	To review extensive-stage SCLC.	Extensive-stage SCLC continues to be a difficult management issue. While response rates to therapy are relatively high, durable responses are rare, and long-term survival rates are dismal. Although many attempts have been made to develop new therapies, cisplatin-based combination chemotherapy remains the mainstay in the management of these patients. In this review we highlight recent developments in the treatment and management of this malignancy, and discuss future prospects in treatment.	4

Radiation Therapy for Small-Cell Lung Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
48. Evans WK, Shepherd FA, Feld R, Osoba D, Dang P, Deboer G. VP-16 and cisplatin as first-line therapy for small-cell lung cancer. *J Clin Oncol* 1985; 3(11):1471-1477.	4	28 patients	To evaluate VP-16 and cisplatin as first-line therapy for SCLC.	The median duration of response for patients with limited disease was 39 weeks and for those with extensive disease, 26 weeks. The median survival time for the whole group of responding (CR and PR) limited disease patients was 70 weeks (range, 28 to 181 + weeks), and for responding extensive disease patients, it was 43 weeks (range, 17 to 68 weeks). Gastrointestinal toxicity was mild, but leukopenia and thrombocytopenia were common. -here were 4 febrile episodes during periods of drug-induced neutropenia and this led to one treatment-related death. Nephrotoxicity occurred in 15 patients and required discontinuation of cisplatin in two. These results compare favorably with reports of standard induction chemotherapy regimens and provide further evidence of the activity of the VP-16 and cisplatin regimen in patients with SCLC.	2
49. Okamoto H, Watanabe K, Kunikane H, et al. Randomized phase III trial of carboplatin(C) plus etoposide (E) vs. split doses of cisplatin (P) plus etoposide (E) in elderly or poor-risk patients with extensive disease small cell lung cancer (ED-SCLC): JCOG9702. *J Clin Oncol (Meeting Abstracts)* 2005; 23(16_suppl):LBA7010-.	1	220 patients	A phase III trial to compare CE with SPE in elderly or poor-risk pts with SCLC.	Baseline characteristics were well balanced between the arms; median age 74 years (92% of patient's ≥70 years), >5% weight loss: 29%, male/female: 88%/12%, performance status 0–1/2–3: 74%/26%. Of these 62% in carboplatin plus etoposide and 65% in split doses of cisplatin plus etoposide completed 4 courses. Most toxicities except for thrombocytopenia were similar between the arms. Major Grade 3-4 toxicities were (% carboplatin plus etoposide/split doses of cisplatin plus etoposide): leukopenia 54/50, neutropenia 95/88, anemia 30/24, thrombocytopenia 55/16, infection 7/6, hypoxemia 7/3. Grade ≥ 2 toxicities were (% carboplatin plus etoposide/split doses of cisplatin plus etoposide): nausea/vomiting 24/28, diarrhea 9/4, alopecia 21/14. Data for efficacy endpoints (OS, PFS, response rate, palliation score) will be available for the final analysis at Feb 2005.	2

Radiation Therapy for Small-Cell Lung Cancer
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
50. Noda K, Nishiwaki Y, Kawahara M, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med* 2002; 346(2):85-91.	1	154 patients	Randomized trial compared irinotecan plus cisplatin with EP in patients with extensive (metastatic) SCLC.	The median survival was 12.8 months in the irinotecan-plus-cisplatin group and 9.4 months in the etoposide-plus-cisplatin group (P=0.002 by the unadjusted log-rank test). At 2 years, the proportion of patients surviving was 19.5% in the irinotecan-plus-cisplatin group and 5.2% in the etoposide-plus-cisplatin group. Severe or life-threatening myelosuppression was more frequent in the etoposide-plus-cisplatin group than in the irinotecan-plus-cisplatin group, and severe or life-threatening diarrhea was more frequent in the irinotecan-plus-cisplatin group than in the etoposide-plus-cisplatin group. Irinotecan plus cisplatin is an effective treatment for metastatic SCLC.	1
51. Hanna N, Bunn PA, Jr., Langer C, et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. *J Clin Oncol* 2006; 24(13):2038-2043.	1	331 total patients: 221 irinotecan/cisplatin; 110 EP	To determine if a modified weekly regimen of irinotecan/cisplatin would provide superior survival with less toxicity than EP.	Selected Grade 3/4 toxicities for irinotecan/cisplatin / EP were: neutropenia (36.2% vs 86.5%; P<.01), febrile neutropenia (3.7% vs 10.4%; P=.06), anemia (4.8% vs 11.5%; P=.02), thrombocytopenia (4.3% vs 19.2%; P<.01), vomiting (12.5% vs 3.8%; P=.04), and diarrhea (21.3% vs 0%; P<.01). There was no significant difference in response rates (48% vs 43.6%), median time to progression (4.1 vs 4.6 months), or OS (median survival time, 9.3 months vs 10.2 months; P=.74). Treatment with this dose and schedule of irinotecan/cisplatin did not result in improved survival when compared with EP. Fewer patients receiving irinotecan/cisplatin had Grade 3/4 anemia, thrombocytopenia, neutropenia, and febrile neutropenia compared with patients receiving EP, but more had Grade 3/4 diarrhea and vomiting.	1

Radiation Therapy for Small-Cell Lung Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
52. Girling DJ. Comparison of oral etoposide and standard intravenous multidrug chemotherapy for small-cell lung cancer: a stopped multicentre randomised trial. Medical Research Council Lung Cancer Working Party. *Lancet* 1996; 348(9027):563-566.	1	339 total patients: 171 patients 4 cycles of 50 mg oral etoposide twice daily for 10 days; 168 (cyclophosphamide, doxorubicin, and vincristine, controls)	Randomized trial to compare oral etoposide and standard intravenous multidrug chemotherapy for SCLC.	The palliative effects of treatment were similar in the etoposide group and control group (41% vs 46%). Grade 2 or worse haematological toxicity occurred in 35 (29%) etoposide-treated patients and 26 (21%) controls. Controls had a higher overall response rate than etoposide-treated patients (51% vs 45%). There was a small disadvantage in survival associated with oral etoposide (HR 1.35 [95% CI, 1.03-1.79], P=0.03). Median survival was 130 days in the etoposide group and 183 days in the controls; survival rates were 35% and 49% at 6 months and 11% and 13% at 12 months, respectively. Oral etoposide 50 mg twice daily for 10 days every 3 weeks for 4 cycles is inferior to standard intravenous multidrug chemotherapy in the palliative treatment of patients with SCLC and poor performance status. Oral etoposide alone should no longer be used in the treatment of such patients.	1
53. Lowenbraun S, Bartolucci A, Smalley RV, Lynn M, Krauss S, Durant JR. The superiority of combination chemotherapy over single agent chemotherapy in small cell lung carcinoma. *Cancer* 1979; 44(2):406-413.	1	288 patients	Randomized trial to compare the two noncycle-active induction regimens of cyclophosphamide vs the combination of cyclophosphamide, doxorubicin and imidazole carboximide.	The survival curve for all the combination-treated patients was significantly better than for those treated with cyclophosphamide alone (P=0.012). There was no demonstrable statistical superiority in length of remission or survival for patients on the combination who received in addition cycle-active consolidation therapy. In the combination chemotherapy group, survival duration was longer for patients with limited disease than extensive disease (P=0.035). There was a strong correlation between quality of remission produced by the combination and survival.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
54. Souhami RL, Spiro SG, Rudd RM, et al. Five-day oral etoposide treatment for advanced small-cell lung cancer: randomized comparison with intravenous chemotherapy. *J Natl Cancer Inst* 1997; 89(8):577-580.	1	155 patients	Randomized trial to determine if the effects of oral etoposide therapy on survival and quality of life are equivalent to those of intravenous chemotherapy.	Survival was inferior at 1 year in the oral etoposide group compared with intravenous therapy (9.8% for oral vs 19.3% for intravenous; difference = 9.5%; 95% CI of difference = 0.3%-18.7%; P<.05), and there was a trend toward inferior OS. Median survival was 4.8 months for oral treatment and 5.9 months for intravenous therapy. PFS was worse in the oral etoposide arm (median = 3.6 months vs 5.6 months; P<.001), as well as overall response rate (32.9% vs 46.3%; P<.01). With the exception of acute nausea and vomiting associated with intravenous chemotherapy, all aspects of symptom control and quality of life were either the same or worse in the oral etoposide group. Study closure was recommended. These interim results show that this schedule of oral etoposide is inferior to intravenous chemotherapy in the treatment of advanced SCLC and should not be used as first-line treatment of this disease.	1
55. Loehrer PJ, Sr., Ansari R, Gonin R, et al. Cisplatin plus etoposide with and without ifosfamide in extensive small-cell lung cancer: a Hoosier Oncology Group study. *J Clin Oncol* 1995; 13(10):2594-2599.	1	171 patients	To determine whether the addition of ifosfamide to cisplatin plus etoposide improves the response rate, time to disease progression, or OS in previously untreated patients with extensive-stage SCLC.	The median follow-up duration is 26 months. All patients were assessable for survival; 163 were fully assessable for response and 162 for toxicity. Myelosuppression was greater with cisplatin, ifosfamide and etoposide. Objective responses were observed in 55/82 (67%) and 59/81 (73%) assessable patients treated with EP and cisplatin, ifosfamide and etoposide, respectively (difference not significant). The difference in the median time to progression was statistically different (P=.039). The median survival times on EP and cisplatin, ifosfamide and etoposide were 7.3 months and 9.0 months, respectively (P=.045 for survival curves by stratified log-rank test) with 2-year survival rates of 5% vs 13%, respectively. Cisplatin, ifosfamide and etoposide combination chemotherapy is associated with an improved time to progression and OS over EP therapy in patients with extensive SCLC.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
56. Mavroudis D, Papadakis E, Veslemes M, et al. A multicenter randomized clinical trial comparing paclitaxel-cisplatin-etoposide versus cisplatin-etoposide as first-line treatment in patients with small-cell lung cancer. *Ann Oncol* 2001; 12(4):463-470.	1	133 patients: 62 patients received 261 cycles of TEP; 71 patients 323 cycles of EP	Randomized multicenter study to compare the TEP combination to EP regimen as front-line treatment in patients with SCLC.	In an intention-to-treat overall analysis both regimens were equally active with a CR and PR rate of 50% (95% CI: 37.5%-62.4%) for TEP and 48% (95%) CI: 36.2%-59.5%) for EP (P=0.8). The median time to disease progression was 11 months for TEP and 9 months for EP (P=0.02). The duration of response, 1-year survival and OS were similar in the two arms. Similarly, in an intention-to-treat subgroup analysis of patients with limited or extensive stage disease, there was no difference in the activity between the two regimens except of a longer median time to disease progression in the extensive stage in favor of the TEP regimen, 8 vs 6 months (P=0.04). However, there were 8 toxic deaths in the TEP arm vs none in the EP arm (P=0.001). Moreover, the TEP regimen was associated with more severe toxicity than the EP regimen in terms of Grade 4 neutropenia (P=0.04), Grade 3-4 thrombocytopenia (P=0.02), febrile neutropenia (P=0.08), Grade 3-4 diarrhea (P=0.01), Grade 3-4 asthenia (P=0.05) and Grade 3 neurotoxicity (P=0.06). In this early terminated study, the TEP regimen was significantly more toxic than the EP regimen. The TEP regimen is associated with significant toxicity and mortality, and should not be used outside of a protocol setting. For future investigations, dose and schedule modifications are necessary to reduce toxicity.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
57. Niell HB, Herndon JE, 2nd, Miller AA, et al. Randomized phase III intergroup trial of etoposide and cisplatin with or without paclitaxel and granulocyte colony-stimulating factor in patients with extensive-stage small-cell lung cancer: Cancer and Leukemia Group B Trial 9732. *J Clin Oncol* 2005; 23(16):3752-3759.	1	565 patients: 282 received EP; 283 assigned to receive paclitaxel to EP	To determine, in a randomized comparison, whether the addition of paclitaxel to EP improves the time to progression and OS in patients with extensive SCLC compared with standard EP and to compare the regimens' toxicity.	Overall response rates were 68% for the EP arm and 75% for the paclitaxel to EP arm. Median failure-free survival time was 5.9 months for the EP arm and 6 months for the paclitaxel to EP arm (P=.179). Median OS time was 9.9 months for patients on EP and 10.6 months for patients on paclitaxel to EP (P=.169). Toxic deaths occurred in 2.4% of the patients on EP and 6.5% of patients on paclitaxel to EP. Paclitaxel to EP did not improve the time to progression or survival in patients with extensive SCLC compared with EP alone and was associated with unacceptable toxicity.	1
58. Pujol JL, Daures JP, Riviere A, et al. Etoposide plus cisplatin with or without the combination of 4'-epidoxorubicin plus cyclophosphamide in treatment of extensive small-cell lung cancer: a French Federation of Cancer Institutes multicenter phase III randomized study. *J Natl Cancer Inst* 2001; 93(4):300-308.	1	226 total patients: 109 EP; 117 PCDE	To determine whether drug intensification improves survival of patients with extensive SCLC.	Patients in the PCDE arm had a statistically significant higher frequency of combined complete plus PR compared with those in the EP arm (21% plus 55% vs 13% plus 48%, respectively; P=02 for difference in combined objective responses). Patients in the PCDE arm survived longer than those in the EP arm (1-year survival rate: 40% and 29%, respectively; median survival: 10.5 and 9.3 months, respectively; log-rank P=.0067). In the Cox model, the RR of death for patients in the PCDE arm compared with those in the EP arm was 0.70 (95% CI, 0.51 to 0.95); the disease also progressed more slowly in patients in the PCDE arm. Hematologic toxicity was higher in the PCDE arm (22% with documented infections compared with 8% in the EP arm; P=.0038), and the toxicity-related death rate was 9% in the PCDE arm vs 5.5% in the EP arm (P=.22). The global health status showed similar improvement in both arms during treatment. Compared with the EP regimen, the PCDE regimen yielded higher response rates and better survival rates in patients with extensive SCLC without affecting the quality of life of the patients during chemotherapy.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
59. Schiller JH, Adak S, Cella D, DeVore RF, 3rd, Johnson DH. Topotecan versus observation after cisplatin plus etoposide in extensive-stage small-cell lung cancer: E7593--a phase III trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2001; 19(8):2114-2122.	1	402 patients	Randomized trial to determine the efficacy of topotecan in combination with standard chemotherapy in previously untreated patients with extensive-stage SCLC, the Eastern Cooperative Oncology Group (ECOG) conducted a phase III trial.	CR and PR rates to induction EP were 3% and 32%, respectively. A 7% response rate was observed with topotecan (CR, 2%; PR, 5%). The median survival time for all eligible patients was 9.6 months. PFS from date of randomization on step 2 was significantly better with topotecan compared with observation (3.6 months vs 2.3 months; P<.001). However, OS from date of randomization on step 2 was not significantly different between the observation and topotecan arms (8.9 months vs 9.3 months; P=.43). Grade 4 neutropenia and thrombocytopenia occurred in 50% and 3%, respectively, of EP patients in step 1 and 60% and 13% of topotecan patients in step 2. Grade 4/5 infection was observed in 4.6% of EP patients and 1.8% of topotecan patients. Grade 3/4 anemia developed in 22% of patients who received topotecan. 4cycles of EP induction therapy followed by 4 cycles of topotecan improved PFS but failed to improve OS or quality of life in extensive-stage SCLC. Four cycles of standard PE remains an appropriate first-line treatment for extensive-stage SCLC patients with good performance status.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
60. Sculier JP, Berghmans T, Castaigne C, et al. Maintenance chemotherapy for small cell lung cancer: a critical review of the literature. *Lung Cancer* 1998; 19(2):141-151.	7	N/A	To review maintenance chemotherapy for SCLC.	A quantitative overview or meta-analysis was unpracticable because of the lack of data for calculation of the odds ratio in the publications and because of the heterogeneity of the studies' designs. A qualitative overview was carried out using two scales: the Chalmers scores and the European Lung Cancer Working Party (ELCWP) score. Correlation between both scores was excellent. The overall quality of the publications was not good, with important methodological aspects missing, such as a clear definition of the primary objective or an a priori estimate of the sample size necessary to conduct the trial. It is concluded that maintenance chemotherapy could have some indications and that good quality trials, as reflected by very high quality scores, need to be carried out in the future.	4
61. Jeremic B, Shibamoto Y, Nikolic N, et al. Role of radiation therapy in the combined-modality treatment of patients with extensive disease small-cell lung cancer: A randomized study. *J Clin Oncol* 1999; 17(7):2092-2099.	1	210 total patients: 55 patients carboplatin/etoposide followed by two cycles of EP (group 1); 54 patients additional 4 cycles of EP (group 2)	To investigate the efficacy and toxicity of EP chemotherapy with or without accelerated hyperfractionated RT and concurrent daily carboplatin/etoposide in patients with extensive-disease SCLC.	The median survival time was 9 months and the 5-year survival rate was 3.4%. Patients in group 1 had significantly better survival rates than those in group 2 (median survival time, 17 vs 11 months; 5-year survival rate, 9.1% vs 3.7%, respectively; P=.041). Local control was also better in group 1, but the difference was only marginally not significant (P=.062). There was no difference in distant metastasis-free survival between groups 1 and 2. Acute high-Grade toxicity was higher in group 2 than in group 1.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
62. Slotman B, Faivre-Finn C, Kramer G, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med* 2007; 357(7):664-672.	1	286 total patients	Randomized trial to assess PCI in extensive SCLC.	Patients in the irradiation group had a lower risk of symptomatic brain metastases (HR, 0.27; 95% CI, 0.16 to 0.44; P<0.001). The cumulative risk of brain metastases within 1-year was 14.6% in the irradiation group (95% CI, 8.3 to 20.9) and 40.4% in the control group (95% CI, 32.1 to 48.6). Irradiation was associated with an increase in median DFS from 12.0 weeks to 14.7 weeks and in median OS from 5.4 months to 6.7 months after randomization. The 1-year survival rate was 27.1% (95% CI, 19.4 to 35.5) in the irradiation group and 13.3% (95% CI, 8.1 to 19.9) in the control group. Irradiation had side effects but did not have a clinically significant effect on global health status. PCI reduces the incidence of symptomatic brain metastases and prolongs DFS and OS.	1
63. Slotman BJ, Mauer ME, Bottomley A, et al. Prophylactic cranial irradiation in extensive disease small-cell lung cancer: short-term health-related quality of life and patient reported symptoms: results of an international Phase III randomized controlled trial by the EORTC Radiation Oncology and Lung Cancer Groups. *J Clin Oncol* 2009; 27(1):78-84.	4	286 patients	To assess the effects of PCI on health-related quality of life are reported here.	Compliance with the health-related quality of life assessment was 93.7% at baseline and dropped to 60% at 6 weeks. Short-term results up to 3 months showed that there was a negative impact of PCI on selected health-related quality of life scales. The largest mean difference between the two arms was observed for fatigue and hair loss. The impact of PCI on global health status as well as on functioning scores was more limited. For global health status, the observed mean difference was eight points on a scale 0 to 100 at 6 weeks (P=.018) and 3 months (P=.055). PCI should be offered to all responding extensive disease SCLC patients. Patients should be informed of the potential adverse effects from PCI. Clinicians should be alert to these; monitor their patients; and offer appropriate support, clinical, and psychosocial care.	2

Evidence Table Key

Study Type Key

Numbers 1-7 are for studies of therapies while numbers 8-15 are used to describe studies of diagnostics.

1. Randomized Controlled Trial — Treatment
2. Controlled Trial
3. Observation Study
    a. Cohort
    b. Cross-sectional
    c. Case-control
4. Clinical Series
5. Case reviews
6. Anecdotes
7. Reviews
8. Randomized Controlled Trial — Diagnostic
9. Comparative Assessment
10. Clinical Assessment
11. Quantitative Review
12. Qualitative Review
13. Descriptive Study
14. Case Report
15. Other (Described in text)

Strength of Evidence Key

- Category 1 - The conclusions of the study are valid and strongly supported by study design, analysis and results.
- Category 2 - The conclusions of the study are likely valid, but study design does not permit certainty.
- Category 3 - The conclusions of the study may be valid but the evidence supporting the conclusions is inconclusive or equivocal.
- Category 4 - The conclusions of the study may not be valid because the evidence may not be reliable given the study design or analysis.

Abbreviations Key

CI = Confidence interval

CR = Complete response

CS = Clinically staged

CT = Computed tomography

DFS = Disease-free survival

EP = Cisplatin etoposide

FDG-PET = Fluorine-18-2-fluoro-2-deoxy-D-glucose-positron emission tomography

HR = Hazard ratio

LS-SCLC = Limited-stage small-cell lung cancer

NSCLC = Non-small-cell lung cancer

OS = Overall survival

PCDE = Etoposide plus cisplatin plus 4'-epidoxorubicin plus cyclophosphamide

PCI = Prophylactic cranial irradiation

PFS = Progression-free survival

PR = Partial response

RR = Relative risk

RT = Radiation therapy

SCLC = Small-cell lung cancer

SD = Standard deviation

TEP = Paclitaxel-cisplatin-etoposide

TRT = Thoracic radiotherapy

VAP = Vincristine, adriamycin, and procarbazine