Evidence Report/Technology Assessment
Number 143

Management of Small Cell Lung Cancer

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. 290-02-0026

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AHRQ Publication No. 06-E016
July 2006

This report is based on research conducted by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-02-0026). The findings and conclusions in this document are those of the author(s) who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help clinicians, employers, policymakers, and others make informed decisions about the provision of health care services. This report is intended as a reference and not as a substitute for clinical judgment.

Suggested Citation:
Seidenfeld J, Samson DJ, Bonnell CJ, Ziegler KM, Aronson N. Management of Small Cell Lung Cancer. Evidence Report/Technology Assessment No. 143. (Prepared by Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under Contract No. 290-02-0026.) AHRQ Publication No. 06-E016. Rockville, MD: Agency for Healthcare Research and Quality. July 2006.

No investigators have any affiliations or financial involvement (e.g., employment, consultancies, honoraria, or stock options, expert testimony, grants, or patients received or pending, or royalties) that conflict with material presented in this report.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to **epc@ahrq.hhs.gov.**

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Acknowledgments

The research team would like to acknowledge the efforts of Maxine A.Gere, M.S., for general editorial assistance and program support; Carol Gold-Boyd for administrative support; Mark D. Grant, M.D., M.P.H., and Thomas A. Ratko, Ph.D., for fact-checking; Tracey Perez, R.N., J.D., for program support; and William F. Lawrence, M.D., M.S., of the Agency for Healthcare Research and Quality for advice as our Task Order Officer.

Structured Abstract

Objectives: This is a systematic review of evidence on issues in managing small cell lung cancer (SCLC). Key questions addressed are: the sequence, timing and dosing characteristics of primary thoracic radiotherapy (TRTx) for limited-stage disease; primary TRTx for extensive-stage disease; effect of prophylactic cranial irradiation (PCI); positron emission tomography (PET) for staging; treatment of mixed histology tumors; surgery; and second- and subsequent-line treatment for relapsed/progressive disease.

Data Sources: MEDLINE®, EMBASE, and the Cochrane Register

Review Methods: The review methods were defined prospectively in a written protocol. We sought randomized controlled trials that compared the interventions of interest. Where randomized trials were limited or nonexistent, we sought additional studies. We performed meta-analysis of studies that compared early and late TRTx.

Results: The strongest evidence available for this Report is a patient-level meta-analysis showing that PCI improves survival of SCLC patients who achieved complete response following primary therapy from 15.3 percent to 20.7 percent ($p=0.01$). No other question yielded evidence so robust. The case for concurrent over sequential radiation delivery rests largely on a single multicenter trial. Support for early concurrent therapy comes from one multicenter trial, but two other multicenter trials found no advantage. Our meta-analysis did not find significant reductions in 2- and 3-year mortality for early TRTx. Favorable results from a single-center trial on TRTx for extensive stage disease need replication in a multicenter setting. For other questions (i.e., management of mixed histology disease; surgery for early limited SCLC), relevant comparative studies were nonexistent. PET may be more sensitive in detecting disease outside the brain than conventional staging modalities, but studies were of poor quality and reliable estimates of performance are not possible.

Conclusions: PCI improves survival among those with a complete response to primary therapy. A research agenda is needed to optimize the effectiveness of TRTx and its components. PET for staging may be useful, but its role awaits clarification by rigorous studies. No relevant evidence was available to address management of mixed histology disease or surgery for early limited SCLC.

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http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf

Executive Summary

Introduction

Small-cell lung cancer (SCLC) accounts for 13–20 percent of the 172,570 new cases and 163,510 deaths from lung cancer expected in the U.S. in 2005 (American Cancer Society, 2005; Murren, Glatstein, and Pass, 2001; Simon and Wagner, 2003; Physicians Data Query 2005; Chua, Steer, and Yip, 2004; Ettinger, 2004; Stupp, Monnerat, Turrisi, et al., 2004). Untreated SCLC is aggressive, with a median survival of 2 to 4 months after diagnosis (Physicians Data Query, 2005).

The American College of Chest Physicians (ACCP), nominated SCLC as a topic for an evidence report to support updating of its 2003 guideline. Consultation with technical experts, some nominated by ACCP, identified nine key issues in need of systematic review:

1. For limited-stage SCLC, what are the relative benefits and harms (survival, toxicity, and quality of life) of thoracic radiotherapy (TRTx) combined with chemotherapy either in alternating fashion, concurrently or sequentially?

2. For limited-stage SCLC, do outcomes (survival, toxicity, or quality of life) differ if concurrent TRTx is given in early versus late chemotherapy cycles?

3. For limited-stage SCLC, do outcomes (survival, toxicity, quality of life) of primary therapy differ if one varies dose rate, treatment interval, or fractionation scheme for delivering TRTx? Comparisons of interest include:

    - accelerated regimens (>10 Gy per week completed over a short interval) versus standard duration regimens (<10 Gy per week) versus split courses delivered over the standard interval; and

    - single daily fractions versus hyperfractionated (two or more daily fractions or concomitant boost).

4. What are the relative benefits and harms (survival, toxicity, and quality of life) of adding TRTx to chemotherapy for primary treatment of extensive-stage SCLC?

5. What are the benefits and harms (survival, toxicity and quality of life) of prophylactic cranial irradiation (PCI)?

6. Does the addition of positron emission tomography (PET) scanning improve the accuracy of staging for patients diagnosed with SCLC, over the use of other techniques, including computed tomography (CT) and magnetic resonance imaging (MRI), without PET?

7. What are the outcomes (survival, toxicity and quality of life) of treatments used to manage patients with mixed small cell/non-small cell lung cancers?

8. What is the role of surgery and what is its impact on survival in patients with early stage SCLC? How do available studies define early stage SCLC?

9. What are the outcomes of second- or subsequent-line therapy in patients with relapsed or progressive SCLC? Where available data permit, patients with limited- and extensive-stage disease will be addressed separately, as will those with refractory disease (relapse or progression within 3 months of primary treatment).

Methods

The review methods were defined prospectively in a written protocol. A technical expert group provided consultation. The draft report was also reviewed by other experts and stakeholders.

Primary outcomes include: duration of survival, disease- or progression-free survival; quality of life; brain metastasis; and adverse events. Secondary outcomes include: response rates; response duration; and recurrence. For key question 6 (PET staging) additional outcomes are diagnostic accuracy and changes in patient management.

Electronic database searches of MEDLINE (through 12/21/04), EMBASE (through 3/04/05), and the Cochrane Controlled Trials Register (through 3/11/05).were conducted. The search was not limited to English language, but foreign-language references without abstracts were excluded. Relevant conference proceedings were searched electronically.

We sought randomized, controlled trials (RCTs) that compared the interventions of interest. Where randomized trials were limited or nonexistent, we sought additional studies. For question 8 (surgery), we also sought nonrandomized comparative trials, prospective or retrospective. For question 9 (second- or subsequent line therapy), we also sought phase II multicenter studies reporting on at least 25 patients. For question 6 (PET staging), we sought single-arm trials that permitted computation of specificity and sensitivity in relation to an appropriate reference standard.

A single reviewer screened titles and abstracts for full-text retrieval; citations marked as uncertain were reviewed by a second reviewer. Review of full-text articles was conducted in the same fashion to determine inclusion in the systematic review. One reviewer performed primary data abstraction and a second reviewer reviewed the evidence tables for accuracy. All disagreements were resolved by consensus.

The general approach to assessing quality of evidence from studies of therapeutic interventions developed by the U.S. Preventive Services Task Force (Harris, Helfand, Woolf, et al., 2001) was applied. For diagnostic studies, we used the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool.

We performed meta-analysis that combined studies included in key questions 1 and 2. The metrics were 2-year and 3-year mortality relative risks (RRs). Publication bias was tested using Egger's linear regression (Egger, Davey Smith, Schneider, et al., 1997). A standard test for heterogeneity, the Q statistic, was used (Cochran, 1954). If significant, the combined RR point

estimate was computed with a random effects (RE) model (DerSimonian and Laird, 1986). If not, a fixed effects (FE) model would be used (Cochran, 1937). Pooled estimates of treatment effects were derived using the inverse variance-weighted method (Cochran, 1937). Subgroup/sensitivity analyses were performed for earliest initiation of TRTx, hyperfractionation; platinum chemotherapy; concurrent TRTx; and study quality. Analyses were performed using STATA 9.0 and Microsoft Excel 2002.

Results

1. For limited-stage SCLC, what are the relative benefits and harms of TRTx combined with chemotherapy either in alternating fashion, concurrently, or sequentially?

One multicenter trial and one single-center trial (n=307) compared concurrent and sequential TRTx. Results are not conclusive but suggest better outcomes for concurrent TRTx. Overall survival adjusted for confounders significantly favored concurrent TRTx in the Takada, Fukuoka, Kawahara, et al. trial (2002; n=228), although unadjusted results were not significant. Additionally, the Park, Kim, Jeong, et al. (1996) trial found significantly longer response duration for concurrent TRTx. Of 11 types of adverse events reported, only leukopenia occurred significantly more frequently in the concurrent TRTx group in both studies.

No conclusions could be drawn on alternating TRTx. No significant differences in overall or progression-free survival were found in any of four trials: two (n=458) comparisons to sequential TRTx; one (n=156) comparison concurrent TRTx; and one (n=199) comparison of early and late alternating TRTx.

2. For limited-stage SCLC, do outcomes differ if concurrent TRTx is given in early versus late chemotherapy cycles?

The evidence is equivocal, finding no difference or small advantage for early concurrent TRTx. One large multicenter trial of good quality significantly favored concurrent therapy given in an early cycle (Murray, Coy, Pater, et al., 1993/Coy, Hodson, Murray, et al., 1994/Feld, Payne, Hodson, et al., 1988), as did 2 smaller trials. Of the two large multicenter trials that found no significant difference in survival, one did not use platinum chemotherapy (Perry, Eaton, Propert, et al., 1987/Ahles, Silberfarb, Rundle, et al., 1994/Perry, Herndon, Eaton, et al., 1988) and the other is published only in abstract (James, Spiro, O'Donnell, et al., 2003). Leukopenia/neutropenia appeared to be more common with early TRTx.

Meta-analysis was performed in an attempt to obtain clearer results. Studies selected for Key Questions 1 and 2 were viewed as comparing early and late TRTx, and were pooled to give a more robust analysis. We did not find statistically significant reductions in 2- and 3-year mortality for early TRTx over late TRTx. The relative risk (RR) at 2 years was 0.921 (95 percent CI: 0.844–1.005) and the RR at 3 years was 0.991 (95 percent CI: 0.955–1.029).

3. For limited-stage SCLC, do outcomes (survival, toxicity, quality of life) of primary therapy differ if one varies dose rate, treatment interval, or fractionation scheme for delivering TRTx?

Evidence to compare dose rates, treatment intervals, or fractionation schemes is limited. Two RCTs compared one versus two fractions a day for previously untreated SCLC. One compared an accelerated regimen versus the standard duration, while the other compared a split-course regimen versus the standard duration.

Compared to a single daily fraction, two daily fractions delivered concurrently with platinum chemotherapy improved overall survival (23 vs. 19 months, log rank p=0.04) in a large multicenter trial of good quality (Turrisi, Kim, Blum, et al., 1999/Yuen, Zou, Turrisi, et al., 2000; n=417). The second trial is difficult to interpret, since multiple variables were studied simultaneously (Schild, Bonner, Shanahan, et al., 2004/Sloan, Bonner, Hillman, et al., 2002/Bonner, Sloan, Shanahan, et al., 1999; n=161), but there was no difference in survival with one versus two fractions per day.

Esophagitis was more frequent with two fractions daily.

4. What are the relative benefits and harms (survival, toxicity, and quality of life) of adding thoracic radiation therapy to chemotherapy for primary treatment of extensive-stage SCLC?

One single-center RCT (Jeremic, Shibamoto, Nikolic, et al., 1999; 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 suggest little to no benefit for other patients. Grades 3/4 esophagitis were more common with TRTx.

5. What are the benefits and harms (survival, toxicity and quality of life) of prophylactic cranial irradiation?

An individual patient data meta-analysis on seven RCTs (N=987) conducted by the Cochrane PCI Overview Collaborative Group shows that PCI improves survival of SCLC patients in CR after primary therapy. PCI increases 3-year survival from 15.3 percent to 20.7 percent (p=0.01), an absolute increase of 5.4 percent. PCI also significantly decreases the risk for brain metastasis and increases the likelihood of disease-free survival. The sole trial reported after the meta-analysis generally agrees with these findings.

Subgroup analyses showed that PCI significantly decreases brain metastases for SCLC patients in CR regardless of age, disease stage or performance status at diagnosis, and whether or not TRTx is part of the induction regimen. Survival benefit does not appear to differ among subgroups.

Additional subgroup analyses suggested that increasing the PCI dose from 8 to 40 Gy and starting PCI within the first 6 months after achieving complete response may reduce the likelihood of brain metastases. However, these hypotheses, derived from subgroup analyses, require formal testing in RCTs.

Although data are scant, acute toxicities of PCI seem tolerable at the doses used in these

trials (8–40 Gy in 1.8 to 3 Gy fractions) and neurocognitive deficits no greater than existed prior to PCI.

6. Does the addition of PET scanning improve the accuracy of staging for patients with SCLC over the use of other techniques, including CT and MRI, without PET?

The evidence is limited and of poor quality, thus no conclusions can be drawn. Six studies (N=277) suggest that, except for brain metastases, PET added to conventional staging is more sensitive in detecting disease. However, there is so much uncertainty about the execution and interpretation of the reference standard in all of these studies that confidence is quite low in estimates of diagnostic and staging accuracy. The frequency of incorrect changes in stage attributable to PET is unknown due to incomplete reporting.

7. What are the outcomes (survival, toxicity and quality of life) of treatments used to manage patients with mixed small cell/non-small cell lung cancers?

There are few studies of any design that included patients with mixed histology. No conclusions can be drawn from the available evidence.

8. What is the role of surgery and what is its impact on survival in patients with early stage SCLC? How do available studies define early stage SCLC?

We sought studies that compared surgery to no surgery in patients with very early limited SCLC, defined as no preoperative evidence of involved nodes (clinically N0). Two randomized controlled trials and 8 nonrandomized comparative studies were reviewed. None studied a homogeneous group of patients with respect to nodal status; nor were separate outcomes reported for a subgroup of patients without evidence of nodal involvement. Thus no conclusion can be drawn.

9. What are the outcomes of second- or subsequent-line therapy in patients with relapsed or progressive SCLC?

Nine RCTs address second- or subsequent-line treatment of SCLC, each of which compared different sets of chemotherapy regimens. Two randomized trials directly compared chemotherapy with best supportive care for recurrent SCLC. The first studied second-line methotrexate plus doxorubicin and found an overall response rate of 23 percent for the chemotherapy arm. The second reported that oral topotecan resulted in a statistically significant increase in survival (26 weeks vs. 14 weeks) and slower decline in quality of life. High-grade neutropenia occurred in one-third of patients. Another trial compared oral versus intravenous topotecan; leukopenia and neutropenia were more frequent with the intravenous route, but survival and response were no greater. Other RCTs found higher rates of adverse events for one treatment over another, but no associated survival advantage that would offset increased high grade toxicity.

Five multicenter phase II trials of note published since 2000 have reported overall response rates of 20 percent or more. Only one study, using topotecan plus cisplatin, enrolled more than 50 patients. Approximately one-fourth of both sensitive and refractory patients responded.

Three-quarters or more of both patient groups had high-grade leukopenia and neutropenia. A small study of irinotecan plus cisplatin found very high rates of partial response and low hematologic toxicity. The combination of paclitaxel, ifosfamide, and cisplatin achieved a high overall response rate and high-grade leukopenia in nearly all patients. One-quarter of those given paclitaxel plus carboplatin had a response and about half had high-grade neutropenia. In a study of doxorubicin plus carboplatin, nearly half of patients responded; however, 4 out of 5 had grade 3 or 4 granulocytopenia.

Discussion and Future Research

The strongest evidence available for this report is a patient-level meta-analysis showing that PCI improves survival of SCLC patients who achieved CR following primary therapy. No other question yielded evidence so robust. Our conclusions typically relied on a single trial showing treatment effects that were modest at best, and sometimes equivocal. This was apparent in our review of evidence for the sequence, timing, dosing and fractionation of TRTx. For example, the case for concurrent over sequential delivery rests largely on a single multicenter trial (Takada, Fukuoka, Kawahara, et al., 2002). Support for early concurrent therapy comes from the multicenter trial by Murray-Coy-Field (Murray, Coy, Pater, et al., 1993/Coy, Hodson, Murray, et al., 1994/Feld, Payne, Hodson, et al., 1988); however, two other multicenter trials, (Perry, Eaton, Propert, et al., 1987/Ahles, Silberfarb, Rundle, et al., 1994/Perry, Herndon, Eaton, et al., 1988; James, Spiro, O'Donnell, et al., 2003 [abstract]) found no advantage. However, the meta-analysis of 11 studies did not find significant reductions in 2- and 3-year mortality for early TRTx. For some questions (i.e., management of mixed histology disease; surgery for early limited SCLC) comparative trials were nonexistent.

Results reported by Jeremic, Shibamoto, Nikolic, et al., (1999) on TRTx for extensive-stage disease, need replication in a multicenter setting.

PET may be more sensitive in detecting disease outside the brain than conventional staging modalities. Future studies should fully report the frequency of correct and incorrect staging changes when PET is added to conventional tests and should link diagnostic performance to outcomes such as improvement in survival or reduced morbidity. Studies should be conducted according to standards described by the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) and reported according to the Standards for Reporting of Diagnostic Accuracy (STARD) statement.

Complicating the evaluation of SCLC treatment are overall poor outcomes and small effect sizes, necessitating large numbers of patients in trials. Furthermore, interventions are multimodal with a multiplicity of variables that might contribute to the effectiveness.

Trials that are poorly designed, conducted, or reported waste limited resources. To advance clinical knowledge and practice, the field should adhere to standards of research quality and set an agenda for research priorities. Given modest gains in survival, quality of life assessment should be integral to clinical trials and should adhere to recommended research methods, including handling of missing data.

Conclusions

PCI improves survival among those with a complete response to primary therapy. A research agenda is needed to optimize the effectiveness of TRTx and its components. PET for staging may be useful, but its role awaits clarification by rigorous studies. No relevant evidence was available to address management of mixed histology disease or surgery for early limited SCLC.

Chapter 1. Introduction

This systematic review summarizes and analyzes evidence on selected aspects of managing patients diagnosed with small cell lung cancer (SCLC). This section outlines the review's clinical scope, highlights relevant aspects of the disease's epidemiology and public health impact, describes briefly current treatment guidelines and uncertainties, and overviews key questions to be addressed.

Objective of Systematic Review

The American College of Chest Physicians (ACCP) is preparing to update its 2003 evidence-based guideline on diagnosis and management of lung cancer. To support this effort, the ACCP nominated SCLC as a topic for systematic review by one of the Agency for Healthcare Research and Quality's (AHRQ) Evidence-based Practice Centers (EPC). Consultation with technical experts, some nominated by ACCP, identified key issues in need of systematic review.

Epidemiology and Public Health Impact of Small Cell Lung Cancer

Small cell lung cancer (SCLC) accounts for 13–20 percent of the estimated 172,570 new cases and 163,510 deaths from lung cancer expected in the U.S. in 2005 (American Cancer Society, 2005; Murren, Glatstein, and Pass 2001; Simon and Wagner, 2003; Physicians Data Query 2005; Chua, Steer, and Yip, 2004; Ettinger 2004; Stupp, Monnerat, Turrisi, et al., 2004). Untreated SCLC has the most aggressive clinical course of any lung tumor, with a median survival of only 2 to 4 months after diagnosis (Physicians Data Query, 2005). Since it metastasizes rapidly, SCLC is present outside the hemithorax of origin in most patients at diagnosis (Physicians Data Query, 2005).

Current Staging and Treatment Strategies for Small Cell Lung Cancer

Staging and Classification

SCLC is also known as "oat cell" carcinoma or small cell undifferentiated carcinoma (American Cancer Society, 2004). SCLC can be subtyped according to cellular classification as 1) small cell carcinoma; 2) mixed small cell/large cell carcinoma; or 3) combined small cell

carcinoma (i.e., small cell lung cancer combined with neoplastic squamous and/or glandular components) (Physician Data Query, 2005).

Although the TNM classification scheme used for non-SCLC is applicable to SCLC staging (Cameron and Schwartz, 2005), most clinicians use a simplified two-stage scheme developed by the Veterans Administration Lung Cancer Study Group (Simon and Wagner, 2003; Physician Data Query, 2005). Limited-stage SCLC (approximately 30 percent of patients at diagnosis) includes those with tumor confined to the hemithorax of origin, the mediastinum, or the supraclavicular lymph nodes (Simon and Wagner, 2003; Physicians Data Query, 2005). In extensive-stage SCLC, tumor has spread outside these limits; patients with distant metastases are always considered to have extensive disease (Physician Data Query, 2005). At the time of diagnosis, 60–65 percent of SCLC patients have extensive disease (Osterlind, 2001). Estimates of median survival with current therapies are 16–24 months for those with limited-stage disease, and 6–12 months for those with extensive-stage disease (Physician Data Query, 2005).

Diagnostic procedures commonly used to establish the presence of distant metastases include bone marrow aspiration, brain scans using computed tomography (CT) or magnetic resonance imaging, chest and abdomen scans using CT, and radionuclide bone scans (Physician Data Query, 2005; Murren, Turrisi, and Pass, 2005). Whether positron emission tomography (PET) metabolic scanning using 18-fluorodeoxyglucose (18-FDG) provides any additional information to current staging techniques is uncertain (Murren, Turrisi, and Pass, 2005; Simon and Wagner, 2003).

Treatment Strategies

Treatments for SCLC are selected by stage and other features of disease extent (Physician Data Query, 2005). Few patients with extensive SCLC currently attain long-term survival. Their survival at 2 years after diagnosis is approximately 5 percent and at 5 years is less than 1 percent (Murren, Turrisi, and Pass, 2005).

Over time, there has been better success in the management of patients with limited disease. The proportion of long-term survivors among these patients has doubled from the 1970s to the 1990s (Janne, Freidlin, Saxman, et al., 2002; Murren, Turrisi, and Pass, 2005). While this may be due in part to stage migration, it is probably more associated with the change in practice of using platinum-based, rather than cyclophosphamide-based, combination chemotherapy regimens (Murren, Turrisi, and Pass, 2005). Attempts to improve on those results, either by adding a third drug or by substituting newer drugs have not yielded more long-term survivors thus far. It appears that further improvement requires both more and more complete responses to primary therapy (i.e., chemotherapy and radiation). Absent that, other interventions seem to largely alter the pattern of relapse, but not overall survival.

Chemotherapy. Chemotherapy is used for most patients, either as adjuvant therapy for the few patients eligible for surgery, or as primary therapy for patients with inoperable tumors. Preferred regimens have evolved over time (Murren, Turrisi, and Pass, 2005). Current guidelines recommend platinum-etoposide combinations in patients with limited-stage disease and platinum-based regimens in patients with extensive-stage disease (Simon and Wagner, 2003; Osterlind, 2001). According to the 2003 ACCP guidelines, there is no evidence on the benefit of maintenance chemotherapy in any patient achieving a partial or complete remission, and maintenance therapy is not recommended outside of a clinical trial (Simon and Wagner, 2003).

Surgery. Surgery is usually limited to patients with smaller tumors (T1 or T2) and no evidence of nodal involvement or spread outside the hemithorax of origin (Physician Data Query, 2005). Whether surgery added to chemotherapy for patients with limited-stage disease improves survival is currently uncertain.

Thoracic Radiotherapy. Meta-analyses published in the 1990s demonstrated the benefit of adding thoracic radiotherapy (TRTx) to chemotherapy in patients with limited-stage disease (Warde and Pignon, 1992; Pignon, Arrigada, Ihde, et al., 1992). Addition of TRTx to chemotherapy increased 2- to 3-year overall survival by an absolute 5.4 percent over chemotherapy alone (Warde and Payne, 1992; Pignon, Arrigada, Ihde, et al., 1992; Carney, 1999). Addition of TRTx to chemotherapy in patients with limited-stage SCLC is now the recommended course of therapy (Simon and Wagner, 2003). However, uncertainties remain with respect to optimal timing, sequencing, and radiation regimens (i.e., dosages and fractionation schemes) (Turrisi, 1994; Osterlind, 2001). Table 1 summarizes factors that might influence how chemotherapy and radiation may interact when used for primary treatment of limited stage SCLC.

Meta-analyses using different study inclusion criteria have addressed the timing of TRTx given with chemotherapy for limited-stage SCLC. Cancer Care Ontario (2003) included 5-year survival data for 4 studies involving 777 patients, finding no difference between early and late TRTx. Huncharek and McGarry compared the impact of early (i.e., given with the first or second course of systemic therapy) versus delayed (i.e., with the final courses) TRTx in patents with limited disease (Huncharek and McGarry, 2004). The analysis pooled data from 8 randomized, controlled trials enrolling over 1,500 patients and found that early, concurrent TRTx (i.e., administered during the same time period as chemotherapy) improved 1, 2, and 3-year overall survival relative to delayed TRTx, and that TRTx with etoposide/cisplatin regimens performed better compared with non-etoposide/cisplatin regimens. This meta-analysis was flawed by double-counting data from one study (i.e., Goto, Nishiwaki, Takada, et al. 1999 and Takada, Fukuoka, Kawahara, et al., 2002).

A meta-analysis by the Cochrane Collaboration (Pijls-Johannesma, De Ruysscher, Lambin, et al. 2004), included 7 studies, 6 of which overlapped with those in the Huncharek and McGarry meta-analysis, and found that the 2–3 year survival difference as a function of timing was less certain. The Cochrane meta-analysis identified patient selection issues and differences in systemic regimens as potential confounders. Fried, Morris, Poole, et al. (2004) included 7 studies with 1,500 patients and found that 2-year survival was significantly improved by early TRTx, but the pooled result was not significant at 3 years. Two-year subgroup analysis showed that using hyperfractionation and platinum chemotherapy were associated with significant advantages favoring early TRTx, but significant results were not obtained in studies using conventional fractionation and non-platinum chemotherapy.

The role of radiation therapy in extensive disease is less established than in patients with limited-stage disease (Murren, Turrisi, and Pass, 2005). Several large studies reported in the 1980s by the Southwest Oncology Group (SWOG) and that did not randomize patients to TRTx versus no TRTx, suggested that, although thoracic radiation reduced initial relapse at the primary tumor site, there was no effect on overall survival (Murren, Turrisi, and Pass, 2005; Livingston, Mira, Chen, et al., 1984; Livingston, Schulman, Mira, et al., 1986).

Prophylactic Cranial Irradiation. The frequency of brain metastasis in SCLC patients led to the hypothesis that subclinical metastases are commonly present in the brain at diagnosis. Thus, clinicians often add prophylactic cranial irradiation (PCI), particularly for patients achieving a complete remission (CR) after primary therapy. Without PCI, patients who achieve an extracranial CR have a 50–80 percent actuarial risk of developing CNS metastases within 2–3 years (Simon and Wagner, 2003; Murren, Turrisi, and Pass, 2005; Carney, 1999). In addition, among patients who achieve a CR with chemotherapy, approximately 15 percent have brain metastases as the initial or only manifestation of recurrence (Carney, 1999). A patient-level meta-analysis of almost 1,000 patients in complete remission from 7 randomized, controlled

Summary Table 1. Alternatives for Combined Chemotherapy and Radiation to Treat Limited SCLC

treatment variable	alternatives	known or possible advantages	known or possible disadvantages
chemotherapy regimen	platinum/etoposide (PE)	most effective regimen in multiple meta-analyses	relapse common despite initial high response rate
	cyclophosphamide- and/or doxorubicin-based (CD)	none known	response rates, survival inferior to PE
	alternating PE/CD	less likely to select PE-resistant cells for survival	uncertain; limits choices for 2nd-line therapy?
	PE + third (newer) drug	less likely to select PE-resistant cells for survival	increased toxicity without evidence of better survival
cumulative radiation dose (once daily fractions)	30 to 40 Gy	less normal tissue toxicity than larger doses	local failure rate ~80%
	>40 to 50 Gy	decreases local failure rate to 30–50%	increases normal tissue toxicity
	>50 to 65 Gy	may increase tumor kill, decrease local failure rate	further increases normal tissue toxicity
radiation target volume	larger volume (includes regional lymphatics)	may reduce regional failure rate	must limit total dose to avoid toxicity
	smaller volume (limited to involved fields)	smaller target permits larger dose; may decrease failure, yet avoid toxicity	tumor cells beyond target may survive, leading to relapse and progression
fraction size	>2 Gy per fraction	increases tumor cell kill per fraction	increases normal tissue acute and late toxicities
	≤2 Gy per fraction	permits delivering larger total dose in standard time without excess toxicity	reduces tumor cell kill per fraction
frequency of fractions	once daily	more convenient (patients) and efficient (facilities)	permits tumor cell repair (normal cells faster)
	hyperfractionation (≥2/day)	permits accelerated radiotherapy with equal or less toxicity	less convenient (patients) and efficient (facilities)
duration of radiation therapy	standard schedule: 4–6 weeks (≤10 Gy/week)	less risk for acute and late toxicity to normal tissues	radiation-resistant tumor cell clone may emerge
	accelerated schedule: ≤3 weeks (>10 Gy/week)	more effective for fast-growing tumors (e.g., SCLC); also permits dose escalation	may increase risk of acute and late toxicities
sequence of chemotherapy and radiation therapy	sequential	smaller radiation target if tumor shrinks; fewer radiation-resistant hypoxic tumor cells	sacrifices potential drug-radiation synergy
	concurrent	potential for synergy if one modality sensitizes cells to other's effects	may also synergize damage to normal cells (esophagus, bone marrow)
	alternating or split course	permits recovery from acute toxicity	permits tumor cells to repopulate
radiation timing relative to chemotherapy course	early cycles	less survival of chemotherapy resistant tumor cells	more hematopoietic toxicity
	late cycles	less hematopoietic toxicity	chemotherapy-resistant tumor cells may emerge

trials showed the addition of PCI can reduce the risk of CNS metastases by over half and significantly improves survival (Auperin, Arriagada, Pignon, et al. 1999; Prophylactic Cranial Irradiation Overview Collaborative Group, 2000; Carney, 1999).

Definitive recommendations regarding optimal timing of PCI and radiation dosage issues (e.g., optimizing dose to balance efficacy and toxicity, fractionation) still require additional study (Prophylactic Cranial Irradiation Overview Collaborative Group, 2000; Boher and Wenz, 2002). According to one of the PCI meta-analyses, "Establishing the optimal dose and timing of treatment so as to reduce further the incidence of brain metastases with minimal and acceptable toxicity should be the aim of future clinical trials" (Prophylactic Cranial Irradiation Overview Collaborative Group, 2000).

Data on the adverse effects of PCI, both acute (e.g., skin burns, headaches) and late-developing (e.g., neurocognitive impairment, overt cerebral necrosis) are also not well characterized from analyses of controlled trials (Boher and Wenz, 2002). Although many retrospective studies describe an association between PCI and neurotoxicity, evidence from prospective, controlled trials does not appear to support that association (Bohrer and Wenz, 2002).

Second-Line Therapy. Most patients respond to primary therapy, but relapse after remissions of varying duration (Murren, Turrisi, and Pass, 2005). Second-line therapy is offered to most patients if the first remission has lasted 3–6 months; relapse after 3 months or more is also known as "sensitive relapse" (Murren, Turrisi, and Pass, 2005). Evidence of benefit is lacking from second-line therapy for refractory SCLC (i.e., no remission after primary therapy). Response to second-line therapy appears to be related to the chemotherapy agents given in both the induction and second-line regimens (Murren, Turrisi, and Pass, 2005). It is also unknown whether third or subsequent lines of therapy for relapsed or progressive SCLC improve outcomes compared with best supportive care.

Key Questions for this Systematic Review

As stated previously, consultation with experts has identified critical concerns deserving of inquiry to support the ACCP update to guidelines on the diagnosis and management of lung cancer. Thus, this systematic review of the literature will address the following questions regarding managing patients with small cell lung cancer:

1. For limited-stage SCLC, what are the relative benefits and harms (survival, toxicity, and quality of life) of TRTx combined with chemotherapy either in alternating fashion, concurrently or sequentially?

2. For limited-stage SCLC, do outcomes (survival, toxicity, or quality of life) differ if concurrent TRTx is given in early versus late chemotherapy cycles?

3. For limited-stage SCLC, do outcomes (survival, toxicity, quality of life) of primary therapy differ if one varies dose rate, treatment interval, or fractionation scheme for delivering TRTx? Comparisons of interest include:

- accelerated regimens (>10 Gy per week completed over a short interval) versus standard duration regimens (<10 Gy per week) versus split courses delivered over the standard interval; and

- single daily fractions versus hyperfractionated (two or more daily fractions or concomitant boost).

4. What are the relative benefits and harms (survival, toxicity, and quality of life) of adding TRTx to chemotherapy for primary treatment of extensive-stage SCLC?

5. What are the benefits and harms (survival, toxicity and quality of life) of prophylactic cranial irradiation (PCI)?

6. Does the addition of PET scanning improve the accuracy of staging for patients diagnosed with SCLC, over the use of other techniques, including CT and MRI, without PET?

7. What are the outcomes (survival, toxicity and quality of life) of treatments used to manage patients with mixed small cell/non-small cell lung cancers?

8. What is the role of surgery and what is its impact on survival in patients with early stage SCLC? How do available studies define early stage SCLC?

9. What are the outcomes of second- or subsequent-line therapy in patients with relapsed or progressive SCLC? Where available data permit, patients with limited- and extensive-stage disease will be addressed separately, as will those with refractory disease (relapse or progression within 3 months of primary treatment).

Chapter 2. Methods

The objective of this Evidence Report is to systematically review and synthesize available evidence on managing patients diagnosed with small cell lung cancer (SCLC). The Key Questions addressed here were proposed by the American College of Chest Physicians, the partner organization for this evidence report and were refined after consultation with experts.

Peer Review

A technical expert group provided consultation for the systematic review. The draft report was reviewed by 10 external reviewers, including members of the technical expert group, the Task Order Officer, other invited technical experts, and stakeholders (Appendix E).* Revisions were made to the draft report based on reviewers' comments.

Study Selection Criteria

Types of Studies

All questions, except Question 6, addressed therapeutic interventions. We sought randomized, controlled trials that compared the interventions of interest. No minimum number of patients per study arm was required for randomized, controlled trials. Because there were few randomized, controlled trials available to address Questions 8 and 9, we sought additional studies. For Question 8 (surgery), we also sought nonrandomized comparative trials, both prospective and retrospective in design. For Question 9 (second- or subsequent-line therapy), we also sought phase II multicenter trials reporting on at least 25 patients.

Question 6 (PET for staging) addresses a diagnostic intervention. Although we sought randomized, controlled trials comparing the outcomes of SCLC patients staged with and without use of PET, no such studies were identified. We then sought prospective, single-arm trials that reported on at least 25 patients undergoing imaging to stage SCLC; correlated 18-fluorodeoxyyglucose (FDG) PET findings with findings from other imaging modalities and an appropriate reference standard; and permitted computation of sensitivity and specificity.

Our search and selection criteria included English-language studies, as well as foreign-language studies that had an English-language abstract.

Studies were excluded if no outcome of interest to this review was reported. Studies were also excluded if the patient population of interest was fewer than 80 percent of included patients, or, alternatively, results for the patient population of interest were not separately reported. When

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf

multiple reports were available for the same study, it was counted as a single trial and outcome data from the report with the longest follow-up were used.

Types of Participants

- Key Questions 1–3 (First-line chemotherapy with thoracic radiotherapy [TRTx]) — patients with a histopathologically confirmed diagnosis of SCLC staged as limited disease.

- Key Question 4 (thoracic radiation therapy) — Patients with a histopathologically confirmed diagnosis of SCLC staged as extensive disease undergoing first-line therapy.

- Key Question 5 (prophylactic cranial irradiation) — Patients with a histopathologically confirmed diagnosis of SCLC that has completely responded to primary therapy (regardless of stage).

- Key Question 6 (PET staging) — Patients with a histopathologically confirmed diagnosis of SCLC.

- Key Question 7 (management mixed disease) — Patients with a histopathologically confirmed diagnosis of mixed small cell/non-small cell lung cancer.

- Key Question 8 (surgery) — Patients with a histopathologically confirmed diagnosis of SCLC staged as limited disease with small tumors and no nodal involvement

- Key Question 9 (second- or subsequent-line therapy) — Patients with a histopathologically confirmed diagnosis of SCLC that either relapsed or progressed after a response that lasted at least 3 months following primary therapy for: (a) limited-stage or (b) extensive-stage disease; or (c) patients with refractory disease (defined as no response or progression within 3 months of primary therapy).

Types of Interventions

- **Key Question 1** — Comparison of chemotherapy combined with sequential TRTx, chemotherapy combined with concurrent TRTx and chemotherapy combined with alternating TRTx.

- **Key Question 2** — Chemotherapy combined with concurrent TRTx initiated early cycles (i.e., 1 or 2) versus chemotherapy combined with concurrent TRTx initiated in late cycles (i.e., 3 or later).

- **Key Question 3** — Chemotherapy combined with standard-interval TRTx versus chemotherapy combined with accelerated TRTx: OR chemotherapy combined with split-course TRTx chemotherapy combined with standard-interval TRTx; OR chemotherapy combined with single daily fractions of TRTx; OR chemotherapy combined with hyperfractionated TRTx.

- **Key Question 4** — Chemotherapy combined with TRTx versus chemotherapy alone.

- **Key Question 5** — Prophylactic cranial irradiation (PCI) versus no prophylactic radiation after primary therapy is completed and response is assessed.

- **Key Question 6** — Positron-emission tomography (PET) vs. no PET, added to other staging modalities, including computed tomography (CT) and magnetic resonance imaging (MRI).

- **Key Question 7** — Chemotherapy with or without TRTx delivered in any sequence or schedule used for limited-stage SCLC

- **Key Question 8** — Surgical excision of SCLC tumors, preceded by neoadjuvant chemotherapy or followed by adjuvant chemotherapy, and either with or without TRTx and PCI, versus no surgical excision

- **Key Question 9** — Chemotherapy using drugs approved by the U.S. Food and Drug Administration for at least one indication to treat a malignant disease (various regimens).

Types of Outcomes

Primary (health) outcomes of interest include:

- duration of survival, disease-free survival, and/or progression-free survival
- quality of life
- brain metastasis-free survival and subsequent treatment(s) for brain metastasis
- palliation of measurable symptoms
- treatment-related adverse events
- perioperative adverse events

Secondary (intermediate) outcomes include:

- objective response rates (complete and partial responses; separately and summed)
- response durations
- pathologically complete resection rates
- recurrence rates

For key question 6 (PET staging) additional outcomes of interest are:

- diagnostic accuracy
- outcomes other than diagnostic accuracy, such as staging accuracy, change in stage and impact on management decisions

Search Strategy and Review

Search Strategy

Electronic databases. The following databases were searched for citations. The full search strategy is displayed in Appendix A.* The search was not limited to English-language references, but foreign-language references without abstracts were disregarded.

- MEDLINE® (through 12/21/04)
- EMBASE (through 03/04/05)
- Cochrane Controlled Trials Register (through 03/11/05)

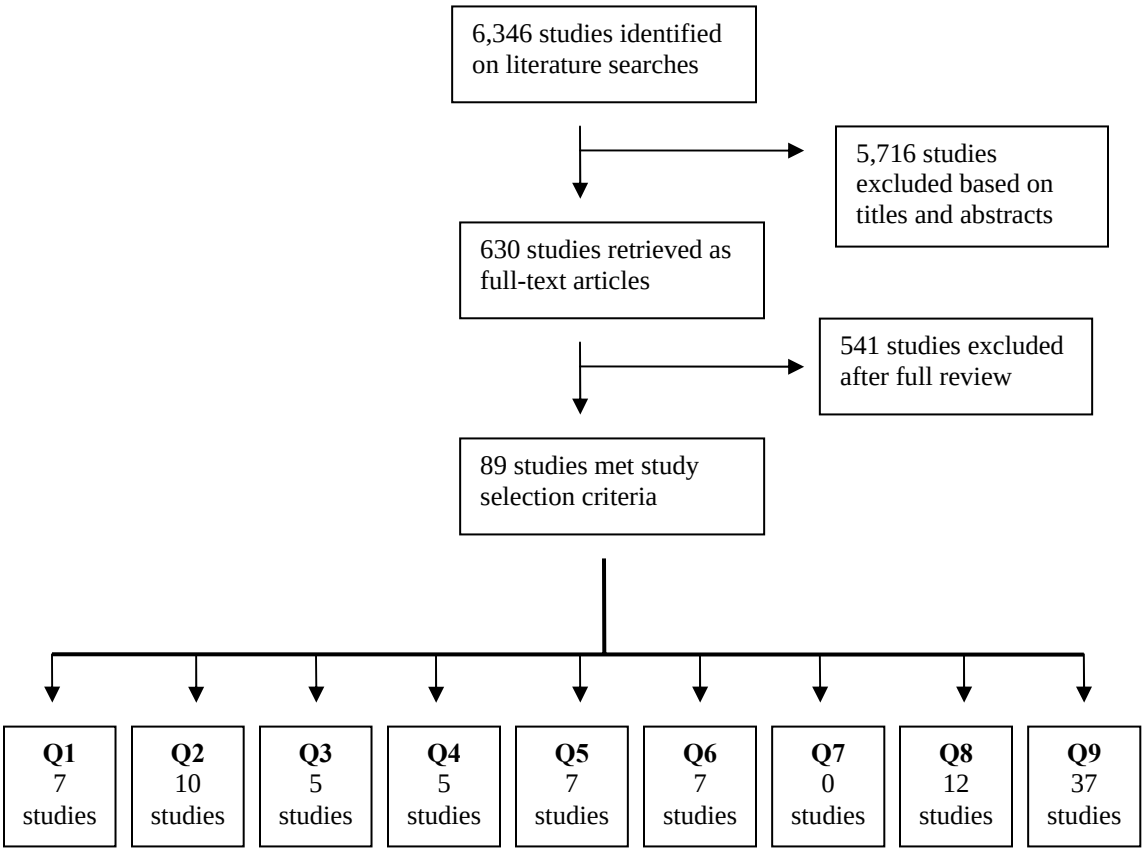
Additional Sources of Evidence. The Technical Expert Panel and individuals and organizations providing peer review were asked to inform the project team of any studies relevant to the key questions that were not included in the draft list of selected studies.

Search Screen

Search results were stored in a ProCite® database. Using the study selection criteria for screening titles and abstracts, a single reviewer marked each citation as either: (1) eligible for review as full-text articles; (2) ineligible for full-text review; or (3) uncertain. Citations marked as uncertain were reviewed by a second reviewer and resolved by consensus opinion, with a third reviewer to be consulted if necessary. Using the final study selection criteria, review of full-text articles was conducted in the same fashion to determine inclusion in the systematic review. A total of 630 references were retrieved at a full-text level; 89 were included in this review (Figure 1). Records of the reason for exclusion for each paper retrieved in full-text, but excluded from the review, were kept in the ProCite® database (see Appendix D, Excluded Studies).

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf.

Figure 1. QUOROM Flow Diagram



Data Extraction and Analysis

Data Elements

The data elements below were abstracted, or recorded as not reported, from therapeutic intervention studies.

- critical features of the study design (for example, patient inclusion/exclusion criteria, number of subjects, use of blinding);
- potential patient characteristic confounders:
  - age
  - gender

    - race
    - extent of disease and stage
    - performance status
    - comorbidities
- treatment protocols (for example, treatment intensity, frequency, duration, other prior and concurrent treatment factors);
- patient monitoring procedures (for example, follow-up duration and frequency, outcome assessment methods); and
- the specified key outcomes and data analysis method (when statistical test results were lacking for adverse events data, reviewers performed tests with the STATMAN statistical program).

The data elements below were abstracted, or recorded as not reported, from diagnostic accuracy studies of imaging modalities used in staging SCLC:

- patient selection criteria
- details about the reference standard (validity and degree of detail in description)
- decision rules for determining which patients received the reference standard
- whether the index test and reference standard were interpreted blind to each other
- whether verification bias (index test results influenced decisions to perform reference standard) was avoided
- details about the index test (degree of detail about performing of test, interpretation)
- study design (prospective, retrospective)
- reporting of diagnostic accuracy results (completeness, appropriate calculation of accuracy measures, use of confidence intervals)
- outcomes other than diagnostic accuracy, such as staging accuracy, change in stage and impact on management decisions

Evidence Tables

Templates for evidence tables were created in Microsoft Excel® and Microsoft Word® Appendix B).* One reviewer performed primary data abstraction of all data elements into the evidence tables, and a second reviewer reviewed the evidence tables for accuracy. Disagreements were resolved by discussion, and if necessary, by consultation with a third reviewer. When small differences occurred in quantitative estimates of data from published figures, the values obtained by the two reviewers were averaged.

Assessment of Study Quality

Therapeutic Studies

The general approach to grading evidence developed by the U.S. Preventive Services Task Force (Harris et al. 2001) was applied. Quality of the abstracted studies was assessed by one reviewer and fact-checked by a second. Discordant quality assessments were resolved by discussion or by consultation with a third reviewer, if necessary. The quality criteria for randomized, controlled trials were as follows:

- Initial assembly of comparable groups: adequate randomization, including concealment and whether potential confounders (e.g., baseline characteristics, other concomitant care) were distributed equally among groups
- Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination)
- Important differential loss to follow-up or overall high loss to follow-up
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- All important outcomes considered
- Analysis: adjustment for potential confounders, intention-to-treat analysis

Diagnostic Studies

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool underwent a rigorous development process by Whiting, Rutjes, Dinnes, et al. (2004) and includes the following items:

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf.

- Was the spectrum of patients representative of the patients who will receive the test in practice?
- Were selection criteria clearly described?
- Is the reference standard likely to classify the target condition correctly?
- Is the period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?
- Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?
- Did patients receive the same reference standard regardless of the index test result?
- Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?
- Was the execution of the index test described in sufficient detail to permit replication of the test?
- Was the execution of the reference standard described in sufficient detail to permit replication of the reference standard?
- Were the index test results interpreted without knowledge of the results of the reference standard?
- Were the reference standard results interpreted without knowledge of the results of the index test?
- Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?
- Were uninterpretable/intermediate test results reported?
- Were withdrawals from the study explained?

Definition of Ratings Based on Criteria

The rating of therapeutic intervention studies encompasses the 3 quality categories described below. No analogous quality categories have been incorporated into the QUADAS tool for assessing diagnostic accuracy studies. Rather, each of the 14 QUADAS items is considered individually.

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, for randomized, controlled trials (RCTs), intention to treat analysis (i.e., all patients randomized were analyzed) is used.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is done for RCTs.

Poor: Studies will be graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention-to-treat analysis is lacking.

Meta-Analysis

Quantitative synthesis of evidence was carried out by combining studies meeting selection criteria for key questions 1 and 2. Eleven such randomized controlled trials (RCTs) could be viewed as comparing early and late thoracic radiotherapy (TRTx) for limited-stage small cell lung cancer (see "Results: Results of Meta-Analysis/Meta-Regression"). This Review defines early TRTx as given in cycles 1 or 2 and late as given in cycle 3 or later and at least 3 weeks after the start of early TRTx. Of the 11 RCTs, all provide 3-year overall survival data and 9 give 2-year data. The metrics used in the meta-analysis were 2-year and 3-year mortality relative risks (RRs). Estimates of survival were multiplied by sample sizes and rounded to the nearest whole number to derive the numbers alive and dead at 2 years and 3 years. While this method has been used in 4 previous meta-analyses on the timing of TRTx for limited SCLC, it does not take into account censoring and therefore may inflate subject counts. Even if a consensus method to incorporate censoring was available, it could not be applied to 6 of 11 studies due to insufficient detail in articles. Our method assures easy comparisons with previous meta-analyses and inclusion of more studies.

Meta-analysis was not worth pursuing for other questions in this Review. For key questions 3, 4, 7, 8, and 9, there was either an inadequate number of studies or excessive heterogeneity of treatments for pooled analysis. Question 5 was the subject of a recent patient-level meta-analysis (Auperin, Arriagada, Pignon, et al. 1999; Prophylactic Cranial Irradiation Overview Collaborative Group, 2000; Carney, 1999) and thus, a meta-analysis was not necessary for this Review. Uncertainty about the reference standard used in studies on question 6 was so great that a meta-analysis could give unwarranted weight to uniformly poor quality studies.

The first step in the meta-analysis was to assess whether publication bias was likely. This was first done visually with funnel plots, in which the trials are sorted along the vertical axis in ascending order of the standard error of the log odds ratio. A formal test for publication was performed using Egger's linear regression (Egger, Davey Smith, Schneider, et al., 1997). Trial standardized effect estimates were fit to precision values (the inverse of the standard error), using least squares and trial's inverse variance as weights. Asymmetry suggestive of publication bias would be indicated by a regression intercept value that significantly deviates from zero.

The next step in the meta-analysis is to determine whether significant heterogeneity of treatment effects exists. A standard test for heterogeneity is the Q statistic (Cochran, 1954). The null hypothesis of homogeneity is rejected below an alpha level of 0.10. If rejected, the combined RR point estimate should be computed with a random effects (RE) model (DerSimonian and Laird, 1986). Where necessary, the between-study variance component (tau squared) was calculated using the algebraic method described by Sutton, Abrams, Jones, et al. (2000). If the null hypothesis of homogeneity is not rejected, a fixed effects (FE) model would be used (Cochran, 1937).

Pooled estimates of treatment effects were derived using the inverse variance-weighted method (Cochran, 1937). Meta-analysis results are presented graphically in forest plots. Subgroup/sensitivity analyses were performed for these variables: whether early TRTx was given at the earliest opportunity; whether hyperfractionation was used; whether platinum was included in chemotherapy (CTx); whether early TRTx was given concurrent with CTx; and whether the trial was rated as being of good quality. Influence analysis was conducted by excluding each trial individually to reveal the impact on effect estimates. Results are presented graphically.

Random effects meta-regression, as described by Berkey, Hoaglin, Mosteller, et al. (1995), was conducted to explore sources of heterogeneity. All covariates are dichotomous variables, the same variables as those in subgroup/sensitivity analyses. Single variables were tested first. Multiple variables were included only as an exercise due to concerns of overfitting. Analyses were carried out using STATA 9.0 and Microsoft Excel 2002.

Chapter 3. Results

Key Question 1

For limited-stage small cell lung cancer (SCLC), what are the relative benefits and harms (survival, toxicity, and quality of life) of thoracic radiotherapy (TRTx) combined with chemotherapy, either in alternating fashion, concurrently or sequentially?

This question concerns how TRTx is given in relation to chemotherapy. Alternating TRTx is administered between chemotherapy cycles. Concurrent TRTx is TRTx given at the same time as chemotherapy. Sequential TRTx is given after completion of chemotherapy.

Overview

As summarized in Summary Table 2, 6 randomized, controlled trials (RCTs) made comparisons of alternating, concurrent and sequential TRTx for limited stage SCLC. Two trials (n=307) compared concurrent and sequential TRTx (Takada, Fukuoka, Kawahara, et al., 2002; Park, Kim, Jeong, et al., 1996). Two trials compared alternating to sequential TRTx (Gregor, Drings, Burghouts, et al., 1997; Sun, Zhang, Yin, et al., 1995; n=458). One trial compared alternating to concurrent TRTx (Lebeau, Urban, Brechot, et al., 1999, n=156). The Work and colleagues trial (Work, Nielsen, Bentzen, et al., 1997/Work, Bentzen, Nielsen, et al., 1996) compared early alternating and late alternating TRTx (n=199). Collectively, the 6 trials randomized 228 patients to concurrent treatment, 337 patients to alternating treatment, and 385 patients to sequential treatment. It is worth noting that these studies were generally small in size and likely underpowered to find small but clinically significant differences in survival.

Study populations and treatment protocols are summarized in Summary Table 3. Additional details are in Appendix Tables 1A–D, 1H.[*] Information in the tables came exclusively from articles except for the Park, Kim, Jeong, et al. (1996) study. Park, Kim, Jeong, et al. (1996) did not report survival probabilities at yearly intervals, so an author was contacted directly and additional data were sought. The data obtained from the author represented a larger patient sample than described in the article.

Concurrent vs. Sequential

Interventions. Two trials compared concurrent and sequential TRTx. Radiation dose in the Takada, Fukuoka, Kawahara, et al. (2002) study was 45 Gy, while it varied between 40 and 50 Gy in the Park, Kim, Jeong, et al. (1996) study. Both studies gave concurrent TRTx in weeks 1-3. Sequential TRTx occurred in weeks 13-15 in the Takada, Fukuoka, Kawahara, et al. (2002) trial and between weeks 19 and 24 in the Park, Kim, Jeong, et al. (1996) study. Takada, Fukuoka, Kawahara, et al. (2002) delivered 2 daily fractions of TRTx in both groups, while Park, Kim, Jeong, et al. (1996) gave it to the concurrent group. Both studies gave prophylactic cranial

[*] Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf

irradiation (PCI). Platinum-based chemotherapy was used by Park, Kim, Jeong, et al. (1996), but not by Takada, Fukuoka, Kawahara, et al. (2002).

Summary Table 2. Overall Summary of Question 1 Trials

Study	Treatment arm	Control arm	Treat-ment n	Control n	Pt?	CTx	TRTx Dose (Gy) #Fracs /d	TRTx Timing		PCI ?	Quality Rating
								Tx	Control		
Takada, Fukuoka, Kawahara, et al., 2002 Multicenter	concurrent	sequential	114	114	yes	PE	45 2/d	wk 1-3	wk 13-15	yes	Good
Park, Kim, Jeong, et al., 1996 Single center	concurrent	sequential	32	47	yes	CAV-CbPE	40-50 2/d,1/d	wk 1-3	wk 19-24	yes	Poor
Sun, Zhang, Yin, et al., 1995 Multicenter	alternating	sequential	64	59	no/ yes	COM E, CE-CAP	30-60 1/d	wk 4-9	wk 13-18	?	Poor
Gregor, Drings, Burghouts, et al., 1997 Multicenter	alternating	sequential	170	165	no	CAE	50 1/d	wk 7,11, 15,19	wk 15-18	?	Good
Lebeau, Urban, Brechot, et al., 1999 Multicenter	alternating	concurrent	74	82	no	CAE-CVE	55/50 1/d	wk 6-7, 10-11, 14-16	wk 5-9	yes	Good
Work, Nielsen, Bentzen, et al. 1997/Work, Bentzen, Nielsen, et al., 1996 Single center	early alternating	late alternating	99	100	yes	CAV-PE	40-45 1/d	wk 1-2, 6-7	wk 18-19, 23-24	yes	Fair

Abbreviations table provided at the end of the Report.

Summary Table 3. Sample and Treatments: Alternating, Concurrent, or Sequential Radiotherapy

Study	n		Age	% Female	% Performance Status				CTx Regimen	RTx Regimen		
Gregor, Drings, Burghouts, et al., 1997 EORTC LCCG Multiple European institutions, 3/89 -1/95	Total	335	md (rng)		0	1	2	3		Dose	Schedule	PCI?
	Seq	165	61 (33-75)	32.1	46.1	47.9	4.2	1.8	CAE	50 Gy	wks 15-18, 20 frac, 1/d, 5/wk	possible if CR
	Alt	170	61 (34-74)	34.1	47.1 ECOG	44.7	5.9	2.4	same	50 Gy	wks 7, 11, 15, 19; 20 frac, 1/d, 5/wk	same
Lebeau, Urban, Brechot, et al., 1999 26 French institutions, 5/88 – 5/94	Total	156	mn		0	1	2-3	NR		Dose	Schedule	PCI?
	Alt	74	58	14.9	50.0	44.6	4.1	1.4	CAE-CVE	55 Gy	wks 6-7, 10-11, 20 Gy, 8 frac, 12 d, wks 14-15, 15 Gy, 6 frac, 10 d	if CR
	Conc	82	57	20.7	51.2 ECOG	46.3	2.4	0.0	same	50 Gy	wks 5-9, 40 Gy, 16 frac, 7 d	same
Takada, Fukuoka, Kawahara, et al., 2002 15 Japanese institutions, 5/91 - 1/95	Total	228	md (rng)		0	1	2			Dose	Schedule	PCI?
	Seq	114	64 (30-74)	18.4	28.9	65.8	5.3		PE	45 Gy	wks 13-15, 30 frac, 2/d, 5/wk	if CR, near-CR
	Conc	114	65 (39-74)	20.2	21.9 ECOG	72.8	5.3		same	45 Gy	wks 1-3, 30 frac, 2/d, 5/wk	sane
Sun, Zhang, Yin, et al., 1995 15 Chinese institutions, 1983 -1989	Total	123								Dose	Schedule	PCI?
	Seq	59							COME, CE-CAP	45-60 Gy 30-45 Gy	Local dis, after 2 CTx cyc, 6 wks MS/SC LNs, 3-4 wks	not specified
	Alt	64							Same	45-60 Gy 30-45 Gy	Local dis, between 2 CTx cyc, 6 wks MS/SC LNs, 3-4 wks	

Abbreviations table provided at the end of the Report.

Summary Table 3. Sample and Treatments: Alternating, Concurrent, or Sequential Radiotherapy (continued)

Study	n		Age	% Female	% Performance Status				CTx Regimen	RTx Regimen		
Work, Nielsen, Bentzen, et al. 1997/Work, Bentzen, Nielsen, et al., 1996 single-center study, 3/81-9/89	Total	199	md (rng)		100	90-80	70-60	50-40		Dose	Schedule	PCI?
	L Alt	100	59 (36-69)	29	10.0	70.0	15.0	5.0	CAPE	40-45 Gy	wks 18-19, 23-24, 1 frac/d	all
	E Alt	99	61 (36-70)	45	13.1 KPS	68.7	14.1	4.0	Same	40-45 Gy	wks 1-2, 6-7, 1 frac/d	same
Park, Kim, Jeong, et al., 1996 Korean Center 5/91 – 5/96	Total	51	mn (sd)		0	1	2			Dose	Schedule	PCI?
	Seq	24	60.6 (8.9)	20.8	25.0	45.8	29.2		CAV-CbPE	40-50 Gy	wks 19-24, 1 frac/d	if CR maintained
	Conc	27	57.5 (8.8)	14.8	14.8	63.0	22.2		Same	45 Gy	wks 1-3, 2 frac/d	same

Populations. Groups were well-balanced on age, gender and performance status in the Takada, Fukuoka, Kawahara, et al. (2002) study (n=228). The sample of 51 patients in the Park, Kim, Jeong, et al. (1996) article was also well-balanced on these characteristics, but the survival data represented 79 patients and no comparison of baseline characteristics is available for all.

Quality and Reporting. The Takada, Fukuoka, Kawahara, et al. (2002) trial was rated as being of good quality. The Park, Kim, Jeong, et al. (1996) study was rated as poor due to insufficient information about assembly and maintenance of comparable groups, in addition to uncertainty about full accounting of subjects in data analysis.

Results. Survival outcomes are shown in Summary Table 4 and adverse events in Summary Table 5. More detailed results are in Appendix Tables 1E-1G.* Both studies showed survival results favoring concurrent TRTx, but were generally not statistically significant. Unadjusted overall survival did not differ significantly between concurrent and sequential TRTx, although p values were nearly significant. Overall median survival favored concurrent therapy by 5.1 months (Park, Kim, Jeong, et al., 1996) and 7.5 months (Takada, Fukuoka, Kawahara, et al., 2002). A Cox proportional hazards model regression found that treatment was a significant predictor of survival, producing a hazard ratio of 0.70 (95 percent confidence interval [CI]: 0.52–0.94) for concurrent relative to sequential TRTx. Takada, Fukuoka, Kawahara, et al. (2002) also reported that median progression-free survival favored the concurrent group by 2 months (p=0.084), but Park, Kim, Jeong, et al. (1996) did not report on progression.

Neither study reported on quality of life, but both reported tumor response data. Both found nonsignificantly higher overall response rates (ORRs) in the concurrent group, although the Park, Kim, Jeong, et al. (1996) study found a fairly large difference in rates that approached significance. In the Takada, Fukuoka, Kawahara, et al., 2002) study, ORRs were 96.5 percent; for concurrent and 92.1 percent for sequential (p=0.25). The complete responses (CRs) were higher in the concurrent group (39.5 percent) than in the sequential group (27.2 percent, p=0.07). In the Park, Kim, Jeong, et al. (1996) trial, the concurrent group achieved an ORR of 88 percent, versus 63 percent for sequential (p=0.13). Mean response duration was longer in the sequential group than in the concurrent group (395 days vs. 180 days, p=0.03).

Among 12 categories of adverse events, 5 were reported by both studies (Summary Table 6). Significant between-group differences were not found in either trial for anemia, thrombocytopenia, infection and fever. Both studies found significantly higher risks of leukopenia for those in the concurrent arm. In the Takada, Fukuoka, Kawahara, et al. (2002) study, grade 3 or 4 leukopenia was seen in 88.4 percent of concurrent-arm patients and in 53.6 percent of sequential-arm patients (p=0.001). The risk of higher grade leukopenia among concurrent TRTx patients in the Park, Kim, Jeong, et al. (1996) study was 51.8 percent, compared with 16.7 percent of sequential TRTx patients (p=0.02). One study reported data on each of 7 adverse events, none of which was marked by significant differences between concurrent and sequential TRTx: treatment-related mortality, nausea/vomiting, esophagitis, renal toxicity; alopecia, arrhythmias, and hepatic toxicity.

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf

Summary Table 4. Survival Outcomes: Alternating, Concurrent and Sequential Radiotherapy

Study	N		OS Md (mo)	1 yr	2 yr	3 yr	4 yr	5 yr	PFS Md (mo)	1 yr	2 yr	3 yr	4 yr	5 yr
Gregor, Drings, Burghouts, et al., 1997	Seq	165	15	64%	23%	15%	~14%	~12%	12	50%	22%	17%	15%	5%
	Alt	170	14	60%	26%	12%	~10%	~4%	10	43%	16%	10%	8%	8%
	Difference:		-1	-4%	3%	-3%	-4%	-8%	-2	-7%	-6%	-7%	-7%	3%
			(CPHM: RR 0.88, 95% CI 0.68-1.1, p=0.237; p=0.288, log-rank)						(Log-rank p=0.07)					
Lebeau, Urban, Brechot, et al., 1999	Alt	74	14.0	63%	17%	11%	6%	6%						
	Conc	82	13.5	54%	13%	6%	4%	4%						
	Difference		-0.5	-9%	-4%	-5%	-2%	-2%						
			(p=0.15, log-rank, 66 Alt deaths, 77 Conc deaths)											
Takada, Fukuoka, Kawahara, et al., 2002	Seq	114	19.7	~80%	35.1%	20.2%	~20%	18.3%	~10	~38%	~19%	~15%	~14%	~14%
	Conc	114	27.2	~80%	54.4%	29.8%	~25%	23.7%	~12	~50%	~28%	~25%	~20%	~17%
	Difference		7.5	0%	19.3%	9.6%	5%	5.4%	2	12%	9%	10%	6%	3%
			(p=0.097 eligible patients, p=0.086 all randomized, log-rank; CPMH: HR 0.70, 95% CI 0.52-0.94, p=0.02)						(p=0.084, log-rank))					
Sun, Zhang, Yin, et al., 1995	Seq	59		64.0%	13.6%	12.0%								
	Alt	64		62.5%	28%	16.0%								
	Difference			-1.5%	14.4%	4%								
Work, Nielsen, Bentzen, et al. 1997/Work, Bentzen, Nielsen, et al., 1996	L Alt	100	12.0	~49%	18.8%	~12%	~12%	12.0%	NR ~15	~58%	31.7%	~27%	~27%	27%
	E Alt	99	10.5	~43%	20.2%	~13%	~12%	10.8%	NR ~9	~42%	27.7%	25%	23%	23%
	Difference		-1.5	-6%	1.4%	1%	0%	-1.2%		-18%	-4%	0.2%	3.2%	2.8%
			(p=0.41, not significant, RR 0.88, 95% CI 0.66-1.08)						(PWIFR, HR 0.79, 95% CI 0.56-1.12)					
Park, Kim, Jeong, et al., 1996	Seq	47	16.0	74.4%	27.7%	8.8%	4.4%	2.2%						
	Conc	32	18.4	81.3%	29.0%	13.8%	10.7%	7.4%						
	Difference		2,4 (p=0.11)	6.9%	1.3%	5.0%	6.3%	5.2%						

Abbreviations table provided at the end of the Report.

Summary Table 5. Adverse Events: Alternating, Concurrent, or Sequential Radiotherapy

Toxicity Type	Study	Severity or Grade	Group	n	%	Group	n	%	p	Not Reporting
Treatment-related mortality	Lebeau 1999	Deaths from aplasia	Alt	74	2.7	Conc	82	3.7	0.67	Gregor 1997; Sun 1995; Work 1997/1996; Park, 1996
		Deaths from pulmonary fibrosis	Alt	74	1.4	Conc	82	7.3	0.05	
	Takada 2002		Seql	110	3.6	Conc	112	2.7	0.72	
	Work 1997		L Alt	100	0	E Alt	99	0	1.00	
Nausea/Vomiting	Gregor 1997	Or vomiting, acute (WHO grade)								Lebeau 1999; Sun 1995; Work 1997/1996; Park, 1996
		0	Seql	165	25.5	Alt	169	36.1	0.129	
		1			21.8			21.3		
		2			37.6			25.4		
		3			13.3			15.4		
		4			0.6			1.2		
		NR			1.2			0.6		
	Takada 2002	Or vomiting (WHO grade ≥ 3)	Seql	110	19.1	Conc	112	10.7	0.09	
Anorexia										Lebeau 1999; Gregor 1997; Takada 2002; Sun 1995; Work 1997/1996; Park, 1996
Lethargy										Lebeau 1999; Gregor 1997; Takada 2002; Sun 1995; Work 1997/1996; Park, 1996
Neurosensory	Work 1997/1996	Moderate neurotoxicity (grade ≤ 3)	in 11 (of 199); no difference between groups							Lebeau 1999; Gregor 1997; Takada 2002; Sun 1995; Park, 1996
Hearing loss										Lebeau 1999; Gregor 1997; Takada 2002; Sun 1995; Work 1997/1996; Park, 1996
Esophagitis	Gregor 1997	Acute (WHO grade)								Lebeau 1999; Sun 1995; Work 1997/1996; Park, 1996
		0	Seql	165	83.0	Alt	169	75.7	0.198	
		1			7.9			11.8		
		2			6.1			9.5		
		3			3.0			3.0		
		Late esophageal stenosis (WHO grade)	Seql	143	82.5	Alt	135	94.1	0.010	
		0			11.2			3.0		
		1			2.8			1.5		
		2			2.1			0.7		
		3			1.4			0.7		
		NR								
	Takada 2002	WHO grade ≥ 3	Seql	110	3.6	Conc	112	8.9	0.17	

Abbreviations table provided at the end of the Report.

Summary Table 5. Adverse Events: Alternating, Concurrent, or Sequential Radiotherapy (continued)

Toxicity Type	Study	Severity or Grade	Group	n	%	Group	n	%	p	Not Reporting
Bronchopulmonary	Gregor 1997	Late Lung fibrosis (RTOG grade)								Takada 2002; Sun 1995; Work 1997/1996; Park, 1996
		0	Seql	143	19.6	Alt	135	11.1	0.135	
		1			19.6			20.0		
		2			21.7			27.4		
		3			18.2			14.8		
		4			18.9			24.4		
		NR			2.1			2.2		
	Lebeau 1999	Pulmonary fibrosis	Alt	74	2.7	Conc	82	8.5	0.17	
Pneumonitis										Lebeau 1999; Gregor 1997; Takada 2002; Sun 1995; Work 1997/1996; Park 1996
Kidney	Work 1997/1996		quantified by chromium-edathamil clearance; did not differ between groups							Lebeau 1999; Gregor 1997; Takada 2002; Sun 1995
	Park 1996	ECOG grade 3	Seql	24	0	Conc	27	0	1.00	
		ECOG grade 4			0			0		
Anemia	Takada 2002	WHO grade 3	Seql	110	41.8	Conc	112	53.6	0.08	Lebeau 1999; Gregor 1997; Sun 1995; Work 1997/1996
	Park 1996	ECOG grade 3	Seql	24	0	Conc	27	3.7	1.00	
		ECOG grade 4			0			0		
Thrombocytopenia	Gregor 1997	Acute (WHO grade)								Lebeau 1999; Sun 1995;
		0	Seql	165	55.2	Alt	169	24.9	<0.001	
		1			13.9			17.2		
		2			10.9			23.1		
		3			12.7			11.8		
		4			6.7			20.7		
		NR			0.6			2.4		
	Takada 2002	(WHO grade)								
		3	Seql	110	12.7	Conc	112	29.5	0.11	
		4			13.6			7.1		
		$\geq$ 3			26.4			36.6		
	Work 1997/1996	WHO grades 3 & 4	L Alt	100	13	E Alt	99	13	1.00	
	Park 1996	ECOG grade 3	Seql	24	0	Conc	27	0	1.00	
		ECOG grade 4			0			3.7		

Summary Table 5. Adverse Events: Alternating, Concurrent, or Sequential Radiotherapy (continued)

Toxicity Type	Study	Severity or Grade	Group	n	%	Group	n	%	p	Not Reporting
Leukopenia or neutropenia	Gregor 1997	Acute leukopenia (WHO grade) 0 1 2 3 4 NR	Seql	165	6.7 5.5 10.9 34.5 41.8 0.6	Alt	169	4.1 1.2 3.6 17.8 71.6 1.8	<0.001	Sun 1995
	Lebeau 1999	Neutropenia (grade 3 or 4)	Alt	74	60.8	Conc	82	58.5	0.87	
	Takada 2002	Leukopenia (WHO grade) 3 4 3 or 4	Seql	110	44.5 9.1 53.6	Conc	112	50.9 37.5 88.4	0.001	
	Work 1997/1996	WHO grades 3 & 4 leukopenia WHO grade 4 leukopenia	L Alt	100	39 6	E Alt	99	67 23	<0.001 0.0006	
	Park 1996	Leukopenia ECOG grade 3 ECOG grade 4	Seql	24	12.5 4.2	Conc	27	40.7 11.1	0.0176	
Infection	Takada 2002	WHO grade ≥3	Seql	110	0.9	Conc	112	5.4	0.12	Lebeau 1999; Gregor 1997; Sun 1995
	Work 1997/1996		neutropenic fever in 8 patients; no difference between groups							
	Park 1996	ECOG grade 3 ECOG grade 4	Seql	24	0 0	Conc	27	3.7 0	1.00	
Other	Takada 2002	Alopecia (WHO grade ≥3)	Seql	109	12.7	Conc	109	11.6	0.99	
	Takada 2002	Fever (WHO grade ≥3)	Seql	110	1.8	Conc	112	1.8	0.99	
	Takada 2002	Arrhythmias (WHO grade ≥3)	Seql	110	0.0	Conc	112	1.8	0.50	
	Park 1996	Hepatic ECOG grade 3 Hepatic ECOG grade 4	Seql	24 0	0	Conc	27 0	0	1.00	

Summary Table 6. Adverse Events Reported in Takada and Park Trials

Adverse Event	Takada	Park
Treatment-related Mortality		NR
Nausea/vomiting		NR
Esophagitis		NR
Anemia		
Thrombocytopenia		
Leukopenia	▲	▲
Kidney	NR	
Infection		
Fever		
Alopecia		NR
Arrhythmias		NR
Hepatic	NR	

▲=significantly more frequent in concurrent than in sequential arm; ▼=significantly less frequent in concurrent than in sequential arm; NR=not reported; blank cell=outcome reported, but arms not significantly different

Summary. These 2 studies suggest better efficacy outcomes for concurrent TRTx than for sequential TRTx, with inconsistent statistical significance, along with similar rates of adverse events of all types except leukopenia, which was more common for concurrent TRTx. Unadjusted analyses of overall survival found nearly significant differences favoring concurrent over sequential TRTx in 2 studies. One study using adjustment by Cox regression found a significant treatment effect for concurrent TRTx. One study that analyzed progression-free survival reported a nearly significant difference in favor of concurrent TRTx. CRs were more common with concurrent therapy in both studies, but not significantly so (p values were 0.07 and 0.13). One study found a significantly longer response duration for concurrent TRTx. Only 1 of 11 types of adverse events showed significant between-group differences. Leukopenia was more common for concurrent TRTx in both studies.

Alternating vs. Sequential

Interventions. Both Sun, Zhang, Yin, et al. (1995) and Gregor, Drings, Burghouts, et al. (1997) delivered TRTx in single fractions per day. There was a wide range of total doses in the Sun, Zhang, Yin, et al. (1995) study (30–60 Gy), while the Gregor, Drings, Burghouts, et al. (1997) study gave 50 Gy to all patients. Alternating TRTx was given between weeks 4 and 9 in the Sun, Zhang, Yin, et al. (1995) study, whereas Gregor, Drings, Burghouts, et al. (1997) administered it every 4 weeks between 7 and 20 weeks. In the Gregor, Drings, Burghouts, et al. (1997) study, 4 weeks of TRTx in the alternating arm was given over a period of 13 weeks

wherease sequential TRTx was given over 4 consecutive weeks. Sun, Zhang, Yin, et al. (1995) provided TRTx over 6 consective weeks in both the alternating and sequential arms. That study also used platinum-based chemotherapy in the later period of the trial, but no patients received it in the Gregor, Drings, Burghouts, et al. (1997) study. Neither report made clear whether patients received PCI.

Populations. The Sun, Zhang, Yin, et al. (1995) article did not report any baseline patient characteristics; it simply stated that 123 patients had localized disease. Patient groups in the Gregor, Drings, Burghouts, et al. (1997) study (n=335) were well-matched on the 3 key characteristics: age, gender and performance status.

Quality and Reporting. Gregor, Drings, Burghouts, et al. (1997) received a good study quality rating. Sun, Zhang, Yin, et al. (1995) was rated as poor because details were lacking for all quality domains.

Results. Gregor, Drings, Burghouts, et al. (1997) did not find a statistically significant difference between groups in adjusted survival. Median survival was 15 months in the sequential group and 14 months in the alternating group. The entire survival curve for the sequential TRTx group was slightly higher than that of the alternating group. Between 1 and 4 years, survival probabilities differed by 4 percent or less, while the difference was 8 percent at 5 years. In the Sun, Zhang, Yin, et al. (1995) study, statistical test results for survival were missing. At 1 year, the survival probability was higher in the sequential group by 1.5 percent, whereas at 2 an 3 years, it was higher for the alternating group by 14.4 percent and 4 percent. Relative risks (RR) for death at 2 years and 3 years were computed for purposes of meta-analysis. At 2 years, the RR of 0.831 significantly favors alternating TRTx (95 percent CI: 0.692–0.999). The difference is smaller and in the same direction at 3 years, with an RR of 0.957, but nonsignificant (95 percent CI: 0.831–1.102). The difference in progression-free survival favoring sequential TRTx in the Gregor, Drings, Burghouts, et al. (1997) study approached statistical significance (p=0.07). Neither study reported on tumor response or quality of life.

Sun, Zhang, Yin, et al. (1995) reported no data on adverse events (Summary Table 7), while Gregor, Drings, Burghouts, et al. (1997) gave data on 6 types. There were no between-group differences in the incidence of nausea/vomiting, acute esophagitis, or late pulmonary fibrosis. Late esophagitis was significantly less frequent in the alternating group, compared to the sequential group (p=0.01). Both thrombocytopenia and leukopenia were more common ($p<0.001$) in the alternating group.

Summary Table 7. Adverse Events Reported in Gregor and Sun Trials

Adverse Event	Gregor	Sun
Nausea/vomiting		NR
Acute Esophagitis		NR
Late Esophagitis	▼	NR
Late Pulmonary Fibrosis		NR
Thrombocytopenia	▲	NR
Leukopenia	▲	NR

▲=significantly more frequent in alternating than in sequential arm; ▼=significantly less frequent in alternating than in sequential arm; NR=not reported; blank cell=outcome reported, but arms not significantly different

Summary. Results are mixed on the relative impact on outcomes for alternating and sequential TRTx. One study reported that the survival curve for sequential TRTx was always higher than that for alternating TRTx, but the difference was not significant. The other study showed a significant difference in the RR of death at 2 years favoring alternating TRTx. The study reporting progression-free survival found a nearly significant advantage for sequential TRTx. Late esophagitis was more common for the sequential group, but thrombocytopenia and leukopenia were more frequent in the alternating group. These data do not show a clear advantage for either sequential or alternating TRTx.

Alternating vs. Concurrent

Interventions. The Lebeau, Urban, Brechot, et al. (1999) study delivered doses of 55 Gy to the alternating TRTx group and 50 Gy to the concurrent TRTx group.[*] Radiation was given in once daily fractions to both groups. Concurrent TRTx was offered across 5 weeks from week 5 through 9, while alternating TRTx occurred across 11 weeks during weeks 6–7, 10–11 and 14–16. Both groups received PCI. Non-platinum chemotherapy was administered.

Populations. The 2 groups of patients in this study (n=156) were well-matched on baseline characteristics.

Quality and Reporting. This trial received a good study quality rating.

[*] During final preparation of this report, a second comparison was published of concurrent versus alternating TRTx (Blackstock, Bogart, Matthews, et al., 2005). The study compared five weeks of continuous radiation concurrent with chemotherapy cycles 1-2 (n=56) versus split-course alternating radiation given during weeks without chemotherapy in cycles 1-3 (n=54). Overall survival did not differ between the two groups (median, 14 versus 15 months; survival at 2 years, 36% versus 31%; survival at 5 years 18% versus 17%). Since radiation began in week 1 for the continuous arm and in week 2 for the alternating arm, this study did not meet inclusion criteria for meta-analysis of early versus late radiation therapy.

Results. The entire survival curve for alternating TRTx lies slightly above that for concurrent TRTx, but the difference overall was not significant. Differences in survival probabilities ranged from a high at 1 year of 9 percent to a low of 2 percent at 5 years. Progression-free survival and quality of life was not reported. There was no statistically significant difference between groups in tumor response rates.

Four types of adverse events (Summary Table 8) were noted by Lebeau, Urban, Brechot, et al. (1999). The only outcome that showed a statistically significant between-group difference was deaths from pulmonary fibrosis, which were more common in the concurrent TRTx group (p=0.05).

Summary Table 8. Adverse Events Reported in Lebeau Trial

Adverse Event	Lebeau
Deaths from aplasia	
Deaths from Pulmonary Fibrosis	▲
Pulmonary Fibrosis	
Neutropenia	

▲=significantly more frequent in concurrent than in alternating arm; ▼=significantly less frequent in concurrent than in alternating arm; NR=not reported; blank cell=outcome reported, but arms not significantly different

Summary. The single study comparing alternating and concurrent TRTx does not suggest a meaningful improvement in survival associated with alternating TRTx. Overall survival did not differ significantly, with a difference between medians of only 0.5 months favoring alternating TRTx. Deaths from pulmonary fibrosis were more frequent in the concurrent TRTx group.

Early Alternating vs. Late Alternating

Interventions. The dose given to both groups in the early phase of the Work and colleagues study (Work, Nielsen, Bentzen, et al., 1997/Work, Bentzen, Nielsen, et al., 1996) was 40 Gy; it was increased later to 45 Gy. Radiation was delivered as a single daily fraction in both treatment arms. TRTx was given during weeks 1–2 and 6–7 in the early-alternating group and in weeks 18–19 and 23–24 in the late-alternating group. Given the somewhat lower total dose in this study compared with other studies addressed above and administration in split-course fashion, TRTx was given at a relatively low dose rate. Both groups received PCI. The chemotherapy regimen for all patients was platinum-based; however the regimen was given in an unusual schedule and the doses of drugs actually delivered is unclear..

Populations. Groups receiving early and late alternating TRTx were well-balanced on baseline patient characteristics.

Quality and Reporting. This study was rated as fair in quality. The key deficiency was an inadequate description of the randomization method.

Results. Work and colleagues (Work, Nielsen, Bentzen, et al., 1997/Work, Bentzen, Nielsen, et al., 1996) reported that median survival was slightly longer in the late-alternating group (1.5 months), while 2- and 3-year survival probabilities were slightly higher in the early-alternating group. Overall, there was no significant difference in survival between groups. There was an 18 percent difference at 1 year in percentage without in-field recurrence (PWIFR) favoring late-alternating TRTx, but differences at later times were much smaller and the groups did not differ significantly. Tumor response rates did not differ for the 2 patient groups. No quality of life data were collected.

Of the 6 categories of adverse events, only leukopenia showed a difference between groups (Summary Table 9). This outcome was significantly more common among those receiving early alternating TRTx.

Summary Table 9. Adverse Events Reported in Work Trial

Adverse Event	Work
Treatment-related Mortality	
Neurotoxicity	
Kidney	
Thrombocytopenia	
Leukopenia	▲
Infection	

▲=significantly more frequent in early alternating than in late alternating arm; ▼=significantly less frequent in early alternating than in late alternating arm; NR=not reported; blank cell=outcome reported, but arms not significantly different

Summary. The single study comparing early and late alternating is does not support conclusions about the relative effectiveness of these approaches to TRTx. There was no significant difference between groups on overall survival, percentage without in-field recurrence and tumor response. Of 6 types of adverse events reported, groups differed only in the frequency of leukopenia, which was significantly higher among those receiving early alternating TRTx.

Conclusions

Among 6 studies meeting selection criteria for Key Question 1, two trials (n=307) compared concurrent and sequential TRTx. Two trials compared alternating to sequential TRTx (n=458).

One trial compared alternating to concurrent TRTx (n=156). The final trial compared early alternating and late alternating TRTx (n=199). Comparing these trials with others addressing TRTx delivery, survival is generally lower is this set relative to studies assessing the effect of hyperfractionation. Although an explanation is not readily apparent, possible reasons include patient selection, stage drift and the adequacy of chemotherapy.

Concurrent vs. Sequential. Results are not conclusive but suggest better outcomes for concurrent TRTx. Although not statistically significant, unadjusted overall survival and CR rates favored concurrent TRTx in both studies. However, adjusted overall survival in the larger study was significantly in favor of concurrent TRTx. A smaller study found significantly longer response duration for concurrent TRTx in 1 study. Out of 11 types of adverse events, only leukopenia occurred significantly more frequently, in the concurrent TRTx group in both studies.

Alternating vs. Sequential. Inconsistent findings were observed in the 2 studies and no conclusions can be drawn that one is superior to the other. The direction of the advantage on overall survival differed in the 2 studies.

Alternating vs. Concurrent. In the single study comparing alternating and concurrent TRTx, there was no statistically significant effect on survival and no conclusions of differential efficacy could be drawn.

Early Alternating vs. Late Alternating. In the single study comparing early versus late alternating TRTx, there was no statistically significant difference in survival, thus no conclusions of differences in efficacy can be reached.

Key Question 2

For limited-stage SCLC, do outcomes (survival, toxicity, or quality of life) differ if concurrent TRTx is given in early versus late chemotherapy cycles?

Overview

Six randomized, controlled trials (RCTs) compared outcomes of alternate times to administer TRTx concurrently in first-line therapy for limited stage SCLC (N=1,177). Summary Table 10 summarizes selected study variables; further details are in Summary Table 11 and Appendix Tables 2A-C, 2H.* Each of the three larger trials randomized from 125 to 166 patients per arm (Murray, Coy, Pater, et al., 1993/Coy, Hodson, Murray, et al., 1994/Feld, Payne, Hodson, et al., 1988 [hereafter referred to as "Murray-Coy-Feld"]; Perry, Eaton, Propert, et al., 1987/Ahles, Silberfarb, Rundle, et al., 1994/Perry, Herndon, Eaton, et al., 1988; [hereafter referred to as "Perry-Ahles-Perry"]; James, Spiro, O'Donnell, et al., 2003). Together, the three smaller trials

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf.

included less than one-fourth of all patients studied (Jeremic Shibamoto, Acimovic, et al., 1997; Qiao, Zhou, Xin, et al., 2004; Skarlos, Samantas, Briassoulis, et al., 2001).

Summary Table 10. Selected study parameters of RCTs comparing times to give concurrent TRTx

study	N		Pt?	chemoTx regimen	TRTx dose (Gy)	# fracs	TRTx timing		PCI ?	# centers	pub type	quality rating
	early	late					early	late				
Murray, Coy, Pater, et al., 1993/Coy, Hodson, Murray, et al., 1994/Feld, Payne, Hodson, et al., 1988	155	153	yes	CAV/PE	40	1/d	wk 4-6	wk 16-18	yes	multi	full	good
Perry, Eaton, Propert, et al., 1987/Ahles, Silberfarb, Rundle, et al., 1994/Perry, Herndon, Eaton, et al., 1988	125	145	no	CAVE	50	1/d	wk 1-5	wk 10-14	yes	multi	full	fair
Jeremic Shibamoto, Acimovic, et al., 1997	52	51	yes	PE/CbE	54	2/d	wk 1-4	wk 6-9	yes	one	full	fair
Qiao, Zhou, Xin, et al., 2004	45	45	yes	CbE	50 or 60	1/d	wk 1-5/6	wk 12-16/17	?	one	full	fair
Skarlos, Samantas, Briassoulis, et al., 2001	42	39	yes	CbE	45	2/d	wk 1-3	wk 10-12	yes	multi	full	fair
James, Spiro, O'Donnell, et al., 2003	159	166	yes	CAV/PE	40	1/d	wk 4-6	wk 16-18	yes	multi	abstr	not rated

Abbreviations table provided at the end of the Report.

Summary Table 11. Sample and Methods: Early Versus Late Radiotherapy

Study	N		Age	% Female	% Performance Status	CTx Regimen	RTx Regimen		
Murray, Coy, Pater, et al., 1993/Coy, Hodson, Murray, et al., 1994/Feld, Payne, Hodson, et al., 1988 22 centers 1/85 - 12/88	Total	308	md		0 1 2 3		Dose	Schedule	PCI?
	Early	155	61.8	40.6	21.9 65.2 12.3 0.6	CAV-PE	40 Gy	wks 4-6, 1/d, 5/wk, 15/course	25 Gy, 10 frac
	Late	153	61.6	34.6	22.2 68.0 9.2 0.7 ECOG	same	40 Gy	wks 16-18, 1/d, 5/wk, 15/course	same
Perry, Eaton, Propert, et al., 1987/Ahles, Silberfarb, Rundle, et al., 1994/Perry, Herndon, Eaton, et al., 1988 22 centers 1/81 - 6/84	Total	270	% < 60		0 1 2/3		Dose	Schedule	PCI?
	Early	125	48	38	38 48 13	CAVE	50 Gy	wks 1-5, 40 Gy+10 Gy boost	30 Gy, 10 frac, con-current with TRTx
	Late	145	45	37	42 45 9 CALGB	same	50 Gy	wks 10-14, 40 Gy+10 Gy boost	
Jeremic Shibamoto, Acimovic, et al., 1997 single center 1/88-12/92	Total	103	mn (rng)		90, 100 50-80		Dose	Schedule	PCI?
	Early	52	57 (40-67)	40.4	52 48	PE/Cb-E	54 Gy	wks 1-4, 2/d, 5/wk	25 Gy, 10 frac, wks
	Late	51	57 (44-66)	39.2	47 53 KPS	same	54 Gy	wks 6-9, 2/d, 5/wk	16, 17

Abbreviations table provided at the end of the Report.

Summary Table 11. Sample and Methods: Early Versus Late Radiotherapy (continued)

Study	N	Age	% Female	% Performance Status	CTx Regimen	RTx Regimen		
Qiao, Zhou, Xin, et al., 2004 single center 3/93-1/98	Total 90 Early 45 Late 45	md (rng) 57 (36-58) 56 (38-69)	 24.3 33.3	all randomized patients had KPS ≥70 (excluded if ≤60)	 Cb-E same	Dose 50-60 Gy 50-60 Gy	Schedule begun 1st CTx cyc, over 6 wks begun after 4th CTx cyc, over 6 wks	PCI? not specified for either arm
Skarlos, Samantas, Briassoulis, et al., 2001 multicenter 12/93 - 11/99	Total 81 Early 42 Late 39	md (rng) 61 (40-76) 60 (37-76)	 7 10	0 1 2 3 26 50 24 41 44 15 ECOG	 Cb-E same	Dose 45 Gy 45 Gy	Schedule wks 1-3, 2/d, 5/wk wks 10-12, 2/d, 5/wk	PCI? 20 Gy, CR 5 4 Gy frac same
James, Spiro, O'Donnell, et al., 2003 (abstract only) multicenter; 1/93 -1/02	Total 325 Early 159 Late 166	md (rng) 62 (34-74) 62 (33-74)	 40 43	0-1 2-3 91 9 89 11 ECOG	 CAV-PE same	Dose 40 Gy 40 Gy	Schedule wks 4-6, 1/d, 5/wk wks 16-18, 1/d, 5/wk	PCI? 25 Gy, 10 frac, neg brain scan

Interventions. Available studies did not uniformly define early and late concurrent therapy, with respect to either the chemotherapy cycle or weeks during which they administered TRTx. Most trials (4 of 6) began TRTx in chemotherapy cycle 1 (i.e., week 1) for those randomized to early concurrent therapy; two waited until cycle 2 (week 4) (Murray-Coy-Feld; James, Spiro, O'Donnell, et al., 2003). Those randomized to late concurrent therapy began TRTx in cycle 3 (week 6) in one trial (Jeremic Shibamoto, Acimovic, et al., 1997), cycle 4 (week 10 or 12) in three trials (Perry-Ahles-Perry; Qiao, Zhou, Xin, et al., 2004; Skarlos, Samantas, Briassoulis, et al., 2001), and cycle 6 (week 16) in the remaining two trials (Murray-Coy-Feld, James, Spiro, O'Donnell, et al., 2003).

Five of six RCTs used platinum-etoposide chemotherapy regimens, including two of three larger trials; Perry-Ahles-Perry was the exception. Total TRTx dose was $\geq$40 Gy in each RCT, and only two used doses greater than 50 Gy (Jeremic Shibamoto, Acimovic, et al., 1997; Qiao, Zhou, Xin, et al., 2004). Three trials gave TRTx over a 3-week period (Murray-Coy-Feld; Skarlos, Samantas, Briassoulis, et al., 2001; James, Spiro, O'Donnell, et al., 2003 2003), one gave TRTx over four weeks (Jeremic Shibamoto, Acimovic, et al., 1997), and two gave TRTX over five or six weeks (Perry-Ahles-Perry; Qiao, Zhou, Xin, et al., 2004). Thus, weekly doses were 10 Gy in two trials (Perry-Ahles-Perry; Qiao, Zhou, Xin, et al., 2004), 13.35 Gy in two trials (Murray-Coy-Feld; James, Spiro, O'Donnell, et al., 2003), and 15 Gy in two trials (Jeremic Shibamoto, Acimovic, et al., 1997; Skarlos, Samantas, Briassoulis, et al., 2001). Four trials administered single daily fractions (Murray-Coy-Feld; Perry-Ahles-Perry; Qiao, Zhou, Xin, et al., 2004; James, Spiro, O'Donnell, et al., 2003) and two gave two fractions per day (Jeremic Shibamoto, Acimovic, et al., 1997; Skarlos, Samantas, Briassoulis, et al., 2001). Five of six trials included PCI for each arm; Qiao, Zhou, Xin, et al. (2004) did not report PCI use.

Study Populations. Most trials studied patients with relatively favorable baseline characteristics, and were nearly always well-balanced across arms for consistently-reported factors (Summary Table 11). In four of six trials, performance status (PS) was 0-1 at enrollment for 75 percent to 91 percent of patients across arms (Murray-Coy-Feld; Perry Ahles-Perry; Skarlos, Samantas, Briassoulis, et al., 2001; James, Spiro, O'Donnell, et al., 2003). PS also was well balanced across arms in Jeremic Shibamoto, Acimovic, et al. (1997), but many patients (~50 percent) had Karnofsky scores of 50-80. Qiao, Zhou, Xin, et al. (2004) excluded patients with Karnofsky PS $\leq$60, but did not report PS distribution by arm. For all six trials, the median or mean age ranged from approximately 55 to 62 years, and was balanced across arms. Each trial enrolled mostly men (8.6 percent women in one trial, 33 percent to 43 percent across five others), and had similar proportions of women in each arm.

Other prognostic factors and baseline characteristics were reported inconsistently (Appendix Table 2B[*]). Only three trials reported the proportion with weight loss at entry (Perry-Ahles-Perry; Jeremic Shibamoto, Acimovic, et al., 1997; Skarlos, Samantas, Briassoulis, et al., 2001). Only three trials reported the proportion with disease outside the lung (Murray-Coy-Feld, Qiao, Zhou, Xin, et al., 2004; Skarlos, Samantas, Briassoulis, et al., 2001). Only one trial reported the proportion of former smokers (Skarlos, Samantas, Briassoulis, et al., 2001). No trials reported racial distributions.

[*] Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf.

Study Quality and Reporting. The larger studies included one good-quality and one fair-quality multicenter trial, each published in full. The third large trial also was multicenter, but was reported only in abstract and information to rate quality was lacking. Two of three small trials were single-center and one was multicenter; each was of fair quality and published in full.

Results

In one large and two smaller trials, results significantly favored the early TRTx arms for overall (OS), progression-free (PFS), or local recurrence-free (LRFS) survival (Summary Table 12). Murray-Coy-Feld (n=308) reported significantly longer median OS (21.2 versus 16.0 months; p=0.008) and greater 2- and 3-year survival (40 percent versus 33.7 percent and 29.7 percent versus 21.5 percent, respectively) with early TRTx. Murray-Coy-Feld also reported significantly greater PFS with early TRTx (median, 15.4 versus 11.8 months; 26 percent versus 19 percent at 3 years; p=0.036). Qiao, Zhou, Xin, et al. (2004; n=90) reported longer median OS (26 versus 19 months; p<0.05) and greater 3-year survival (33 percent versus 22 percent) with early TRTx, but did not report an outcome related to progression or recurrence. Jeremic Shibamoto, Acimovic, et al. (1997; n=103) reported significantly greater 2- and 3-year LRFS with early TRTx (90 percent versus 69 percent and 73 percent versus 61 percent, respectively; p=0.011). While median OS (34 versus 26 months) and 2- and 3-year survival also favored early TRTx in the Jeremic Shibamoto, Acimovic, et al. (1997) trial, these results were just barely statistically nonsignificant (p=0.052).

Between-arm differences in response rates were not statistically significant in any trial (Appendix Table 2F).

In two large and one smaller RCTs, OS and time to treatment failure (TTF) did not differ significantly between arms randomized to early or late TRTx (Summary Table 12). Perry-Ahles-Perry (n=270), the only trial that did not use platinum, reported non-significant differences in OS (P=0.144) and TTF (p=0.238). James, Spiro, O'Donnell, et al. (2003; n=325), the sole trial published as an abstract, only reported OS and also found no significant difference (p=0.18). Skarlos, Samantas, Briassoulis, et al. (2001; n=81) reported nonsignificant differences for median OS (p=0.65) and median TTF (p=0.6).

A small pilot sub-study from one RCT reported the only data comparing quality of life outcomes after early versus late TRTx. Ahles et al. (1994) scored responses to measures of mood, psychosocial function, and cognitive function for 14-17 patients (of n=121) given early TRTx and 10-12 (of n=141) given late TRTx in the Perry-Ahles-Perry trial (Appendix Table 2F).[*]

Summary Table 12. Survival Outcomes: Early Versus Late Radiotherapy

Study	N	Overall Survival Med	1 yr	2 yr	3 yr	4 yr	5 yr	Other Outcomes (progression, failure, relapse, etc.) Med	1 yr	2 yr	3 yr	4 yr	5 yr
Murray, Coy, Pater, et al., 1993/Coy, Hodson, Murray, et al., 1994/Feld, Payne, Hodson, et al., 1988	Early 155	21.2	~77%	40%	29.7%	23.7%	20%	15.4	~65%	~28%	26%		
	Late 153	16.0	~63%	33.7%	21.5%	15.1%	11%	11.8	~48%	~24%	19%		
	Difference	5.2	14%	6.3%	8.2%	8.6%	9%	3.6	17%	4%	7%		
		(p=0.008, log-rank; 0.005 Wilcoxon)						(PFS, p=0.036, log-rank; 0.014 Wilcoxon)					
Perry, Eaton, Propert, et al., 1987/Ahles, Silberfarb, Rundle, et al., 1994/Perry, Herndon, Eaton, et al., 1988	Early 125	13.0	~53%	~24%	~10%			11.0	~45%	15%	~8%		
	Late 145	14.5	~62%	~30%	~20%			11.2	~50%	25%	~15%		
	Difference	-1.5	-9%	-6%	-10%			-0.2	-5%	-10%	-7%		
		(p=0.144; not significant)						(TTF, p=0.238; not significant)					
Jeremic Shibamoto, Acimovic, et al., 1997	Early 52	34	90%	71%	48%	35%	30%	52	94%	90%	73%	63%	58%
	Late 51	26	71%	53%	39%	25%	15%	51	74%	69%	61%	46%	37%
	Difference	8	19%	18%	9%	10%	15%	1	20%	21%	12%	17%	21%
		(p=0.052)						(LRFS, p=0.011)					
Qiao, Zhou, Xin, et al., 2004	Early 45	26	78%		33%		27%						
	Late 45	19	53%		22%		16%						
	Difference	7	25%		11%		11%						
		(log-rank, p<0.05)											
Skarlos, Samantas, Briassoulis, et al., 2001	Early 42	17.5	~65%	36%	22%			9.5	~40%	~25%	~20%		
	Late 39	17	~80%	29%	13%			10.5	~35%	~15%	~15%		
	Difference	0.5	-15%	7%	9%			-1.0	5%	10%	5%		
		(p=0.65, not significant)						(TTF, p=0.6, not significant)					
James, Spiro, O'Donnell, et al., 2003 (abstract only)	Early 159	13.5			16%								
	Late 166	15.1			20%								
	Difference	-1.6			-4%								
		(HR = 1.18; 95% CI: 0.93, 1.51; p=0.18)											

Abbreviations table available at the end of the Report.

They compared these with scores for another group randomized to chemotherapy without TRTx (not abstracted). Results suggested larger decrements of mood and psychosocial function after chemotherapy plus TRTx than after chemotherapy alone. However, they found no meaningful differences in magnitude of decrement between early and late TRTx groups.

Table 13 shows that leukopenia/neutropenia and esophagitis were the only adverse events consistently reported by all six trials. Although leukopenia/neutropenia was more common in the early arm of five RCTs, only Qiao, Zhou, Xin, et al. (2004; $p<0.05$) and James, Spiro, O'Donnell, et al. (2003; $p=0.006$) reported that differences were statistically significant (Summary Table 14). Of four reporting RCTs, only Murray-Coy-Feld reported significantly more anemia in the early treatment arm (49 percent versus 37 percent, $p=0.03$). Skarlos, Samantas, Briassoulis, et al. (2001) reported significantly more grade 3 esophagitis with late than with early TRTx. However, the arms did not differ significantly when grades 1-3 were pooled, and the other five trials reported no significant differences in grade 3 or 3+4 combined.

Summary Table 13. Adverse Events, Early versus Late Concurrent TRTx

Adverse Event	Murray/Coy/ Feld	Perry/Ahles/ Perry	Jeremic 1997	Qiao 2004	Skarlos 2001	James 2003
leukopenia/ neutropenia				▲		▲
anemia	▲	NR		NR		
esophagitis					▼	

▲=significantly more frequent in early than in late arm; ▼=significantly less frequent in early than in late arm; NR=not reported; blank cell=outcome reported, but arms not significantly different

Between-arm differences in treatment-related mortality (3 reporting trials), nausea/ vomiting (5 reporting trials), neurosensory effects (3 reporting trials), bronchopulmonary effects or pneumonitis (3 reporting trials each), thrombocytopenia (5 reporting trials), and infections (4 reporting trials) were not statistically significant.

Conclusions

Overall, the evidence is equivocal, either finding no difference or a small advantage for early TRTx. One larger trial of good quality significantly favored concurrent therapy given in an early cycle (Murray-Coy-Feld; median OS 21.2 versus 16.0 months; $p=0.008$), as did 2 smaller trials. Of the two larger trials that that found no significant difference, one did not use platinum chemotherapy and the other has not been published in full text. Meta-analysis on the question of early versus late TRTx was performed to attempt to obtain clearer results.

Leukopenia/neutropenia appeared to be more common with early concurrent TRTx, although differences were statistically significant in only two of six reporting trials. Other events do not appear to be more frequent with either early or late TRTx. However, evidence is limited as adverse events were not reported consistently across all trials.

S`1ummary Table 14. Adverse Events: Early Versus Late Radiotherapy

Toxicity Type	Study	Severity or Grade	Early n	%	Late n	%	p	Not Reporting
Treatment-related mortality	Murray 1993 Coy 1994 Feld 1988		155	1.3	153	1.3	NS	Jeremic 1997; Qiao 2004; James 2003
	Perry 1987 Ahles 1994 Perry 1998		125	4	145	1	NS	
	Skarlos 2001		42	0	39	0	NS	
Nausea/Vomiting	Murray 1993 Coy 1994 Feld 1988	required IV fluids	155	11.6	153	15.8	NS	Qiao 2004
	Perry 1987 Ahles 1994 Perry 1998	nausea and vomiting, NOS	122	18	140	10	NS	
	Jeremic 1997	nausea and vomiting, grades 3 & 4	52	9.6	51	7.8	NS	
	Skarlos 2001	grade 3 nausea and vomiting	42	2.5	39	2.5	NS	
	James 2003	nausea and vomiting, grades 3 & 4	159	2	166	3	NS	
Anorexia	Perry 1987 Ahles 1994 Perry 1998	>10% weight loss	?	14	NR	NR		Murray 1993/Coy 1994/Feld 1988; Jeremic 1997; Skarlos 2001; James, 2003
	Qiao 2004	weight loss (% not specified)	45	20	45	33.3	NS	
Lethargy								Murray 1993/Coy 1994/Feld 1988; Perry 1987/Ahles 1994/Perry 1998; Jeremic 1997; Qiao 2004; Skarlos 2001; James, 2003
Neurosensory	Murray 1993 Coy 1994 Feld 1988	severe life-threatening lethal	155	0.6 0 0.6	153	3.3 1.3 0	NS for all 3 levels combined	Jeremic 1997; Qiao 2004; James, 2003
	Perry 1987 Ahles 1994 Perry 1998	“neuromuscular effects”	124	17	144	16	NS	
	Skarlos 2001	grade 2 & 3 neurotoxicity	42	0	39	0	NS	
Hearing loss								Murray 1993/Coy 1994/Feld 1988; Perry 1987/Ahles 1994/Perry 1998; Jeremic 1997; Qiao 2004; Skarlos 2001; James, 2003

Abbreviations table provided at the end of the Report.

Summary Table 14. Adverse Events: Early Versus Late Radiotherapy (continued)

Toxicity Type	Study	Severity or Grade	Early n	%	Late n	%	p	Not Reporting
Esophagitis	Murray 1993 Coy 1994 Feld 1988	fluids only IV fluids	149	11.4 3.4	133	6.8 0.8	NS for both levels combined	
	Perry 1987 Ahles 1994 Perry 1998	not specified	?	10	?	8		
	Jeremic 1997	grades 3 & 4	52	28.9	51	25.5	NS	
	Qiao 2004		45	42.2	45	28.9	NS	
	Skarlos 2001	grade 3	42	2.5	39	18	0.026 (p=0.82 for overall incidence)	
	James 2003	grades 3 & 4	159	7	166	4	NS	
Bronchopulmonary	Perry 1987 Ahles 1994 Perry 1998	not specified	122	9	133	6	NS	Murray 1993/Coy 1994/Feld 1988; Qiao 2004; James 2003
	Jeremic 1997	grades 3 & 4	52	1.9	51	0	NS	
	Skarlos 2001	Grade 3	42	5.0	39	7.5	NS	
Pneumonitis	Murray 1993 Coy 1994 Feld 1988	any lethal	149	3.2 0	133	0.7 0	NS	Jeremic 1997; Skarlos 2001; James, 2003
	Perry 1987 Ahles 1994 Perry 1998	not specified	122	9	133	4.5	NS	
	Qiao 2004	radio-pneumonia	45	8.9	45	6.7	NS	
Kidney	Murray 1993 Coy 1994 Feld 1988	creatinine > 354 μmol/L	155	0	153	0.7	NS	Perry 1987/Ahles 1994/Perry 1998; Jeremic 1997; Qiao 2004; James, 2003
	Skarlos 2001	grade 2 or 3	42	0	39	0	NS	
Anemia	Murray 1993 Coy 1994 Feld 1988	Hb <80 g/L	155	49	153	36.8	0.0275	Perry 1987/Ahles 1994/Perry 1998; Qiao 2004
	Jeremic 1997	grades 3 & 4	52	13.5	51	7.8	NS	
	Skarlos 2001	grades 3 & 4	42	19	39	12.5	NS	
	James, 2003	grades 3 & 4	159	9	166	5	NS	
Thrombocytopenia	Murray 1993 Coy 1994 Feld 1988	$<25 \times 10^9$/L	155	3.9	153	2.6	NS	Qiao 2004
	Perry 1987 Ahles 1994 Perry 1998	$<25 \times 10^9$/L	122	1	140	2	NS	
	Jeremic 1997	grades 3 & 4	52	38.5	51	21.6	NS	
	Skarlos 2001	grades 3 & 4	42	21.5	39	23	NS	
	James, 2003	grades 3 & 4	159	9	166	9	NS	

Summary Table 14. Adverse Events: Early Versus Late Radiotherapy (continued)

Toxicity Type	Study	Severity or Grade	Early n	%	Late n	%	p	Not Reporting
Leukopenia or neutropenia	Murray 1993 Coy 1994 Feld 1988	neutrophils<0.5 x 10^9/L	155	70.3	153	61.4	NS	
	Perry 1987 Ahles 1994 Perry 1998	WBC<1 x 10^9/L	117	35	118	25	NS	
	Jeremic 1997	leukopenia, grades 3 & 4	52	32.7	51	41.2	NS	
	Qiao 2004	grade 2 grade 3 grade 4	45	6.7 71.1 22.2	45	24.4 57.8 17.8	 0.02 (for 3+4)	
	Skarlos 2001	grades 3 & 4 leukopenia	42	35.5	39	20.5	NS	
	James, 2003	grades 3-4 leucopenia	159	74	166	55	0.006	
Infection	Murray 1993 Coy 1994 Feld 1988	neutropenic fever septic shock lethal	155	4.5 0.6 0	153	3.3 0.7 1.3	NS (for all 3 combined)	Qiao 2004; James, 2003
	Perry 1987 Ahles 1994 Perry 1998	sepsis	125	20	140	15	NS	
	Jeremeic 1997	grades 3 & 4	52	13.5	51	13.7	NS	
	Skarlos 2001	neutropenic fever	42	5	39	2.5	NS	
Other	Murray 1993 Coy 1994 Feld 1988	severe dermatitis blisters	149	2.0 4.0	133	1.5 0.7	NS (for both combined)	
	Qiao 2004	mild digestive tract reaction	45	73.3	45	55.6	NS	

Meta-Analysis/Meta-Regression

Overview

All but one of the studies selected for Key Questions 1 and 2 can be viewed as comparing early and late TRTx. Key Question 2 is limited to studies in which both early and late TRTx were given concurrently with chemotherapy, while Key Question 1 included those with arms defined by TRTx given either concurrently, sequentially or in alternating fashion. Only the study by Lebeau, Urban, Brechot et al. (1999) is excluded because only 1 week separated the start of TRTx in the study's 2 arms. Four previous meta-analyses have compared the impact of early and late TRTx, but none have included all 11 studies reviewed here. Three meta-analyses are summarized in Summary Table 25; a meta-analysis by Cancer Care Ontario (2003) is omitted because it used much more restrictive study selection criteria, including only 4 studies. The meta-analysis of 8 studies by Fried, Morris, Poole, et al. (2004) used the most rigorous methods and comprised the largest pool of the previous meta-analyses. The present meta-analysis addresses whether the findings of Fried, Morris, Poole, et al. (2004) can be reproduced in light of a larger study pool and different meta-analytic techniques.

Fried, Morris, Poole, et al. (2004) used the Mantel-Haenszel pooling method and found no significant heterogeneity at either 2 or 3 years; thus, fixed-effects models were employed. A significant increase in 2-year survival was found for early TRTx over late TRTx (RR: 1.17, 95 percent CI: 1.02–1.35). The effect was not significant at 3 years (RR: 1.13, 95 percent CI: 0.92–1.39). Subgroups of studies using hyperfractionation and platinum regimens had significant increases in 2- and 3-year survival favoring early TRTx, nonsignificant results were found for subgroups that did not use hyperfraction and platinum. Random effects meta-regression of risk differences (RDs) found that higher RDs were seen at both 2 and 3 years when studies used both hyperfractionation and platinum chemotherapy. Thus, larger effects of early over late TRTx were associated with combining hyperfractionation and platinum chemotherapy.

The present meta-analysis differs from that of Fried, Morris, Poole, et al. (2004) in the following ways: it included 3 additional studies; it used inverse variance weighting rather than the Mantel-Haenszel pooling method; and random effects meta-regression was carried out using RRs for this analysis and RDs by Fried, Morris, Poole, et al. (2004). In addition, Fried, Morris, Poole, et al. (2004) created 3 subgroups from the combination of hyperfractionation and platinum and used indicator variables for them in the meta-regression. This Review kept these variables separate. It could be argued that the hetereogeneity of comparisons across studies is too great to warrant pooling them. Like previous meta-analyses on this topic, we address this concern by using influence analysis, subgroup/sensitivity analysis, and meta-regression to investigate whether potential sources of hetereogeneity are associated with different results.

2-Year Mortality. The funnel plot in Figure 2 shows asymmetry in the lower right portion, suggestive of publication bias. The Egger regression test (Summary Table 15) reveals that the intercept differs significantly from zero. These results suggest the presence of publication bias.

Summary Table 16 and Figure 3 show 2-year RRs for each individual trial, along with 95 percent confidence intervals (CIs). It should be noted that all RRs were computed based on data from articles for all studies except Park, Kim, Jeong, et al. (1996). The Park, Kim, Jeong, et al. (1996) article did not give survival probabilities at yearly periods so an author was contacted

who provided data for a larger sample than was described in the original articles. The Sun, Zhang, Yin, et al. (1995) and Takada, Fukuoka, Kawahara, et al. (2002) trials both obtained 2-year RRs showing a significant reduction in the risk of mortality for early TRTx. One study (Perry, Herndon, Eaton, et al. 1998) found a slight nonsignificant increase in mortality for early TRTx and the remaining 6 studies yielded nonsignificant decreases in mortality for early TRTx.

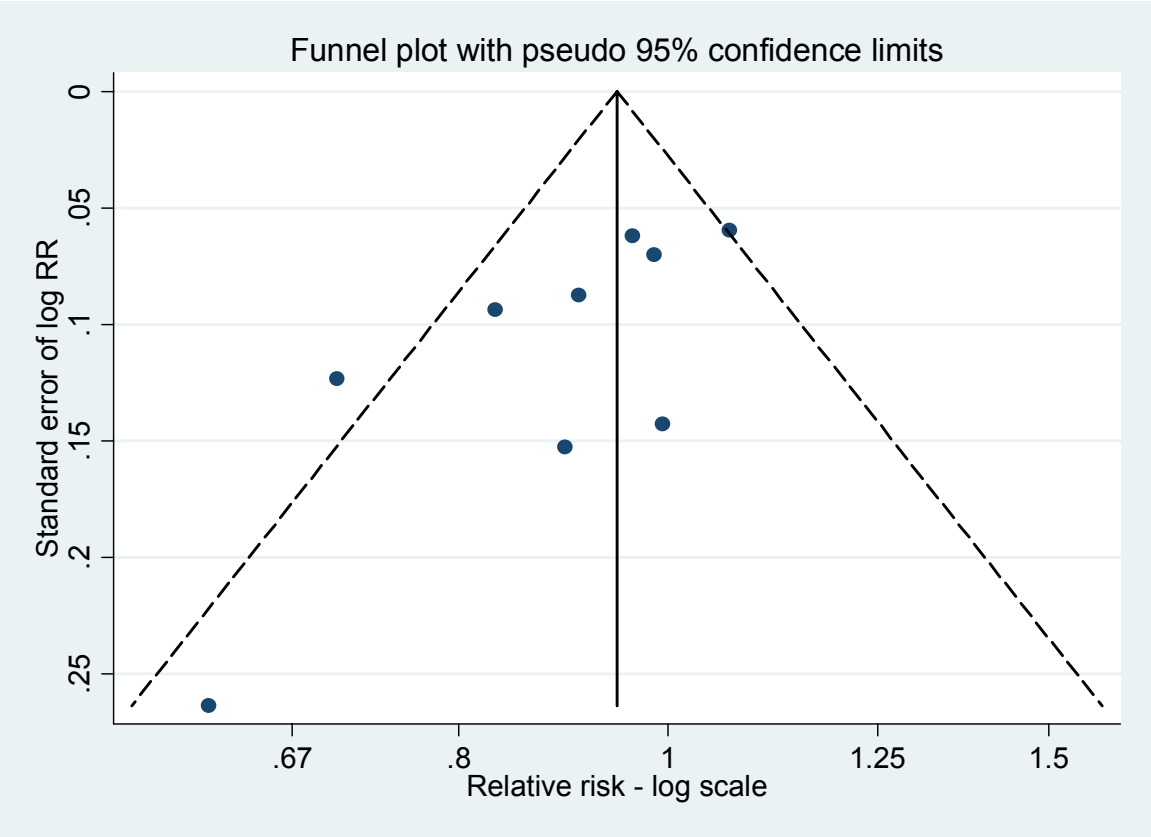


Figure 2: Two-Year Mortality Funnel Plot, Early vs.Late Thoracic Radiotherapy for Limited Stage Small-Cell Lung Cancer

Summary Table 15. Egger Linear Regression Test for Publication Bias, 2-Year Mortality

	Coefficient	Standard Error	L95	U95	t	p value
Intercept	-2.444	0.936	-4.658	-0.230	-2.61	0.035

Summary Table 16. Individual Trial 2-Year Mortality Relative Risks, Confidence Intervals and Covariate Matrix

Study	Early Deaths	Early n	Late Deaths	Late n	RR	L95	U95	Earliest	Hyper	Plat	Conc	GQ
Murray	93	155	101	153	0.909	0.766	1.079	0	0	1	1	1
Sun	46	64	51	59	0.831	0.692	0.999	0	0	0	0	0
Park	23	32	34	47	0.994	0.751	1.314	1	1	1	0	0
Gregor	126	170	127	165	0.963	0.852	1.088	0	0	0	0	1
Jeremic	15	52	24	51	0.613	0.366	1.028	1	1	1	1	0
Work	79	99	81	100	0.985	0.859	1.130	1	0	1	0	0
Perry	104	125	113	145	1.068	0.950	1.200	1	0	0	1	0
Skarlos	27	42	28	39	0.895	0.664	1.208	1	1	1	1	0
Takada	52	114	74	114	0.703	0.552	0.895	1	1	1	0	1

The Q statistic value obtained here (Summary Table 17) exceeds the threshold for concluding that significant heterogeneity of treatment effects exists, therefore a random effects pooled estimate was computed (see forest plot in Figure 3). The pooled RR is 0.921 and the 95 percent CI overlaps the null value of 1.0 (0.844, 1.005). Figure 4 presents the results of influence analysis, in which each individual study is excluded from the random effects pooled estimate. This graph can be interpreted by finding the studies that depart to the greatest extent from the vertical line for the full pooled estimate RR of 0.92. When the Perry study is excluded, the lowest RR estimate, 0.898, is obtained. So Perry exerts the greatest influence of pulling the pooled estimate toward the null or an advantage for late TRTx. Exclusion of the Takada, Fukuoka, Kawahara, et al. (2002) study results in the highest RR estimate, 0.955. Takada, Fukuoka, Kawahara, et al. (2002) is the most influential study in drawing the pooled estimate in the direction favoring early TRTx. Exclusion of the Perry study was the only instance in which a significant pooled result was obtained. However, as a whole, excluding any individual study has little influence on the estimate of the pooled RR.

Summary Table 17. Results from Heterogeneity Tests and Random Effects Meta-Analysis

	Study n	Subject n	Q	p value	RE RR	L95	U95	Z	p Value
2-Year Mortality	9	1726	15.393	0.052	0.921	0.844	1.005	-1.852	0.064

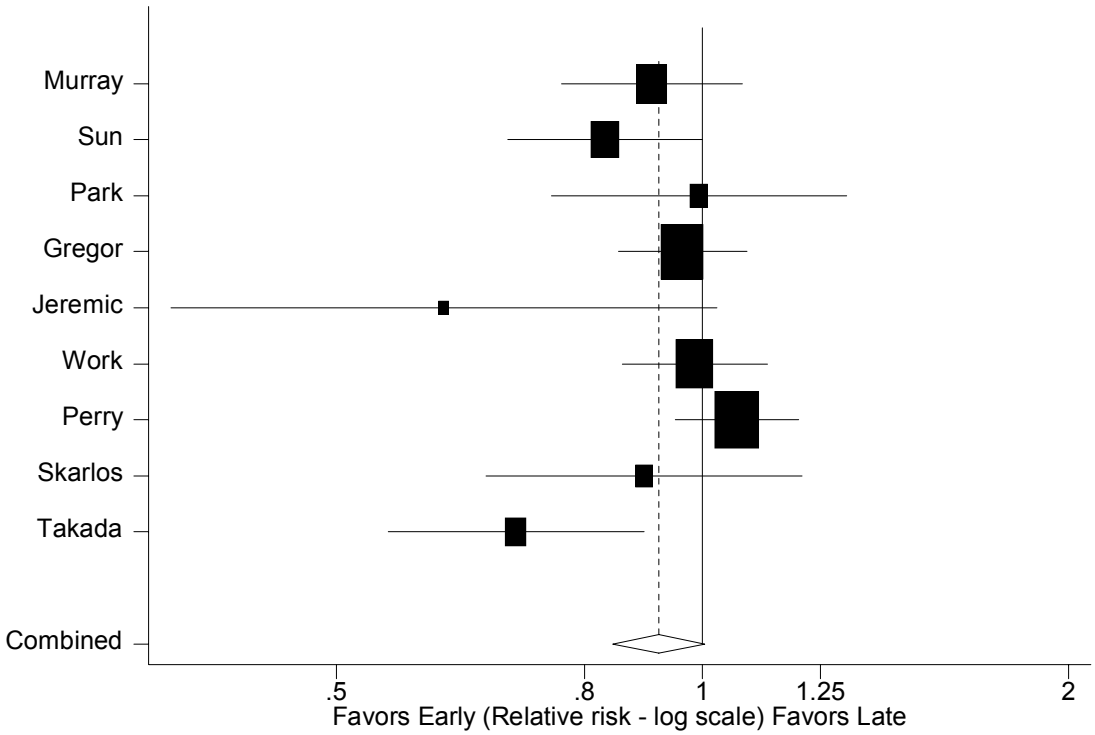


Figure 3: Two-Year Mortality Random Effects Forest Plot, Early vs.Late Thoracic Radiotherapy for Limited Stage Small-Cell Lung Cancer, All Trials

Summary Table 18 gives the results of subgroup/sensitivity analysis. Selection of variables defining subgroups was constrained by the relatively small pool of studies. Fine gradations of variables dilute the power to detect differences between early and late TRTx. Two concerns guide interpretation of subgroup results: the magnitude of differences in RR point estimates for different levels of a variable and whether statistical significance is achieved in any subgroup. Q statistic values exceeded the threshold for significant heterogeneity in 4 instances: among those studies that delivered the early TRTx at the earliest time (beginning in the first week of chemotherapy), those that did not use platinum chemotherapy, those that gave TRTx and chemotherapy concurrently, and those studies rated as being of good quality. These subgroups were pooled using random-effects models, while all other subgroups were pooled with fixed-effects.

Use of hyperfractionation was the variable with the greatest difference in point estimates of RR between subgroups of studies. Inclusion of studies using hyperfractionation produced a significant pooled RR of 0.815 (95 percent CI: 0.702–0.946). Studies that used once daily fractionation had a pooled RR much closer to the null, 0.972 (95 percent CI: 0.913–1.035). There was a moderate difference between point estimates of those studies that did and did not use platinum. Studies using platinum in chemotherapy regimens obtained a greater reduction in mortality, with a significant RR of 0.905 (95 percent CI: 0.829–0.987). Those not using

platinum yielded an RR close to the null, 0.964 (95 percent CI: 0.848–1.096). The set of studies that offered the earliest early TRTx did not result in a statistically significant reduction in mortality at 2 years for early TRTx (RR=0.914, 95 percent CI: 0.792–1.054). The point estimate for those studies not among the earliest was nearly identical and also nonsignificant (RR=0.918, 95 percent CI: 0.841–1.001). .Those using concurrent TRTx had a nonsignificant RR of 0.938 (95 percent CI: 0.799–1.100) and those not using concurrent TRTx had a significant RR of 0.920 (95 percent CI: 0.854–0.992). There was a considerable difference between studies of good quality and lesser quality, but pooled results were nonsignificant for both. Good quality studies produced a RR of 0.874 (95 percent CI: 0.744–1.027). Lesser quality studies had a RR of 0.975 (95 CI: 0.906–1.050). A random effects meta-regression (Table 19) found that no variables was a significant predict of differences in treatment effect at 2 years, but hyperfractionation was nearly significant (p=0.07).

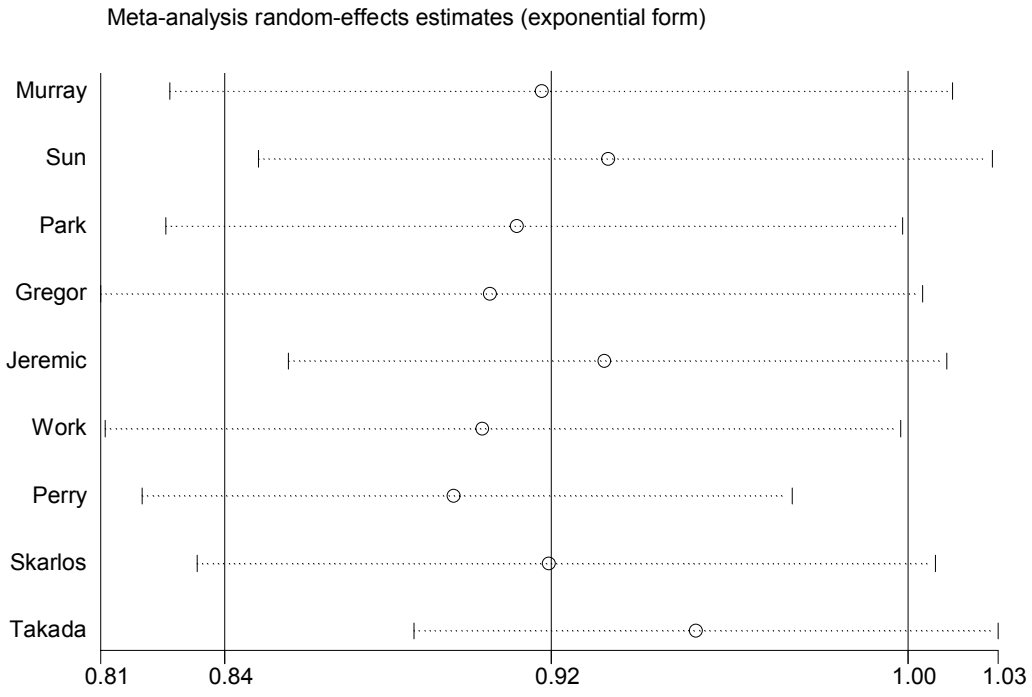


Figure 4: Two-Year Mortality Random Effects Influence Plot, Early vs.Late Thoracic Radiotherapy for Limited Stage Small-Cell Lung Cancer

Summary Table 18. Results of Subgroup/Sensitivity Analyses, Two-Year Mortality

2-Year Mortality	Study n	Subject n	Q	p value	Model	RR	L95	U95	Z	p value
Earliest-Yes	6	960	12.796	0.025	RE	0.914	0.792	1.054	-1.241	0.215
Earliest-No	3	766	1.720	0.423	FE	0.918	0.841	1.001	-1.929	0.054
Hyperfractionation-Yes	4	491	4.921	0.178	FE	0.815	0.702	0.946	-2.691	0.007
Hyperfractionation-No	5	1235	5.893	0.207	FE	0.972	0.913	1.035	-0.890	0.373
Platinum-Yes	6	998	8.300	0.140	FE	0.905	0.829	0.987	-2.258	0.024
Platinum-No	3	728	5.212	0.074	RE	0.964	0.848	1.096	-0.563	0.573
Concurrent RTx-Yes	4	762	6.285	0.099	RE	0.938	0.799	1.100	-0.790	0.430
Concurrent RTx-No	5	964	7.726	0.102	FE	0.920	0.854	0.992	-2.182	0.029
Good Quality-Yes	3	871	5.209	0.074	RE	0.874	0.744	1.027	-1.638	0.101
Good Quality-No	6	855	8.647	0.124	FE	0.975	0.906	1.050	-0.672	0.501

Summary Table 19. Results of Meta-Regression

2 Year Mortality

Model	Z	p value	Initial tau squared	Model tau squared
Earliest	0.26	0.797	0.0077	0.0086
Hyperfractionation	-1.81	0.070		0.0034
Platinum	-0.98	0.327		0.0070
Concurrent	0.57	0.571		0.0074
Good Quality	-0.82	0.414		0.0073

3-Year Mortality. The funnel plot (Figure 5) suggests the presence of publication bias. Point estimates appear to be missing in the lower right region of the plot. Linear regression (Egger test, Table 20) shows that the intercept differs significantly from zero, confirming that publication bias may be present.

Three-year mortality RRs for individual trials are given in Table 21. Three trials obtained RR estimates favoring late TRTx, while the other 8 favor early TRTx. The 95 percent CIs all overlap the null value RR of 1.0.

Table 22 shows that the Q statistic value does not exceed the level for concluding that significant heterogeneity of effects is present. Thus, a fixed effects model was used to compute a pooled 3-year RR (see forest plot in Figure 6). The obtained estimate was 0.991 (95 percent CI: 0.955–1.029). Based on these results, it cannot be concluded that use of early TRTx significant reduces the risk of mortality at 3 years.

The influence analysis plot in Figure 7 shows only extremely small changes in the pooled RR estimate when individual studies are excluded. When the Perry study is excluded, the lowest pooled RR estimate is produced: 0.977. This study has the greatest impact on drawing the pooled RR toward the null or effects favoring late TRTx. The largest pooled RR is derived when the Murray study is excluded: 1.000. Murray has the strongest influence on pulling the pooled RR away from the null, favoring early TRTx. Point estimates changed very little when individual studies were excluded.

Results of subgroup/sensitivity analysis are presented in Summary Table 23. The subset of studies using hyperfractionation yielded a significant pooled RR of 0.908 (95 percent CI: 0.828–0.995). Those that used once daily fractionation had a nonsignificant pooled RR of 1.008 (95 percent CI: 0.968–1.050). No other subgroup produced a significant result. Studies in which platinum was part of chemotherapy regimens had an RR of 0.958 (95 percent CI: 0.910–1.009). Non-platinum studies produced an RR of 1.029 (95 percent CI: 0.975–1.085). The group of studies in which early TRTx was begun at the earliest time produced a nearly null-value RR (0.998, 95 percent CI: 0.953–1.045). Those studies that began early TRTx after the first week of chemotherapy produced a similar RR (0.980, 95 percent CI: 0.921–1.042). Studies that offered concurrent RTx had a similar pooled RR (0.997, 95 percent CI: 0.947–1.051) compared with

those that did not (RR: 0.985, 95 percent CI: 0.935–1.038). There was a modest difference between studies of good quality versus lesser quality. Good quality studies had an RR of 0.948 (95 percent CI: 0.843–1.064), while fair and poor quality studies had an RR of 1.000 (95 CI: 0.956, 1.047). Results of random effects meta-regression are shown in Summary Table 24. Use of hyperfractionation (p=0.04) was the only significant predictor, while use of platinum (p=0.06) was nearly a significant predictor of differences in treatment effects.

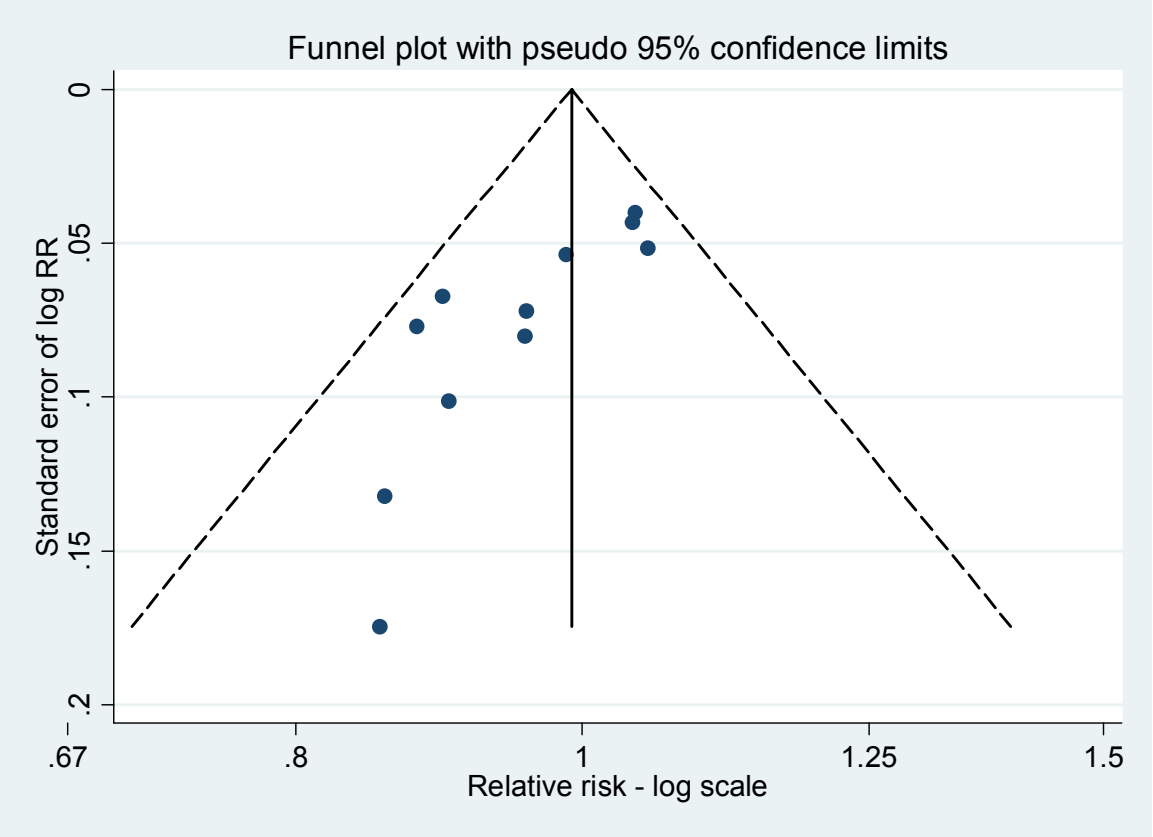


Figure 5: Three-Year Mortality Funnel Plot, Early vs. Late Thoracic Radiotherapy for Limited Stage Small-Cell Lung Cancer

Summary Table 20. Egger Linear Regression Test for Publication Bias, 3Year Mortality

	Coefficient	Standard Error	L95	U95	t	p value
Intercept	-2.351	0.540	-3.573	-1.130	-4.35	0.002

Summary Table 21. Individual Trial 3-Year Mortality Relative Risks, Confidence Intervals and Covariate Matrix

Study	Early Deaths	Early N	Late Deaths	Late n	RR	L95	U95	Earliest	Hyper	Plat	Conc	GQ
Murray	109	155	120	153	0.897	0.786	1.023	0	0	1	1	1
Sun	54	64	52	59	0.957	0.831	1.102	0	0	0	0	0
Park	28	32	43	47	0.956	0.817	1.119	1	1	1	0	0
Gregor	150	170	140	165	1.040	0.955	1.132	0	0	0	0	1
Jeremic	27	52	31	51	0.854	0.607	1.203	1	1	1	1	0
Work	86	99	88	100	0.987	0.888	1.097	1	0	1	0	0
Perry	115	125	128	145	1.042	0.963	1.128	1	0	0	1	0
Skarlos	33	42	34	39	0.901	0.739	1.099	1	1	1	1	0
Takada	80	114	91	114	0.879	0.756	1.023	1	1	1	0	1
James	134	159	133	166	1.052	0.951	1.164	1	0	1	1	0
Qiao	30	45	35	45	0.857	0.662	1.111	0	0	1	1	0

Summary Table 22. Results from Heterogeneity Tests and Fixed Effects Meta-Analysis

	Study n	Subject n	Q	p value	FE RR	L95	U95	Z	p Value
3-Year Mortality	11	2141	12.019	0.284	0.991	0.955	1.029	-0.457	0.648

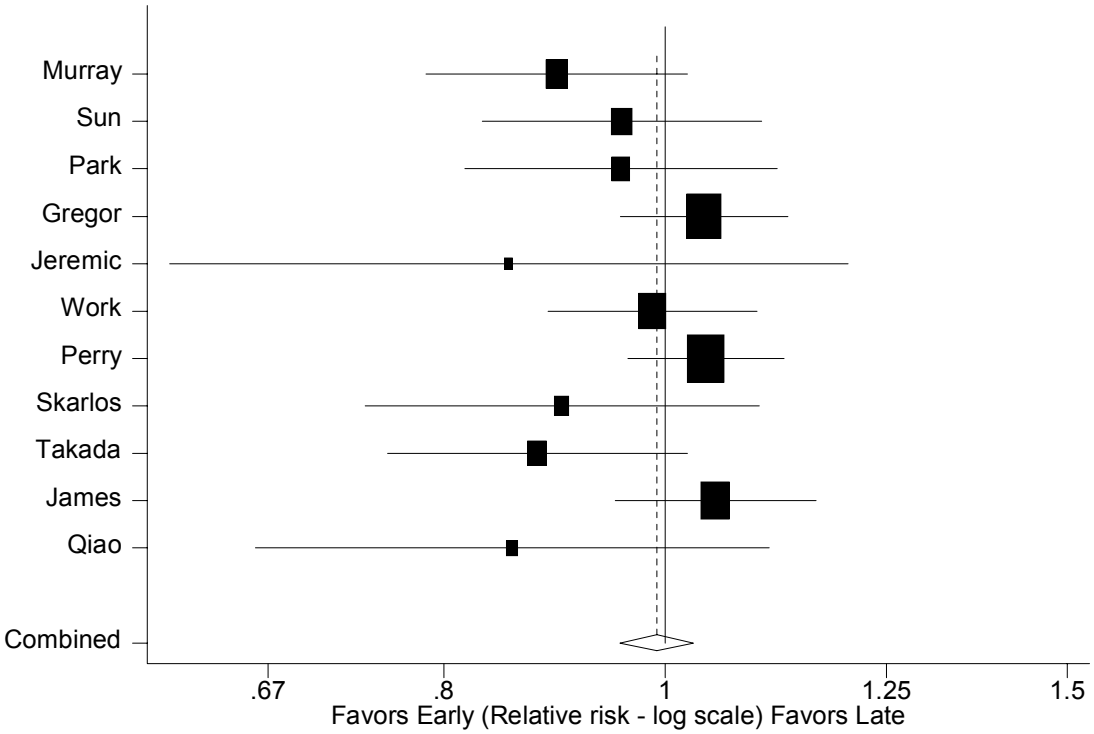


Figure 6: Three-Year Mortality Fixed Effects Forest Plot, Early vs. Late Thoracic Radiotherapy for Limited Stage Small-Cell Lung Cancer, All Trials

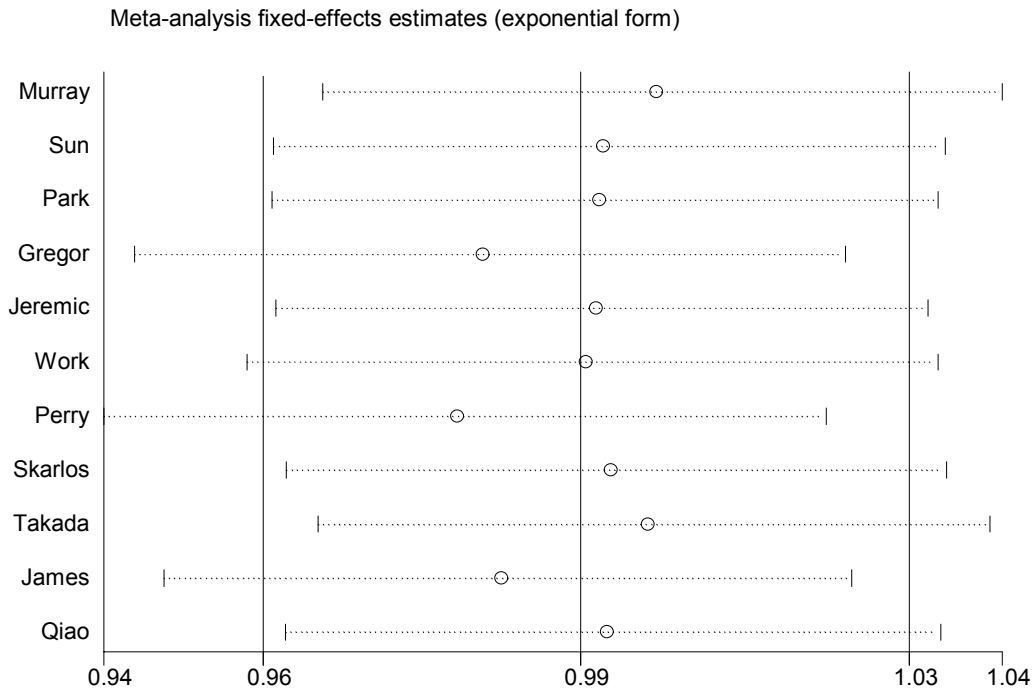


Figure 7: Three-Year Mortality Fixed Effects Influence Plot, Early vs. Late Thoracic Radiotherapy for Limited Stage Small-Cell Lung Cancer

Summary Table 23. Results of Subgroup/Sensitivity Analyses, Three-Year Mortality

3-Year Mortality	Study n	Subject n	Q	p value	Model	RR	L95	U95	Z	p value
Earliest-Yes	7	1285	7.037	0.317	FE	0.998	0.953	1.045	-0.089	0.929
Earliest-No	4	856	4.770	0.189	FE	0.980	0.921	1.042	-0.644	0.520
Hyperfractionation-Yes	4	491	0.722	0.868	FE	0.908	0.828	0.995	-2.061	0.039
Hyperfractionation-No	7	1650	7.095	0.312	FE	1.008	0.968	1.050	0.406	0.685
Platinum-Yes	8	1413	7.302	0.398	FE	0.958	0.910	1.009	-1.637	0.102
Platinum-No	3	728	1.167	0.558	FE	1.029	0.975	1.085	1.039	0.299
Concurrent RTx-Yes	6	1177	7.872	0.163	FE	0.997	0.947	1.051	-0.098	0.922
Concurrent RTx-No	5	964	4.045	0.400	FE	0.985	0.935	1.038	-0.549	0.583
Good Quality-Yes	3	871	5.580	0.061	RE	0.948	0.843	1.064	-0.908	0.364
Good Quality-No	8	1270	5.981	0.542	FE	1.000	0.956	1.047	0.015	0.988

Summary Table 24. Results of Meta-Regression

3 Year Mortality

Model	Z	p value	Initial tau squared	Model tau squared
Earliest	0.40	0.688	0.0008	0.0016
Hyperfractionation	-2.05	0.040		<0.0001
Platinum	-1.88	0.060		<0.0001
Concurrent	0.12	0.906		0.0016
Good Quality	-0.61	0.540		0.0015

Summary Table 25. Summary of Published Meta-Analyses on Early Versus Late Thoracic Radiation Therapy for Limited-Stage Small-Cell Lung Cancer

Study/ Meta-Analysis	Takada 2002	Murray 1993	Perry 1998	Jeremic 1997	Skarlos 2001	Work 1997	James 2003	Gregor 1997	Lebeau 1999	Goto 1999	Sun 1995	Qiao 2004	Park 1996	Method/ Measures	Handling of Hetero-geneity	Results(ratios compare early to late)
Fried, Morris, Poole, et al. (2004)	X	X	X	X	X	X	*	X						Fixed effects (M-H) 2 yr OS 3 yr OS RR RD NNT	M-H χ^2, subgroup analysis, sensitivity analysis, random effects meta-regression	All studies: 2 yr: OS RR 1.17 (1.02, 1.35); 3 yr OS RR 1.13 (0.92, 1.39) M-H χ^2 p=.17, 2 yr, p=.18, 3 yr Excluding Takada had large impact Subgroups: 2 yr p 3 yr p Hyperfractionation Y .001 .04 N NS NS Platinum Y .002 .01 N NS NS Concurrent RTx Y NS NS N NS NS M-R: hyperfractionation, platinum predicted significant difference between RDs
Pijls-Johannesma , De Ruysscher, Lambin, et al. (2005)	X	X	X	X	X	X	X							Random effects 2-3 yr OS 5 yr OS OR, RR	χ^2, subgroup analysis, random effects meta-regression	All studies: 2-3 yr OS OR: 0.84 (0.56, 1.28); 5 yr OS OR 0.80 (0.47, 1.38) χ^2 p=.006, 2-3 yr; p=05, 5 yr Subgroups: 2-3 yr p 5 yr p Platinum Y .01 .01 N .02 NS RTx < 30 d Y NS .006 M-R: significant association between RTx < 30 d and survival, 5 yr
Huncharek & McGarry (2004)	X	X	X	X	X	X			X	X				Fixed effects (Peto) 1 yr OS 2 yr OS 3 yr OS Peto OR	Q, sensitivity analysis	All studies: 1 yr OS P-OR: 1.11 (0.88, 1.40); 2 yr OS P-OR: 1.60 (1.29, 1.99); 3 yr OS P-OR: 1.49 (1.15, 1.93) Q, p<.001, 1 yr; p=.24, 2 yr; p=.81, 3 yr Subgroups: 1 yr p 2 yr p 3 yr p -Work, -Lebeau <.05<.05<.05 Platinum-Y <.05<.05<.05 Double-counted data at 2 yr, 3 yr (Goto is preliminary report of Takada)

* James, Spiro, O'Donnell, et al. (2003) study included by Fried, Morris, Poole, et al. (2004) only in informal post-hoc analysis; M-H: Mantel-Haenszel stratified-adjusted analysis; M-R: meta-regression; N: no; NS: not significant; OR: odds ratio; OS: overall survival; P-OR: Peto odds ratio; Q: heterogeneity statistic; RD: risk difference; RR: risk ratio; RTx: radiation therapy; X: included; Y: yes.

Summary. This meta-analysis indicates that the findings of Fried, Morris, Poole, et al. (2004) are not reproducible when different pooling methods are used and 3 additional studies are included. We found evidence of publication bias at both 2 and 3 years, while Fried, Morris, Poole, et al. (2004) found it at neither time. Significant heterogeneity was observed at 2 years here but not at 3 years. Thus, we used a random effects model at 2 years and a fixed effects model at 3 years, but Fried, Morris, Poole, et al. (2004) did not find significant heterogeneity at either period and used only fixed effects models. While Fried, Morris, Poole, et al. (2004) reported a significant advantage for early TRTx at 2 years and nonsignificance at 3 years, nonsignificant results were obtained here at both periods.

Subgroups including studies using hyperfractionation or platinum yielded significant advantages for early TRTx at 2 years in both Fried, Morris, Poole, et al. (2004) and this meta-analysis. At 3 years, Fried, Morris, Poole, et al. (2004) reported that both subgroups retained significance, while here only hyperfractionation was significant. The current meta-regression found hyperfractionation to be nearly significant (p=0.07) at 2 years; hyperfractionation was significant at 3 years (p=0.04) and platinum was nearly significant at 3 years (p=0.06). Fried, Morris, Poole, et al. found that hyperfractionation and platinum predicted heterogeneity in risk differences.

As an exercise, we ran multiple variable meta-regression models, but none were significant at either period. In particular, hyperfractionation and platinum were not significant independent predictors here in multiple variable models. In contrast, Fried, Morris, Poole, et al. (2004) found larger effects when the variables were combined. Any meta-gresssion with multiple variables models is limited by the risk of overfitting when the pool of studies is small.

Conclusions

All but one of the studies selected for Key Questions 1 and 2 can be viewed as comparing early and late TRTx. Therefore, these studies were pooled to give a more robust analysis of early versus late TRTx. Overall, we did not find significant reductions in 2- and 3-year mortality for early TRTx over late TRTx. The RR at 2 years was 0.921 (95 percent CI: 0.844–1.005) and the RR at 3 years was 0.991 (0.955, 1.029). Although the overall analysis was nonsignificant, sensitivity analysis suggests that if there is an advantage favoring early TRTx it would seem to depend on use of hyperfractionation and possibly use of platinum chemotherapy.

Key Question 3

For limited-stage SCLC, do outcomes (survival, toxicity, quality of life) of primary therapy differ if one varies dose rate, treatment interval, or fractionation scheme for delivering TRTx? Comparisons of interest include:

- accelerated regimens (>10 Gy per week completed over a short interval) versus standard duration regimens ($\leq$10 Gy per week) versus split courses delivered over the standard interval; and

- single daily fractions versus hyperfractionated (two or more daily fractions or concomitant boost).

Overview

Two randomized controlled trials (RCTs) compared one versus two fractions per day for previously-untreated limited stage SCLC (Turrisi, Kim, Blum, et al., 1999/Yuen, Zou, Turrisi, et al., 2000 [hereafter referred to as "Turrisi/Yuen"]; Schild, Bonner, Shanahan, et al., 2004/Sloan, Bonner, Hillman, et al., 2002/Bonner, Sloan, Shanahan, et al., 1999 [hereafter referred to as "Schild/Sloan/Bonner"]; N=678). No other randomized trials directly compared dose rates, treatment intervals or fractionation schemes. Summary Table 26 summarizes selected characteristics; further details are in Appendix Tables 3A-C, 3H.*

Summary Table 26 Selected study characteristics of RCTs comparing one versus two fractions per day

study	N		chemoTx regimen	TRTx dose, Gy		# fractions x size; TRTx duration		TRTx started	PCI?
	2/d	1/d		2/d	1/d	2/day	1/day		
Turrisi, Kim, Blum, et al., 1999/Yuen, Zou, Turrisi, et al., 2000	211	206	PE	45	45	30 x 1.5 Gy; 3 wks	25 x 1.8 Gy; 5 wks	week 1	yes
Schild, Bonner, Shanahan, et al., 2004/Sloan, Bonner, Hillman, et al., 2002/Bonner, Sloan, Shanahan, et al., 1999	130	131	PE	48	50.4	32 x 1.5 Gy; 6 wks*	28 x 1.8 Gy; 6 wks	week 13	yes

* Split course: 16 fractions over 1.5 weeks, 2.5 weeks rest, then final 16 fractions over 1.5 weeks
Abbreviations table provided at the end of the Report.

Interventions. While total radiation doses were similar (45–50 Gy), and each trial compared one versus two fractions per day, they differed with respect to TRTx timing relative to chemotherapy cycles and other regimen features. The Turrisi/Yuen trial began TRTx in week one of cycle one, used the same total dose (45 Gy) in each arm, and gave radiation continuously (5 days/week for 3 or 5 weeks) in each arm. Thus, patients randomized to two fractions per day received 3 Gy daily and 15 Gy weekly, while those randomized to one fraction per day received 1.8 Gy daily and 9 Gy weekly.

The Schild/Sloan/Bonner trial administered three chemotherapy cycles, then restaged and randomized patients and began TRTx at week 13. Patients whose tumor had progressed during the initial three cycles were excluded if a single radiation field no longer encompassed the full extent of disease. Those randomized to two fractions per day received two split courses, each 24 Gy over 1.5 weeks, separated by 2.5 weeks' rest. Those randomized to one fraction per day received 50.4 Gy over 6 weeks, as 5 days/week of continuous TRTx. Thus, patients in the two-per-day arm received 3 Gy each treatment day, and 16 Gy/week in each of two 1.5 week courses. Those in the one-per-day arm received 1.8 Gy daily and 9 Gy weekly for 5 weeks and 3 days.

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf.

Both RCTs used cisplatin-etoposide chemotherapy (Summary Table 26). However, cisplatin dose in the Turrisi/Yuen trial was 60 mg/m^2 each 21-day cycle, but was 30 mg/m^2 each 28 day cycle in the Schild/Sloan/ Bonner trial (Appendix Table 3C).*

Study Populations. Each trial's study population had relatively good prognosis, and was well-balanced across arms for consistently reported baseline characteristics (Summary Table 27, Appendix Table 3B).* More than 90 percent of patients had good performance status (PS) of 0-1 at enrollment. Median or mean age ranged from 61 to 63 years across arms. Each trial enrolled mostly men (41 percent to 43 percent women across arms). Each reported the proportion of patients with weight loss at entry, and few (1–5 percent) had lost more than 10 percent.

The two trials did not consistently report other prognostic factors or baseline characteristics (Appendix Table 3B).* One trial reported both the proportion with disease outside the lung and the patients' racial distribution (Turrisi/Yuen). The other trial stratified patients by response to initial chemotherapy (Schild/ Sloan/Bonner). Neither trial reported the proportion of former or current smokers.

Study Quality and Reporting. Both trials were multicenter studies, published in full, and rated as good quality.

Results

The Turrisi/Yuen trial, using immediate concurrent TRTx, found that overall survival (OS) significantly favored the 2/day arm (Summary Table 28). The trial (n=211 2/day arm, 206 1/day arm) reported significantly longer median OS (23 versus 19 months; HR=1.2, 95 percent CI: 1.0–1.6; p=0.04) and greater 2- and 5-year survival (47 percent versus 41 percent, and 26 percent versus 16 percent, respectively) with two fractions per day (Turrisi/Yuen). However, the difference in failure-free survival at 2 years (29 percent versus 24 percent) was not statistically significant (p=0.10). Between-arm differences in response rates also were not statistically significant (Appendix Table 3F).*

Using late TRTx and split course therapy in the 2/day arm, Schild/Sloan/Bonner reported no significant difference between arms in overall (p=0.68) or progression-free (p=0.68) survival. Since this trial stratified patients by responses to three cycles of chemotherapy given before randomization, excluded any whose disease progressed substantially, and used an extended split-course rather than accelerated schedule in the 2/day arm, response rates could not be compared across arms or trials in a meaningful way.

Neither trial reported quality of life outcomes (Appendix Table 3F).*

The trials differed with respect to the frequency and/or between-arm comparisons of some adverse events, but were similar for others (Summary Table 29). Schild/Sloan/Bonner reported 3 percent treatment-related deaths in the 2/day arm and none in the 1/day arm (p=0.04), while Turrisi/Yuen reported similar rates in each arm (2–3 percent). Turrisi/Yuen reported no significant differences between arms in the proportion of patients experiencing one or more grade 3 (25 percent versus 23 percent), or grade 4 (62 percent versus 63 percent) toxicities. In contrast, Schild/Sloan/ Bonner reported significantly more patients in the 2/day arm than the

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf.

1/day arm with a non-hematologic toxicity of grade $\geq$3 (54.6 percent versus 38.9 percent, p=0.01) or grade 5 (3 percent versus zero, p=0.04).

Summary Table 27. Sample and Methods: Alternative Fractionations Schemes (once versus twice daily)

Study	N	Age	% Female	% Performance Status	CTx Regimen	RTx Regimen		
Turrisi, Kim, Blum, et al., 1999/Yuen, Zou, Turrisi, et al., 2000 multicenter trial 5/89-7/92	Total 417 1 F/d 206 2 F/d 211	md (rng) 63 (34-80) 61 (30-82)	 41 42	0 1 2 3 43 51 5 39 55 5	PE (4 x 21 day cycles; 1 or 2 during, 2 or 3 after TRTx)	Dose 1 F/d: 45 Gy 2 F/d 45 Gy	Schedule 1.8 Gy/frac, 5 d/wk, 5 wks, begun in 1st wk of CTx 1.5 Gy/frac, 5 d/wk, 3 wks, begun in 1st wk of CTx	PCI? 10 x 2.5 Gy, if CR same
Schild, Bonner, Shanahan, et al., 2004/Sloan, Bonner, Hillman, et al., 2002/Bonner, Sloan, Shanahan, et al., 1999 multicenter trial 9/90 -11/96	Total 261 1 F/d 131 2 F/d 130	mn (rng) 61.8 (38-81) 62.1 (37-79)	 42.0 43.1	0-1 2 97.7 5.3 93.1 6.9	PE (6 x 28 day cycles; 3 before, 2 during, 1 after TRTx)	Dose 1 F/d: 50.4 Gy 2 F/d 48 Gy	Schedule 28 x 1.8 Gy fracs, 38 d, 1st 39.6 Gy in AP-PA fields, last 10.8 Gy in oblique fields excluding spine, wks 13-16 32 x 1.5 Gy fracs; ≥4 hours apart; split course (16 fracs in 1.5 weeks; 2.5 weeks rest; then 16 fracs in 1.5 weeks)	PCI? 15 x 2 Gy if CR same

Abbreviations table provided at the end of the Report.

Summary Table28. Survival Outcomes: Alternative Fractionations Schemes (once versus twice daily)

Study	N		Overall Survival Med	1 yr	2 yr	3 yr	4 yr	5 yr	Failure- or Progression-Free Survival Med	1 yr	2 yr	3 yr	4 yr	5 yr
Turrisi, Kim, Blum, et al., 1999/Yuen, Zou, Turrisi, et al., 2000	1 F/d	206	19	~75%	41%	~32%	~29%	16%	FFS:		24%			
	2 F/d	211	23	~70%	47%	~28%	~20%	26%			29%			
	Difference		4 (log-rank p=0.04; HR 1.2, 95% CI: 1.0, 1.6)	~5%	6%	~4%	~9%	10%			5% (p=0.10)			
Schild, Bonner, Shanahan, et al., 2004/Sloan, Bonner, Hillman, et al., 2002/Bonner, Sloan, Shanahan, et al., 1999 multicenter trial 9/90 -11/96	1 F/d	131	20.6	~74%	44%	~33%	~23%	20.4%	PFS: ~14	~57%	31.3%	~25%	~23%	19.8%
	2 F/d	130	20.6	~74%	44%	~31%	~26%	22%	~14	~58%	30.8%	~27%	~21%	21%
	Difference		0 (p=0.68, log-rank)	0%	0%	-2%	3%	1.6%	0 (p=0.68, log-rank)	1%	-0.5%	2%	-2%	1.2%

Abbreviations table provided at the end of the Report.

Summary Table 29. Adverse Events: Alternative Fractionations Schemes (once versus twice daily)

Toxicity Type	Study	Severity or Grade	1 F/d n	%	2 F/d n	%	p	Not Reporting
Treatment-related mortality	Turrisi 1999 Yuen 2000		203	2	206	3	NS	
	Bonner 1999 Sloan 2002 Schild 2004		131	0	130	4	0.04	
Nausea/Vomiting	Turrisi 1999 Yuen 2000	grade 3 vomiting grade 4 vomiting	203	8 2	206	8 1	 NS (3+4)	
	Bonner 1999 Sloan 2002 Schild 2004	≥ grade 3 nausea ≥ grade 3 vomiting	132	16.7 12.1	130	16.9 14.6	NS NS	
Anorexia	Turrisi 1999 Yuen 2000	grade 3 weight loss grade 4 weight loss	203	3 0	206	2 0	 NS (3+4)	
	Bonner 1999 Sloan 2002 Schild 2004	≥ grade 3	132	3.0	130	2.3	NS	
Lethargy	Bonner 1999 Sloan 2002 Schild 2004	≥ grade 3	132	3.0	130	7.7	NS	Turrisi 1999/Yuen 2000
Neurosensory	Bonner 1999 Sloan 2002 Schild 2004	≥ grade 3	132	7.6	130	11.5	NS	Turrisi 1999/Yuen 2000
Hearing loss	Bonner 1999 Sloan 2002 Schild 2004	≥ grade 3	132	1.5	130	3.8	NS	Turrisi 1999/Yuen 2000
Esophagitis	Turrisi 1999 Yuen 2000	grade 3 grade 4	203	11 5	206	27 5	<0.001	
	Bonner 1999 Sloan 2002 Schild 2004	≥ grade 3	132	5.3	130	12.3	0.05 (per investigators; 0.074 by corrected χ^2)	
Bronchopulmonary	Turrisi 1999 Yuen 2000	grade 3 grade 4 & 5	203	3 1	206	4 2	 NS (3-5)	
	Bonner 1999 Sloan 2002 Schild 2004	≥ grade 3	132	4.5	130	6.2	NS	
Pneumonitis	Bonner 1999 Sloan 2002 Schild 2004	≥ grade 3	132	4.5	130	6.2	NS	Turrisi 1999/Yuen 2000
Kidney								Turrisi 1999/Yuen 2000; Bonner 1999/Sloan 2002/Schild 2004
Anemia	Turrisi 1999 Yuen 2000	grade 3 grade 4	203	23 3	206	23 5	 NS (3+4)	
	Bonner 1999 Sloan 2002 Schild 2004	≥ grade 3	132	3.0	130	2.3	NS	

Summary Table29. Adverse Events: Alternative Fractionations Schemes (once versus twice daily) (cont'd)

Toxicity Type	Study	Severity or Grade	1 F/d	n	%	2 F/d	n	%	p	Not Reporting
Thrombocytopenia	Turrisi 1999	grade 3	203	16		206	13			
	Yuen 2000	grade 4		8			8		NS (3+4)	
	Bonner 1999	≥ grade 3	128	60.9		127	45.7		0.0145	
	Sloan 2002	grade 4		24.2			20.5		NS	
	Schild 2004									
Leukopenia or neutropenia	Turrisi 1999	grade 3	203	41		206	38		NS (3+4)	
	Yuen 2000	grade 4		39			44		NS	
	Bonner 1999	≥ grade 3	128	88.3		127	89.8		NS	
	Sloan 2002	grade 4		37.5			36.2		NS	
	Schild 2004									
Hemoglobin	Bonner 1999	≥ grade 3	128	5.3		127	3.8		NS	Turrisi 1999/Yuen 2000
	Sloan 2002									
	Schild 2004									
Infection	Turrisi 1999	grade 3	203	6		206	6			
	Yuen 2000	grades 4 & 5		2			3		NS (3-5)	
	Bonner 1999	≥ grade 3	132	2.3		130	3.8		NS	
	Sloan 2002									
	Schild 2004									
Other	Turrisi 1999	one or more grade 3, no grade 4	203	23		206	25		NS	
	Yuen 2000	one or more grade 4, no grade 5		63			62		NS	
	Bonner 1999	any hematologic, ≥ grade 3	131	90.1		130	89.2		NS	
	Sloan 2002	any hematologic,, ≥ grade 4		43.5			42.3		NS	
	Schild 2004	any nonhematologic, ≥ grade 3		38.9			54.6		0.01	
		any nonhematologic, ≥ grade 4		9.2			13.8		NS	
		any nonhematologic, grade 5		0.0			3.1		0.04	
		any toxicity, ≥ grade 3		91.6			92.3		NS	
		any toxicity, ≥ grade 4		46.6			46.9		NS	
		any toxicity, grade 5		0.0			3.1		0.04	

With respect to hematologic toxicities, Schild/ Sloan/Bonner reported substantially more grade ≥3 thrombocytopenia (46 percent and 61 percent for 2/day and 1/day, respectively) than did Turrisi/Yuen (21 percent and 24 percent for 2/day and 1/day, respectively). The difference significantly favored the 2/day arm in Schild/Sloan/Bonner. However, grade 4 thrombocytopenia did not differ significantly between arms in either trial. Neither trial reported a significant difference between arms in incidence of grade ≥3 anemia, but it was substantially more common with early TRTx and larger cisplatin doses (Turrisi/Yuen; 26 percent and 28 percent) than with late TRTx and smaller cisplatin doses (Schild/Sloan/Bonner; 3 percent and 2.3 percent). Grade ≥3 leukopenia/ neutropenia was common in both trials, and did not differ across arms in either (≥80 percent in each).

With respect to non-hematologic toxicities, esophagitis was more common with twice daily than with once daily TRTx in each trial. Esophagitis also appeared more common in the Turrisi/Yuen trial, which used an accelerated schedule in the hyperfractionated arm, than in the other study, which used a split-course schedule. Both trials reported no significant differences between arms in incidence of vomiting, anorexia, bronchopulmonary effects, and infections. Grade ≥3 vomiting was not uncommon (9–15 percent). The other grade ≥3 adverse events reported by both trials each occurred in ≤10 percent of patients. Only Schild/Sloan/Bonner reported on lethargy, neurosensory effects, hearing loss, and pneumonitis. Between-arm differences were not statistically significant for any of these adverse events.

Conclusions

Evidence to compare dose rates, treatment intervals, or fractionation schemes is limited. One RCT suggests that starting TRTx with the first cycle of cisplatin-etoposide chemotherapy and giving it in two daily fractions over 3 weeks increases overall survival when compared with the same dose begun at the same time but given in one daily fraction over 5 weeks. Evidence from a second trial is difficult to interpret, since multiple variables were studied simultaneously. However, it found no difference in overall survival between treatment arms managed with one versus two fractions per day. Neither trial reported data on quality of life. Esophagitis was the only adverse event reported more frequently with two fractions per day than with one fraction per day in both trials.

Key Question 4

What are the relative benefits and harms (survival, toxicity, and quality of life) of adding TRTx to chemotherapy for primary treatment of extensive-stage SCLC?

Overview

Five small RCTs compared outcomes of chemotherapy with versus without TRTx for previously-untreated extensive stage SCLC (N=238; 110–135 randomized to +TRTx, 103–128 to -TRTx). Summary Table 30 summarizes selected characteristics of these trials; more complete

details are in Summary Table 31 and Appendix Tables 4A-C, 4H.* The Jeremic, Shibamoto, Nikolic, et al. (1999) trial randomized 109 patients; other trials were smaller, ranging from 18 to 54 patients.

Interventions. Of the five available trials, only Jeremic, Shibamoto, Nikolic, et al. (1999) tested effects of TRTx in the context of current treatment strategies (regimens, doses, and schedules). Although both Jeremic, Shibamoto, Nikolic, et al. (1999) and Lebeau, Chastang, Brechot, et al. (1993) used platinum-etoposide chemotherapy regimens, only Jeremic, Shibamoto, Nikolic, et al. (1999) administered chemotherapy and radiation concurrently. Lebeau, Chastang, Brechot, et al. (1993) gave radiation therapy after all chemotherapy was completed (sequential administration), while the other three trials alternated chemotherapy and radiation and did not use platinum-based chemotherapy. Also noteworthy are the wide range of radiation doses used by Lebeau, Chastang, Brechot, et al. (1993), and the low dose and unusual schedule of TRTx used by Brincker, Hindberg, Hansen, et al. (1987).

Another study design feature, unique to Jeremic, Shibamoto, Nikolic, et al. (1999) (Appendix Table 4A),* permits outcomes of randomized (chemotherapy-responsive) patients to be compared with those of nonrandomized patients who responded less completely outside the chest. All patients registered for this trial received 3 cycles of cisplatin/etoposide (PE) before randomization. To be eligible for the RCT, patients had to achieve a complete response (CR) outside the thorax and respond at least partially (PR) in the thorax after three PE cycles. Those who achieved only a PR outside the thorax, and those with less than PR in either site, were not randomized, but were treated with chemotherapy plus TRTx and followed.

Study Populations. Only Jeremic, Shibamoto, Nikolic, et al. (1999) limited enrollment to extensive-stage disease (ESD) patients. The others included both stages (Appendix Table 4A),* but reported at least one outcome separately by arm for those with ESD. Rosenthal, Tattersall, Fox, et al. (1991) did not report the number of ESD patients per treatment arm.
Data on baseline characteristics showed that ESD patients enrolled in each arm of Jeremic, Shibamoto, Nikolic, et al. (1999) and Nou, Brodin, and Bergh (1998) were similar (Summary Table 31, Appendix Table 4B).* The other RCTs pooled baseline characteristics for extensive- and limited-stage patients (Lebeau, Chastang, Brechot, et al., 1993; Brincker, Hindberg, Hansen, et al., 1987) or for all participants (Rosenthal, Tattersall, Fox, et al., 1991), thus similarity of ESD patients was uncertain.

Most patients in Jeremic, Shibamoto, Nikolic, et al. (1999) had good performance at enrollment (67 percent with Karnofsky scores 90-100, excluded if $\leq$60), while Nou, Brodin, and Bergh (1998) included many with poorer performance (median Karnofsky score 60, range 30–90). Median age ranged from 59 to 65 years across study arms. Both trials enrolled mostly men (25 percent to 41 percent women across arms). Just over half of patients in each trial had $\geq$2 metastatic sites (50 percent to 58 percent across arms; Appendix Table 4B).† Less than half of patients in Jeremic, Shibamoto, Nikolic, et al. (1999) had lost $\geq$5 percent of body weight at enrollment, but Nou, Brodin, and Bergh (1998) did not report this potential marker of poor prognosis. Neither trial reported distributions by race.

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf.
† Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf.

Study Quality and Reporting. All five trials were published in full, but only two were multicenter studies (Lebeau, Chastang, Brechot, et al., 1993; Rosenthal, Tattersall, Fox, et al., 1991) and only Nou, Brodin, and Bergh (1998) was a good-quality trial. Jeremic, Shibamoto, Nikolic, et al. (1999) was of fair quality since it did not report on methods used for randomizing patients. The other three were of poor quality to evaluate the role of TRTx for ESD patients (Appendix Table 4H).* Data were unavailable for each of the poor quality trials to evaluate the comparability of randomized ESD patients; two had excessive loss to follow-up (Rosenthal, Tattersall, Fox, et al. 1991; Brincker, Hindberg, Hansen, et al., 1987), and each failed to analyze and report all important outcomes separately for ESD patients.

Summary Table 30. Selected Characteristics of RCTs Comparing Chemotherapy with versus without TRTx

study	N		Pt?	chemoTx regimen	TRTx timing*	TRTx dose	TRTx schedule; fractionation	PCI?	# centers	quality rating
	+TRTx	-TRTx								
Jeremic, Shibamoto, Nikolic, et al., 1999	55	54	yes	PE/CbE	concurrent	54 Gy	wks 10-13; 36 x 1.5Gy, 2/d	yes	one	fair
Nou, Brodin, and Bergh, 1988	28	26	no	CAVML	alternating	40 Gy	wks 10-13; 20 x 2 Gy, 1/d	no	one	good
Lebeau, Chastang, Brechot, et al., 1993	10	8	yes	LCAE/PEVe	sequential	32-65 Gy	wks 36-39; 2 Gy fracs, 1/d	some	multi	poor
Rosenthal, Tattersall, Fox, et al., 1991	27 total; N/arm NR		no	M-CAV	alternating	40 Gy	wks 10-?; 20 x 2 Gy, ?/d	?	multi	poor
Brincker, Hindberg, Hansen, et al., 1987	16	14	no	CAV/LME	alternating	12 Gy	days 60 and 100; 6 Gy each	?	one	poor

* Timing relative to chemotherapy administration
Abbreviations table provided at the end of the Report.

Summary Table 31. Sample and Methods: Chemotherapy with versus without Thoracic Radiation Therapy, Extensive Stage Disease (ESD)

Study	N	Age	% Female	% Performance Status	CTx Regimen	RTx Regimen		
Jeremic, Shibamoto, Nikolic, et al., 1999[1] single center: 01/88 – 06/93	Total 109 +TRTx 55 -TRTx 54 nonrandomized CR/PR: 34 PR/PR: 28 SD/PD 35	md (rng) 59 (38-70 59 (39-71)	 40 41	100 90 80 70 31 36 18 15 24 43 18 15 KPS	PE/Cb-E	Dose 54 Gy	Schedule 24 x 1.5 Gy fracs; 2 frac/d, over 2.5 wks, then 12 x 1.5 Gy fracs, 2 frac/d over 6 d	PCI? 25 Gy, 10 fracs
Nou, Brodin, and Bergh, 1988[2] single center 01/80 - 12/83 (ESD only)	Total 54 +TRTx 28 -TRTx 26	md (rng) 65 (55-78) 60 (41-81)	 25 31	med (rng) 60 (30-90) 60 (30-90) KPS	cytoxan, vincristine, doxorubicin, methotrexate, lomustine	Dose 40 Gy	Schedule 1 frac/d, 2 Gy each, 5 d/wk, over 4 wks	PCI? No
Lebeau, Chastang, Brechot, et al., 1993[3] 27 centers 10/85 - 04/88	Total 18 +TRTx 10 -TRTx 8	≥ 60 48 38.5	 4 8	90-100 70-80 60 63 22 15 46 50 4 KPS	CCNU, cytoxan, doxorubicin, etoposide, cisplatin, vindesine	Dose mn 46.5 Gy (rng: 32-65 Gy)	Schedule begun 4 wks after last CTx cyc; varied schedules: 32 Gy in 9 frac over 11-18 d to 65 Gy in 33 frac over 64 d vincristine,	PCI? some, but N/arm uncertain for ESD
Rosenthal, Tattersall, Fox, et al., 1991[3] 3 centers 01/77 - 07/79	Total 27 +TRTx ? -TRTx ?	md (rng) 60 (26-77)	 24	0 1 2 ? 1 88 3 8	cytoxan, vincristine, doxorubicin; + methotrexate (IV or intra-thecal)	Dose 40 Gy	Schedule 20 fracs between CTx cycs 3, 4	PCI? not specified

Abbreviations table provided at the end of the Report.

Summary Table 31. Sample and Methods: Chemotherapy with versus without Thoracic Radiation Therapy, Extensive Stage Disease (ESD) (continued)

Study	N	Age	% Female	% Performance Status	CTx Regimen	RTx Regimen		
				0 1 2 3		Dose	Schedule	PCI?
Brincker, Hindberg, Hansen, et al., 1987[3]	Total 30	md (rng)			cytoxan, vincristine,			
	+TRTx 16	60 (42-69)	27	34 51 15	doxorubicin, methotrexate	12 Gy	2 fracs, 6 Gy each, day 60 to upper hemi-body and day 100 to lower hemi-body	not specified
single center	-TRTx 14	63 (46-69)	27	24 57 19	, lomustine, etoposide			
03/81 - 01/84								

[1] enrollment limited to ESD patients; [2] enrolled ESD & LSD patients, and reported characteristics of each separately;
[3] enrolled ESD & LSD patients, but only reported characteristics for the two groups pooled

Results

Jeremic, Shibamoto, Nikolic, et al. (1999) reported that adding concurrent TRTx to platinum-based chemotherapy for good-performance patients selected by their response to an initial 3 cycles of platinum-etoposide (PE) significantly improved overall survival (median OS, 17 versus 11 months; 2- and 3-year OS, 38 percent versus 28 percent and 22 percent versus 13 percent respectively; p=0.041) and relapse-free survival (median RFS, 13 versus 9 months; 2- and 3-year RFS, 35 percent versus 22 percent and 20 percent versus 9 percent, respectively; p=0.045) (Summary Table 32). Jeremic, Shibamoto, Nikolic, et al. (1999) also reported that adding TRTx to chemotherapy for these selected patients significantly increased CR rates in the thorax at week 21 (96 percent versus 66 percent; p=0.00005) (Appendix Table 4F). However, the improvement in duration of CRs in the thorax did not achieve statistical significance (mean, 22$\pm$26 versus 14$\pm$16 months; p=0.055).

Only 3% of non-randomized patients who achieved PR outside the thorax and CR in the thorax after three cycles of PE survived at 3 years, despite TRTx and additional chemotherapy (Summary Table 32). Furthermore, no patients who achieved only PR at each site survived at three years. However, data are unavailable to compare these outcomes with similar patients managed without TRTx.

No other trial reported a statistically significant effect of TRTx on survival of ESD patients (Summary Table 32). This includes Lebeau, Chastang, Brechot, et al. (1993), which only randomized patients in CR after eight cycles of chemotherapy (Appendix Tables 4A, 4F)[*] and used a chemotherapy regimen with cisplatin (Summary Table 31). Whether the absence of a significant effect reflects the small size and inadequate statistical power of these trials, or is attributable to their use of chemotherapy regimens, timing and sequencing of TRTx, or radiation doses and schedules that differed from those used in Jeremic, Shibamoto, Nikolic, et al. (1999) is uncertain, since available data are insufficient.

None of the trials reported data on quality of life (Appendix Table 4F).[*] Jeremic, Shibamoto, Nikolic, et al. (1999) reported significantly more grade 3 and 4 esophagitis (27 percent versus zero, p=0.0002), but significantly less grade 3 and 4 nausea and vomiting (9 percent versus 34 percent, p=0.0038) and renal toxicity (zero versus 22 percent, p=0.001) in the arm given TRTx (Summary Table 33). No other statistically significant differences between arms were reported for adverse events.

[*] Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf.

Summary Table 32. Survival Outcomes: Chemotherapy with versus without Thoracic Radiation Therapy, Extensive Stage Disease (ESD)

Study	N	OS Med	1 yr	2 yr	3 yr	4 yr	5 yr	RFS Med	1 yr	2 yr	3 yr	4 yr	5 yr
Jeremic,1999[1]	+TRTx 55	17	65%	38%	22%	13%	9.1%	13	56%	35%	20%	13%	9.1%
	-TRTx 54	11	46%	28%	13%	5.6%	3.7%	9	41%	22%	9.3%	5.6%	1.9%
	Difference	6	19%	10%	9%	7.4%	5.4%	4	15%	13%	10.7%	7.4%	7.2%
		(p=0.041 by log-rank test)											
		unrandomized groups by post-3rd cycle response (thorax/ elsewhere):											
	CR/PR: 34	8	35%	8.8%	2.9%	0%	0%	6	26%	5.9%	0%	0%	0%
	PR/PR: 28	6	21%	3.6%	0%	0%	0%	5	18%	0%	0%	0%	0%
	SD/PD 35	3	0%	0%	0%	0%	0%	NR	0%	0%	0%	0%	0%
Nou 1988[2]	+TRTx 28	9.2	32%	0%	0%	0%							
	-TRTx 26	7.6	26%	0%	0%	0%							
	Difference	1.6	6%	0%	0%	0%							
		(chi-square 0.045, 0.8<p<0.9, by life-table analysis)											
Lebeau 1993[3]	+TRTx 10	~6.3	~10%	~10%	0%	0%	0%						
	-TRTx 8	~7.0	~25%	~12%	~12%	0%	0%						
	Difference	-0.7	-15%	-2%	-12%	0%	0%						
		(p = 0.43 by log-rank test)											
Rosenthal 1991[3]	Total 27												
	+TRTx ?	5 (95% CI: 2-8)											
	-TRTx ?	7 (95% CI: 3-10)											
	Difference	-2											
		(p=0.796)											
Brincker 1987[3]	+TRTx 16	7	~25%	0%	0%	0%	0%	7	~23	0%	0%	0%	0%
	-TRTx 14	10	~30%	0%	0%	0%	0%	8.5	~26	0%	0%	0%	0%
	Difference	-3	-5%	0%	0%	0%	0%	-1.5	-3%	0%	0%	0%	0%
		(p = 0.44)						(p = 0.45)					

[1] enrollment limited to ESD patients; [2] enrolled ESD & LSD patients, and reported characteristics of each separately;
[3] enrolled ESD & LSD patients, but only reported characteristics for the two groups pooled

Summary Table 33. Adverse Events: Chemotherapy with versus without Thoracic Radiation Therapy, Extensive Stage Disease (ESD)

Toxicity Type	Study	Severity or Grade	+TRTx n	+TRTx %	-TRTx n	-TRTx %	p	Not Reporting
Treatment-related mortality	Nou 1988		28	4	26	4	NS	Jeremic 1999; Lebeau 1993; Rosenthal 1991; Brincker 1987
Nausea/Vomiting	Jeremic 1999	acute grades 3/4 nausea and vomiting	55	9	54	34	0.0038	Nou 1988; Lebeau 1993; Rosenthal 1991
	Brincker 1987		"no significant differences between the two treatment groups"					
Anorexia								Jeremic 1999; Nou 1988; Lebeau 1993; Rosenthal 1991; Brincker 1987
Lethargy								Jeremic 1999; Nou 1988; Lebeau 1993; Rosenthal 1991; Brincker 1987
Neurosensory	Brincker 1987		"no significant differences between the two treatment groups"					Jeremic 1999; Nou 1988; Lebeau 1993; Rosenthal 1991
Hearing loss								Jeremic 1999; Nou 1988; Lebeau 1993; Rosenthal 1991; Brincker 1987
Esophagitis	Jeremic 1999	acute grades 3/4 esophageal	55	27	54	0	0.0002	Nou 1988; Lebeau 1993; Rosenthal 1991; Brincker 1987
Bronchopulmonary	Jeremic 1999	acute grade 3 (no grade 4, either arm)	55	5	54	0	0.082	Nou 1988; Lebeau 1993; Rosenthal 1991; Brincker 1987
Pneumonitis	Brincker 1987		no cases observed					Jeremic 1999; Nou 1988; Lebeau 1993; Rosenthal 1991
Kidney	Jeremic 1999	acute grades 3 or 4	55	0	54	22	0.001	Nou 1988; Lebeau 1993; Rosenthal 1991; Brincker 1987
Anemia	Jeremic 1999	acute grades 3 or 4	55	11	54	20	0.39	Lebeau 1993; Rosenthal 1991
	Nou 1988	hemoglobin nadir	Similar medians and ranges between groups					
	Brincker 1987	hemoglobin <6 mmol/L	41 (LSD+ESD)	~50	37 (LSD+ESD)	~27		
Thrombocytopenia	Jeremic 1999	acute grades 3/4	55	27	54	42	0.23	Lebeau 1993; Rosenthal 1991
	Nou 1988	thrombocyte count nadir (10^9/L)	Similar medians between groups					
	Brincker 1987	platelets <75x10^3/μl	41 (LSD+ESD)	~65	37 (LSD+ESD)	~10		

Summary Table 33. Adverse Events, Chemotherapy with versus without Thoracic Radiation Therapy, Extensive Stage Disease (ESD), (continued)

Toxicity Type	Study	Severity or Grade	+TRTx n	+TRTx %	-TRTx n	-TRTx %	p	Not Reporting
Leukopenia or neutropenia	Jeremic 1999	acute grade 3/4 leukopenia	55	44	54	61	0.18	Lebeau 1993; Rosenthal 1991
	Nou 1988	leukocyte count nadir (10^9/L)	Similar medians and ranges between groups					
	Brincker 1987	leukocytes < $2.5x10^3/\mu l$	41 (LSD+ESD)	~37	37 (LSD+ESD)	~18		
Infection	Jeremic 1999	acute grades 3-5	55	23	54	33	0.64	Lebeau 1993; Rosenthal 1991
	Nou 1988	septicemia	Similar medians and ranges between groups					
	Brincker 1987	febrile episodes	No significant differences between arms					
Other	Jeremic 1999	combined late grades 3/4 toxicities	55	5	54	0	0.082	Lebeau 1993; Rosenthal 1991
	Nou 1988	"other serious side effects"	28	29	26	8	NS	
	Brincker 1987	tolerated 75-100% of CTx doses in cycles after hemibody RTx completed	28 (LSD+ESD)	25	32 (LSD+ESD)	91		

Conclusions

Evidence from one small single-center randomized trial suggests adding concurrent TRTx to chemotherapy may improve survival of ESD patients who respond to an initial three cycles of PE chemotherapy with a CR outside the thorax and at least a PR in the thorax. Uncontrolled data from the same trial suggest that there is little to no benefit from adding TRTx to chemotherapy for ESD patients who achieve no better than a PR outside the thorax after three cycles of PE. With the regimens used in Jeremic, Shibamoto, Nikolic, et al. (1999), concurrent TRTx apparently increases grades 3 and 4 esophagitis.

No other trials were able to reproduce the results reported by Jeremic, Shibamoto, Nikolic, et al. (1999). Limitations of these trials include small sample sizes lack of a platinum-containing drug in their chemotherapy regimens, and use of nonconcurrent TRTx.

Key Question 5

What are the benefits and harms (survival, toxicity and quality of life) of prophylactic cranial irradiation (PCI) for patients with SCLC in complete remission (CR) after primary therapy?

Overview

The literature search identified seven RCTs comparing primary therapy for SCLC with versus without PCI (Summary Table 34). One of these was excluded because randomization and PCI preceded completion of primary therapy and evaluation of response (n=51; Niiranen, Holsti, and Salmo, 1989). Thus, each arm included some patients with less than CR. A second was excluded because it also randomized patients to PCI or no PCI before response was known, and because an initial randomization assigned half the patients to radiotherapy without chemotherapy (n=104 in 4 groups; Seydel, Creech, Pagano, et al., 1985). The remaining five trials onlyrandomized patients who achieved CR after primary chemotherapy with or without TRTx (pooled N=922; Arriagada, Le Chevalier, Borie, et al., 1995/Arriagada, Le Chevalier, Riviere, et al., 2002; Laplanche, Monnet, Santos-Miranda, et al., 1998; Gregor, Cull, Stephens, et al., 1997; Ohonoshi, Ueoka, Kawahara, et al., 1993; Cao, Huang, and Tu, 2000).

Four of these five studies were included in a Cochrane review and meta-analysis that collected updated individual patient data from each RCT (Prophylactic Cranial Irradiation Overview Collaborative Group 2000; Auperin, Arriagada, Pignon, et al., 1999). Cao, Huang, and Tu (2000; n=51) was the exception. The Cochrane review also included one study published before 1985 (Aroney, Aisner, Wesley, et al., 1983; n=29) and two unpublished trials (Wagner, Kim, Turrisi, et al., 1996; Danish/NCI trial; pooled N=87) that were not identified by our literature search. Additionally, the Cochrane review collected data on randomized patients excluded from investigators' published analyses, permitting intent-to-treat analysis of results for 987 patients in CR from seven RCTs (526 randomized to PCI, 461 to no PCI). Finally, the Cochrane review collected individual patient data on duration of follow-up and on covariates at randomization including age, gender, extent of disease, performance status, induction regimen (chemotherapy with versus without TRTx), and time since initial therapy, to permit analyses that tested whether these covariates influenced the magnitude of benefit from PCI. The Cochrane

review excluded Niiranen, Holsti, and Salmo (1989) and Seydel, Creech, Pagano, et al. (1985) (as does this review), plus eight other RCTs published before 1985, for similar reasons (some randomized patients not in CR; pooled N=929).

Since individual patient data submitted for the Cochrane review included longer follow up and permitted analyses not possible with abstracted data from a literature-based systematic review, and since only one eligible study was published subsequently (Cao, Huang, and Tu, 2000; N=51), the Results section below summarizes and highlights the principal findings of the Cochrane review, and also summarizes results of the Cao, Huang, and Tu (2000) study.

Summary Table 34. RCTs of PCI versus no PCI for SCLC in CR

Study	N Randomized		all in CR?	Pt?	chemoTx regimen	TRTx	PCI Regimen			publication type
	+ PCI	no PCI					dose	fractions	duration	
Arriagada, Le Chevalier, Borie, et al., 1995	149	151	yes	some	various; # type NR	91%-93% each arm; reg. NR	24 Gy	8 x 3 Gy	12 days (4 d/wk)	full
Laplanche, Monnet, Santos-Miranda, et al., 1998	100	111	yes	??	various; # type NR	not reported	24-30 Gy	≤3 Gy each	≤3 weeks	full
Gregor, Cull, Stephens, et al., 1997	194	120	yes	some	various; # NR	84% each arm; reg. NR	8-40 Gy	2 Gy each	1-3+ weeks	full
Ohonoshi, Ueoka, Kawahara, et al., 1993	23	23	yes	no	same for all	all LS; 20 x 2 Gy/d	40 Gy	20 x 2 Gy	4 weeks	full
Aroney, Aisner, Wesley, et al., 1983	15	14	yes	no	same for all	not reported	30 Gy	10 x 3 Gy	2 weeks	full
Wagner, Kim, Turrisi, et al., 1996	17	15	yes	NR	not reported	57%; reg. NR	24 Gy	8 x 3 Gy	not reported	abstract
Danish/NCI	28	27	yes	NR	not reported	42%; reg. NR	24 Gy	8 x 3 Gy	not reported	none
Cao, Huang, and Tu, 2000	26	25	yes	some	two; # NR	all; 40-64 Gy 1.8-2 Gy/d	25-30 Gy	1.8-2 Gy ea.	2-3 weeks	full
Seydel, Creech, Pagano, et al., 1985	52	51	??	no	one; half only	all; 45 Gy 1.8-2 Gy/d	30 Gy	10 x 3 Gy	2 weeks	full
Niiranen, Holsti, and Salmo, 1989	25	26	no	no	two; half each	all; 25 x 2.2 Gy/d	40 Gy	20 x 2 Gy	4 weeks	full

Results

Cochrane Review and Meta-Analysis.

Study Characteristics. At the time of analysis, median follow-up for the control and PCI groups was 5.3 and 5.9 years, respectively; 846 of 987 randomized patients had died (PCI Overview Collaborative Group 2000; Auperin, Arriagada, Pignon, et al., 1999). Of seven included trials, three enrolled 84 percent of patients (Arriagada, Le Chevalier, Borie, et al., 1995/Arriagada, Le Chevalier, Riviere, et al., 2002; Laplanche, Monnet, Santos-Miranda, et al., 1998; Gregor, Cull, Stephens, et al., 1997) while the other four contributed 29 to 55 each (Aroney, Aisner, Wesley, et al., 1983; Wagner, Kim, Turrisi, et al., 1996; Ohonoshi, Ueoka, Kawahara, et al., 1993; Danish/NCI trial). The control (N=461) and PCI (n=526) groups were well balanced for gender (76–77 percent male), age (median 59 years, ranges 26–80 and 21–79), performance status (66–67 percent PS 0, 30–32 percent PS 1) and other covariates. Reviewers judged each trial to be methodologically sound, including adequate randomization and allocation concealment.

For most patients in these trials, the specific chemotherapy regimens used to induce CR were not reported but it is likely platinum-based regimens were used only for a minority. The large trials did not mandate a uniform chemotherapy regimen (Arriagada, Le Chevalier, Borie, et al., 1995/Arriagada, Le Chevalier, Riviere, et al., 2002; Laplanche, Monnet, Santos-Miranda, et al., 1998; Gregor, Cull, Stephens, et al., 1997). Only Gregor, Cull, Stephens, et al. (1997) reported the variety of regimens used, but since they did not report the proportion given each regimen, an unknown number of patients received cisplatin or carboplatin. Of the four smaller trials, Aroney, Aisner, Wesley, et al. (1983) and Ohonoshi, Ueoka, Kawahara, et al. (1993) each used a uniform regimen, but neither included a platinum drug. While Cochrane reviewers collected individual patient data on whether they received TRTx, information was unavailable (either in the review or in the original publications) on doses, fractionation schemes, or timing relative to chemotherapy. Summary Table 35 summarizes the review's pooled estimates of efficacy outcomes.

Summary Table 35. Meta-analytic Results for Efficacy Outcomes Reported in the Cochrane Review

Outcome	N evaluated		Hazard Ratio	95% CI		p	event-free at 3 yrs (by K-M)		
	+PCI	-PCI		lower	upper		+PCI	-PCI	difference
mortality	526	461	0.84	0.73	0.97	0.01	20.7%	15.3%	5.4%
disease-free survival	526	461	0.75	0.65	0.86	<0.00003			
brain metastasis	524	457	0.46	0.38	0.57	<0.00001	33.3%	58.6%	25.3%
non-brain metastasis	325	332	0.89	0.69	1.15	0.4			
loco-regional recurrence	323	334	0.97	0.75	1.26	0.8			

Mortality and Survival. Although six of seven included trials observed proportionally more deaths in the control arms, the hazard ratio (HR) for mortality did not significantly favor the PCI arm in any single trial. However, meta-analysis showed that PCI significantly decreased the likelihood of death (HR=0.84; 95 percent CI: 0.73–0.97; p = 0.01). Cox modeling to adjust for extent of disease, gender and age did not appreciably change the relative likelihood (HR=0.83;

p=0.009). The HR remained constant despite further adjustment for performance status, induction regimen (with versus without TRTx), and time from induction to randomization. Kaplan-Meier actuarial analysis estimated an absolute increase of 5.4 percent in the proportion of patients alive at 3 years (from 15.3 percent without PCI to 20.7 percent with PCI). The survival benefit persisted beyond 3 years, and there was no evidence of statistical heterogeneity among the seven included trials.

Other Efficacy Endpoints. The HR for brain metastasis significantly favored the PCI arm in five of seven trials; the Danish/NCI and Laplanche, Monnet, Santos-Miranda, et al. (1998) trials were the exceptions. Meta-analysis showed reduced likelihood of brain metastasis among those randomized to PCI (HR = 0.46; 95 percent CI: 0.38–0.57; p <0.001). Kaplan-Meier analysis estimated an absolute decrease of 25.3% in the cumulative rate of brain metastasis at 3 years (from 58.6 percent without PCI to 33.3 percent with PCI).

Additional analyses demonstrated that PCI increased the likelihood of disease-free survival (HR=0.75; 95 percent CI: 0.65–0.86; p < 0.001), but did not reduce extra-cerebral metastases (HR=0.89; 95% CI: 0.69–1.15; p=0.4) or locoregional recurrence (HR=0.97; 95% CI: 0.75–1.26; p=0.8). However, data on non-brain metastases and locoregional recurrence were available for only 67% of randomized patients.

PCI Dose-Response. Trials (and subgroups from different centers in Gregor, Cull, Stephens, et al., 1997) were divided by total radiation dose used for PCI: 8 Gy delivered in one fraction, 24–25 Gy delivered in 8–12 fractions, 30 Gy delivered in 10 fractions, and 36 or 40 Gy delivered in 18 or 20 fractions. Summary Table 36 summarizes results of this and other subgroup analyses.

Evidence was lacking for a trend towards smaller HR (greater impact on survival) with larger PCI dose (p = 0.89), but few patients were treated at the lowest and highest doses. In contrast, the HR to develop brain metastasis decreased significantly as PCI dose increased (p = 0.02), suggesting larger doses had a greater magnitude of beneficial effect.

Summary Table 36. Cochrane Review Subgroup Analyses for Mortality and Brain Metastasis

covariate	subgroups	mortality						brain metastasis					
		N evaluated		hazard ratio	95% CI		p	N evaluated		hazard ratio	95% CI		p
		+PCI	-PCI		lower	upper		+PCI	-PCI		lower	upper	
PCI dose	8 Gy	26	16	0.69	0.35	1.37	0.3	26	16	0.76	0.28	2.10	0.6
	24-25 Gy	330	340	0.88	0.75	1.04	0.12	329	338	0.52	0.41	0.67	<0.00001
	30 Gy	119	82	0.81	0.59	1.12	0.2	118	80	0.34	0.19	0.59	0.0002
	36-40 Gy	51	59	0.81	0.54	1.20	0.3	51	59	0.27	0.14	0.51	0.00001
age	≤54 yrs	147	158	0.84	0.65	1.08	0.18	147	157	0.55	0.39	0.77	0.0005
	55-64 yrs	250	185	0.90	0.73	1.11	0.3	248	184	0.49	0.35	0.68	<0.00002
	≥65 yrs	129	118	0.79	0.60	1.03	0.09	129	116	0.37	0.24	0.59	<0.0001
disease stage	limited	464	383	0.85	0.73	0.99	0.04	462	382	0.48	0.38	0.61	<0.00001
	extensive	62	78	0.77	0.54	1.11	0.16	62	75	0.38	0.23	0.64	0.0002
performance status	0	212	215	0.85	0.69	1.05	0.13	211	214	0.47	0.35	0.63	<0.00001
	1-3	103	111	0.78	0.58	1.04	0.09	103	110	0.50	0.32	0.78	0.003
induction therapy	+TRTx	314	248	0.86	0.71	1.03	0.10	314	248	0.43	0.33	0.57	<0.00001
	-TRTx	94	86	0.88	0.64	1.21	0.4	92	82	0.40	0.23	0.67	0.0005
gender	male	403	352	0.77	0.66	0.90	0.0009	401	348	0.47	0.37	0.60	<0.00001
	female	123	109	1.05	0.78	1.42	0.7	123	109	0.50	0.32	0.78	0.002
time from induction to randomization	<4 mos.	84	77	0.92	0.66	1.29	0.6	83	75	0.27	0.16	0.46	<0.00001
	4-6 mos.	127	152	0.79	0.61	1.02	0.07	126	150	0.50	0.35	0.72	0.0002
	>6 mos.	102	91	1.01	0.74	1.38	0.9	102	91	0.69	0.44	1.08	0.1

Subgroup Analyses. Patient subgroups were evaluated for differences in magnitude of benefit from PCI. Subgroups were defined by individual patient data on age (≤54 versus 55-64 versus ≥65 years), gender, disease stage at diagnosis (limited versus extensive), performance status (0 versus 1-3), induction regimen (with versus without TRTx), and time from beginning induction to randomization (<4 versus 4-6 versus >6 months). Only two subgroup comparisons suggested significant differences in benefit from PCI for overall survival or brain metastasis.

Results for males (n =755) showed statistically significant decreases in mortality (HR=0.77; 95 percent CI: 0.66–0.90; p = 0.0009) and brain metastasis (HR=0.47; 95 percent CI: 0.37–0.60; p<0.0001) among those randomized to PCI. However, results for females (n=232) showed no significant effect of PCI on survival (HR=1.05; 95 percent CI: 0.78–1.42; p=0.7) despite a significant effect on brain metastasis (HR=0.50; 95 percent CI: 0.32–0.78; p=0.0002). A statistical test for interaction of gender with treatment effect on survival was of borderline significance (p=0.07).

PCI delayed by <4 months from start of induction therapy (HR=0.27; 95 percent CI: 0.16–0.46; p<0.0001) or by 4 to 6 months (HR=0.50; 95 percent CI: 0.35–0.72; p=0.0002) significantly reduced the likelihood of brain metastasis. In contrast, PCI delayed >6 months (HR=0.69; 95 percent CI: 0.44–1.08; p=0.10) did not significantly decrease the likelihood of brain metastasis. Note that each fully published trial with some patients given PCI later than 6

months after induction (3 of 4 trials, with 95 percent of 193 patients in this subgroup) specified that patients were randomized to PCI or no PCI within 14 days of achieving CR. This trend (smaller effect on likelihood of brain metastasis as delay lengthened) was statistically significant (p=0.01). However, the relationship between time from induction therapy to PCI and hazard ratio for death did not show a similar statistically significant trend.

Adverse Events. The Cochrane review did not abstract and report data on adverse events. Of five fully-published studies, only Arriagada et al. (1995) reported acute events during PCI; these included fever or asthenia (24 percent), headache (24 percent), vomiting (10 percent), skin erythema (9 percent), and altered mood (6 percent). Adverse event data were unavailable from the two unpublished trials (Wagner, Kim, Turrisi, et al., 1996; Danish/NCI trial).

Two trials prospectively studied neuropsychological or cognitive sequelae of PCI in patients who survived ≥6 months from treatment (Arriagada, Le Chevalier, Borie, et al. 1995; Gregor, Cull, Stephens, et al., 1997; Table 37). The Gregor, Cull, Stephens, et al. (1997) trial also reported data on symptoms that affect quality of life (QoL). Each compared measurements at baseline with measurements at times after PCI. Information was unavailable on ages and other baseline characteristics of those tested for late neuropsychological or cognitive effects. Additionally, available evidence did not permit testing of the hypothesis that the likelihood of neuropsychological deficits may increase with increasing PCI dose.

In Arriagada, Le Chevalier, Borie, et al. (1995), neuropsychological assessments (made by a neurologist at baseline and late after PCI) included evaluation of higher brain function, mood, sensation, walking, cerebellar function, tendon reflexes, and sensibility. Additionally, blinded assessors reviewed pre- and post-PCI brain computed tomography (CT) scans for evidence of structural abnormalities (e.g., cortical atrophy or ventricular dilatation).

Summary Table 37. Adverse Effects Reported from RCTs of PCI versus no PCI

Study	acute toxicities reported ?	most common events	type of assessment	N random-ized	N eval-uated at base-line	# w no or only mild baseline deficits	#, time of reassessments	principal findings
Arriagada, Le Chevalier, Borie, et al., 1995	yes	fever 24% headache 24% vomiting 10%	neuropsy-chological; brain CT	total: 300 +PCI: 149 -PCI: 151	229 114 115	94 44 50	33 of 58 @ 18 mos. 23 of 35 @ 30 mos.	groups did not differ in # of new changes or abnormalities
Gregor, Cull, Stephens, et al., 1997	no		cognitive	total: 314 +PCI: 194 -PCI: 120	125 76 49	diff. tests: 44-58 29-37	59 of 106 @ 6 mos. 32 of 54 @ 1 yr 9 of 20 @ 2 yr	groups did not differ in # of new deficits
			symptoms affecting QoL	total: 314 +PCI: 194 -PCI: 120	not reported	diff tests: 11-21 7-14	re-assessed @ 6 mos., 1 & 2 yr; #'s not reported;	larger proportion of –PCI than of +PCI showed deterioration

Of 300 randomized patients, baseline assessments were available for only 229 (115 controls and 114 randomized to PCI). Only 50 control patients (43 percent) and 44 randomized to PCI (39 percent) were free of neuropsychological abnormalities at baseline assessment. Investigators re-assessed 33 of 58 patients alive at 18 months and 23 of 35 alive at 30 months. They reported no statistically significant differences between treatment groups with respect to appearance of further neuropsychological changes or CT scan abnormalities over two years from PCI. However, only 11 percent or less of all randomized patients contributed to these observations, and the report did not explain why some patients alive at 18 and 30 months were not re-assessed.

Gregor, Cull, Stephens, et al. (1997) assessed cognitive function at baseline, 6 months, and 1 and 2 years with a battery of optional measures including the National Adult Reading Test, Paced Auditory Serial Addition Task, Rey-Osterrieth Complex Figure Test, and Auditory Verbal Learning Test. Of 314 randomized patients, at least one test result was submitted for N=136 (52 controls, 84 PCI). Of these, baseline data were available for N=125, 6-month data for N=59 (of 106 assessable), one-year data for N=32 (of 54 assessable), and two-year data for N=9 (of 20 assessable). Each test showed evidence of new impairments at 6 months and 1 year in some patients free of impairments at baseline. However, investigators reported no evidence of sustained deterioration with time, and no notable differences between the PCI and control groups with respect to new cognitive deficits.

Gregor, Cull, Stephens, et al. (1997) also measured symptoms that affect QoL at the same intervals used for cognitive function, with the Rotterdam Symptom Checklist and the Hospital Anxiety and Depression Scale. Symptoms that showed the greatest deterioration from baseline to 6 months included tiredness, lack of energy, irritability, decreased sexual interest, shortness of breath, and cough. For each symptom, of those who reported themselves with no or mild symptoms at baseline, a larger proportion of controls than of those given PCI reported moderate or severe symptoms at 6 months. Based on these data, investigators concluded deterioration was worse in controls than in the PCI group.

Ohonoshi, Ueoka, Kawahara, et al. (1993) did not formally assess neuropsychological function or measure cognitive function or quality life. However, they reported that one of seven patients who survived more than two years after PCI developed symptoms of late central nervous system toxicity. These included memory impairment and gait ataxia at 30 months, with CT scan evidence of cortical atrophy. Ohonoshi, Ueoka, Kawahara, et al. (1993) did not report on late toxicity in the 4 control patients alive at 2 years.

Subsequent Study. Cao, Huang, and Tu (2000) reported the only eligible RCT of PCI versus no PCI omitted from the Cochrane review and meta-analysis (N = 47; 24 to PCI, 23 to control). Study arms were well-balanced and most patients had relatively favorable baseline characteristics: mean age, 55-56 (range 39–65), Karnofsky score $\geq$70, two females in each arm, all patients initially diagnosed with limited stage disease and in CR after chemotherapy plus TRTx. Chemotherapy regimens were either cyclophosphamide/doxorubicin/vincristine or etoposide plus carboplatin or cisplatin, with most patients also given lomustine. All patients received 40-66 Gy TRTx in 1.8-2 Gy fractions, given sequentially for most (17 controls, 18 PCI) and in alternating fashion for the rest (6 from each group). PCI began 11 to 58 days after achieving CR (mean, 33 days) at a mean dosage of 28.8 Gy (range, 25.2 to 30.6 Gy) in single daily fractions of 1.8 to 2 Gy, 5 days/week.

Cao, Huang, and Tu (2000) reported fewer cranial metastases at 3 years after irradiation in the arm given PCI (3.8 percent versus 28 percent, $p<0.05$). However, differences in survival at

one (85 percent versus 72 percent), two (73 percent versus 40 percent) or three (42 percent versus 32 percent) years were not statistically significant (median, 20 versus 8.3 months; log rank $p>0.05$). Acute reactions to PCI included mild nausea and dizziness, but frequencies were not reported. Late effects in 11 patients who survived $\geq$3 years included two with memory deficits and three with dizziness and lack of strength. Brain CT scans on 7 of the 11 survivors showed no structural abnormalities.

Conclusions

Evidence from an individual patient data Cochrane review and meta-analysis on seven RCTs (N=987) conducted by the PCI Overview Collaborative Group shows that PCI modestly but significantly improves survival of SCLC patients in CR after primary therapy. PCI increases the proportion alive at 3 years from 15.3 percent of controls to 20.7 percent of those randomized to PCI, an absolute increase of 5.4 percent. PCI also significantly decreases the risk for brain metastasis and increases the likelihood of disease-free survival. The sole trial reported after the meta-analysis confirms effects of PCI on brain metastasis, and generally agrees with the modest effect on overall survival.

Subgroup analyses using individual patient data showed that PCI significantly decreases brain metastases for SCLC patients in CR regardless of age, disease stage or performance status at diagnosis, and whether or not TRTx is part of the induction regimen. Although effects of PCI on survival lacks statistical significance for nearly all these subgroups, it does not appear that any subgroup benefits more or less than others with respect to each of these covariates.

Additional subgroup analyses suggested that increasing the PCI dose from 8 to 40 Gy and starting PCI within the first 6 months after achieving CR may decrease the likelihood of brain metastasis. Patient gender also may interact with effects of PCI on survival. However, these hypotheses, derived from subgroup analyses, require formal testing in randomized, controlled trials.

Data on acute toxicities of PCI are scant, but those available suggest they are tolerable at the doses used in these trials (8–40 Gy in 1.8 to 3 Gy fractions). Evidence from two trials suggests neuropsychological and cognitive deficits and structural abnormalities on brain CT scans are relatively common among SCLC patients in CR after primary therapy. However, available evidence did not show greater deterioration of existing deficits or more frequent appearance of new abnormalities among the minority randomized to PCI who survive 1–2 years or more, than among the fewer controls with equivalent survival duration.

Key Question 6

Does the addition of positron emission tomography (PET) scanning improve the accuracy of staging for patients diagnosed with SCLC, over the use of other techniques, including CT and MRI, without PET?

Overview

Evidence of the effect of PET on health outcomes, such as overall survival or avoidance of unnecessary procedures, is of greatest interest to this review. RCTs were sought that compared outcomes of staging tests that included PET versus the same tests without PET in patients who had a confirmed diagnosis of SCLC. No such studies were found.

Single-arm studies with the following characteristics were sought: prospective design; reported on at least 20 patients undergoing imaging to stage SCLC; correlated 18-fluorodeoxyglucose (FDG) PET findings with findings from other imaging modalities and an appropriate reference standard; applied the reference standard to patients with and without metastasis to a given anatomic site (to permit computation of sensitivity and specificity); and reported at least one outcome of interest. Outcomes included: diagnostic and staging accuracy; patient management decisions, which may be altered by imaging results, duration of survival; disease-free survival and/or progression-free survival; quality of life; palliation of measurable symptoms; treatment-related adverse effects; objective response rates; and response durations. Studies were excluded if they did not report data needed to calculate diagnostic accuracy; or if they did not report separate diagnostic accuracy results for SCLC and NSCLC patients. Since the question posed here concerned the incremental value of PET relative to staging tests, the comparison of greatest interest is between results of conventional staging tests alone and conventional staging tests plus PET.

Due to the limited evidence available, the study selection criteria on prospective design and on appropriate reference standard were relaxed. Six studies reporting on a total of 277 patients (range: 20–120) are included in this review. Data from these studies primarily concerned diagnostic and staging accuracy. Characteristics of these studies are summarized in Summary Table 38 (sample selection) and Summary Table 39 (tests and reference standards). Four of the six studies were clearly prospective in design (Bradley, Dehdashti, Mintun et al., 2004; Brink, Schumacher, Mix et al., 2004; Kamel, Zwahlen, Wyss, et al., 2003; Shen, Shiau, Wang, et al., 2002), while 1 study produced a mix of data collected prospectively and retrospectively (Blum, MacManus, Rischin, et al., 2004) and 1 study was of uncertain design (Schumacher, Brink, Mix, et al., 2001). Three studies enrolled consecutive series of patients (Blum, MacManus, Rischin, et al., 2004; Brink, Schumacher, Mix et al., 2004; Kamel, Zwahlen, Wyss, et al., 2003). Three of the 6 studies provide staging accuracy data based on comparisons of conventional staging tests alone and conventional staging plus PET (Blum, MacManus, Rischin, et al., 2004; Bradley, Dehdashti, Mintun et al., 2004; Kamel, Zwahlen, Wyss, et al., 2003). Three studies compared staging results of conventional tests alone and PET alone (Brink, Schumacher, Mix et al., 2004; Shen, Shiau, Wang, et al., 2002; Schumacher, Brink, Mix, et al., 2001).

Study quality was assessed as described in the Methods chapter, using the QUADAS tool (Whiting, Rutjes, Dinnes, et al., 2004). A major weakness of the included evidence is the uniformly poor quality of information reported about the reference standard. None of the 6 studies adequately described the execution of the reference standard and whether the reference standard correctly classifies the target condition. Without these details, the definition of a positive reference standard result is unclear. Thus the poor quality of information reported on reference standards undermines confidence in the estimates of sensitivity, specificity and staging accuracy that can be drawn from this literature.

Summary Table 38. Sample Selection: Positron Emission Tomography for Staging of Small-Cell Lung Cancer

Study	Design	Patient Selection	n	Age (yr)	Gender (%)	Stage Limited %	Stage Extensive %	Representative Sample?
Blum, MacManus, Rischin, et al., 2004	partially prospective, partially retrospective	proven SCLC underwent PET; consecutive patients; newly diagnosed-initial staging in 15, restaging in 21; PET based on review of all clinical data and was performed to guide clinical management;	36	med 64	M 66 F 33			Unclear
Bradley, Dehdashti, Mintun et al., 2004	prospective	newly diagnosed confirmed limited stage SCLC, completed standard staging procedures	24	mn 60 rng 33-90	M 44 F 56	87.5	12.5	Yes
Brink, Schumacher, Mix et al., 2004	prospective	consecutive patients with histologically confirmed SCLC examined with FDG-PET during primary staging	120	mn 60.8 sd 8.9	M 75 F 25	37	63	Unclear
Kamel, Zwahlen, Wyss, et al., 2003	prospective	consecutive patients with SCLC referred for whole-body FDG-PET; initial staging in 24 patients and restaging after therapy in 20 patients (both in 2)	42	mn 62 rng 45-83	M 64 F 36	62.5	37.5	Unclear
Shen, Shiau, Wang, et al., 2002	retrospective	histologically confirmed SCLC; KPS ≥ 60%; total serum bilirubin ≤ 2.0 mg/dL; serum creatinine ≤ 2.5 mg/dL; fasting blood sugar ≤ 150 mg/dL	25	mn 56 sd 7 rng 45-68	M 72 F 28	40	60	Unclear
Schumacher, Brink, Mix, et al., 2001	unclear	histologically proven SCLC, primary staging in 24, therapy follow-up in 4, both in 2; therapy was surgery, RTx and CTx (ACO, EPI-CO, VIP-E, VIC-E); all treatment stopped ≥1 mo before PET	30	mn 57 sd 13 rng 34-78	M 77 F 23	30	70	Unclear

Abbreviations table provided at the end of the Report.

Summary Table39. Test/Reference Standard Procedure and Interpretation: Positron Emission Tomography for Staging of Small-Cell Lung Cancer

Study	PET	Conventional Staging Tests	Reference Standard	PET: Ref Stand Blind?	Ref Stand: PET Blind?	Avoided Verification Bias
Blum, MacManus, Rischin, et al., 2004	≥ 4 hr fast; ± attenuation correction, qualitative interpretation, access to results of the previous imaging and clinical information	initial staging - high-quality CT of chest, upper abdomen, brain, usually bone scan; restaging after initial treatment - CT, bone scan, X-ray;	if discordant results, TP = site biopsy+; or site + only on PET with other progression < 6 mos of PET, no treatment; TN = site biopsy-; or conventional equivocal/negative site with no progression for ≥ 6 mos, no treatment	Unclear	Unclear	Unclear
Bradley, Dehdashti, Mintun et al., 2004	4-hr fast, 10-15 mCi FDG, 50 min delay ± attenuation correction, visual interpretation; 2 experienced nuclear physicians; first, independent, blinded to conventional, then observers reread with conventional, final consensus of blinded readings; also semiquantitative maximum standardized uptake value	history, physical exam, chest X-ray, chest CT, upper abdominal CT, bone scan, contrast-enhanced CT/MRI of brain; all conventional staging procedures completed ≤ 4 wk of PET	protocol-defined approaches for further evaluation or biopsy: PET+ intrapulmonary parenchymal metastases outside RTx portal, do biopsy; thin-cut CT- or US-guided FNA where feasible; liver PET+, do biopsy/FNA cytology; adrenal PET+, do biopsy; bone PET+, evaluate by appropriate imaging studies (X-ray, CT, MRI, repeat bone scan) or biopsy or bone scan/MRI if multiple bone metastases suspected	Unclear	Unclear	Unclear
Brink, Schumacher, Mix et al., 2004	12 hr fast, 5 MBq/kg FDG, 90 min delay; data corrected for dead time, decay, photon attenuation; whole-body PET performed after CT (mean 12 d, range 1-26 d), hard copy and computer workstation, 2 independent investigators blinded to other data; hot spot evaluation, consensus	conventional staging by history, physical exam, bronchoscopy, thoracic/abdominal contrast-enhanced CT, cranial CT/MRI in 91, bone biopsy in 84 (refused in 36)	histology in ~20%; available data; follow-up, committee of physicians (2 clinicians, 2 nuclear specialists) achieved reference standard diagnosis by consensus; when histologic results were unavailable, consensus based on sum of available data, including follow-up, non-validated results excluded from data analysis	Yes	Unclear	No
Kamel, Zwahlen, Wyss, et al., 2003	≥ 4 hr fast, 300-400 MBq FDG; 40-50 min delay; segmented or PET/CT fusion attenuation correction, pre-PET staging and post-PET staging were always performed independently; clinical information available, including CT	history, physical exam, blood tests, bronchoscopy, contrast-enhanced CT of chest, upper abdomen, bone scan, CT/MRI of brain in 9	when possible, biopsies or other imaging studies were performed to resolve discrepancies between modalities	Unclear	Unclear	Unclear

Abbreviations table provided at the end of the Report.

Summary Table39. Test/Reference Standard Procedure and Interpretation: Positron Emission Tomography for Staging of Small-Cell Lung Cancer (continued)

Study	PET	Conventional Staging Tests	Reference Standard	PET: Ref Stand Blind?	Ref Stand: PET Blind?	Avoided Verification Bias
Shen, Shiau, Wang, et al., 2002	6 hr fast; 10 mCi (370 MBq) FDG; 40-50 min delay, agreement of at least 2 of 3 experienced nuclear medicine specialists blind to clinical stage	within 2 wk of PET: history, physical exam, blood chemistry, chest X-ray $\pm$ chest CT/MRI, brain CT/MRI, abdominal CT/MRI $\pm$ hepatic US, pelvic CT/MRI, bone scan, bone marrow biopsy	final stage was verified by pathologic findings from thoracotomyy/mediastinoscopy. other imaging results, follow-up $\geq$ 1 yr	Unclear	Unclear	No
Schumacher, Brink, Mix, et al., 2001	12 hr fast; 5 MBq FDG/kg; 90 min delay attenuation correction ,hard copy and computer workstation; visual interpretation, 2 experienced independent blinded investigators; consensus; standardized uptake value > 4	within 2 wk before or after PET: CT/MRI of brain, thorax, abdomen carried out according to standard protocols, thin-section or contrast enhancement used if needed	if discrepancies between PET and other staging procedures found, selective additional examinations performed or existing images re-evaluated; in some cases, clinical follow-up proved/disproved inconsistent findings; confirmation necessary within 4 wk	Unclear	Unclear	No

Study Populations

The proportion of patients enrolled who had limited stage disease ranged from 30 percent to 87.5 percent in 5 studies; it could not be determined in the study by Blum, MacManus, Rischin, et al. (2004). Three studies (Blum, MacManus, Rischin, et al., 2004; Kamel, Zwahlen, Wyss, et al., 2003; Schumacher, Brink, Mix, et al., 2001) included samples mixed with those undergoing initial staging and other being restaged. In only one study was it clear that selection of patients was not based on referral for PET scanning (Bradley, Dehdashti, Mintun et al., 2004).

Diagnostic Accuracy

Three studies (Blum, MacManus, Rischin, et al., 2004; Brink, Schumacher, Mix et al., 2004; Shen, Shiau, Wang, et al., 2002; total N=181) reported diagnostic accuracy data (Summary Table 40). Results are presented below according to stage or site of disease.

Any Disease. The study by Blum, MacManus, Rischin, et al. (2004) was the only one that reported diagnostic accuracy with reference to any disease. These investigators only included data on sensitivity in 36 patients, which they estimated at 100 percent for PET. This study does not address whether there was additional value to adding PET to staging, information about extent of disease was not reported.

Lymph Nodes. Using the patient (n=118) as the unit of analysis, Brink, Schumacher, Mix et al. (2004) found that PET had a sensitivity of 100 percent for detecting lymph node metastasis, compared with 69.8 percent for conventional staging. PET specificity was 98.5 percent, while it was 93.8 percent for conventional staging. The study by Shen, Shiau, Wang, et al. (2002) also used a patient-based analysis, but grouped lymph nodes into regions. Few patients provided data on negative nodes, so specificity was not reported. Shen, Shiau, Wang, et al. (2002) did not provide separate sensitivity data for PET and conventional imaging. PET was found to be 100 percent sensitive in each of 3 lymph regions: in 9 patients with mediastinal or hilar lymph metastases; in 7 patients with ipsilateral supraclavicular lymph metastases; and in 5 patients with contralateral supraclavicular lymph metastases. There were 2 PET false positives in mediastinal/hilar lymph nodes.

Other Regional Sites. Shen, Shiau, Wang, et al. (2002) reported that sensitivity for ipsilateral lung foci was 100 percent in 2 patients.

Summary Table 40. Diagnostic Accuracy Results: Positron Emission Tomography for Staging of Small-Cell Lung Cancer

Study	Test	Focus	n	TP	FN	FP	TN	Prev	Sens	Sens 95% CIL	Sens 95% CIU	Spec	Spec 95% CIL	Spec 95% CIU	PPV	NPV	DA
Blum, MacManus, Rischin, et al., 2004	PET	any disease	36	36	0				100%	90.3%	100%						
Bradley, Dehdashti, Mintun et al., 2004	PET	Any disease	24	24	0	1	0		100%	85.5%	100%						
Brink, Schumacher, Mix et al., 2004	PET	LNs	118	53	0	1	64	44.9%	100%	93.3%	100%	98.5%	91.7%	100%	98.1%	100%	99.2%
	Conv		118	37	16	4	61	44.9%	69.8%	55.7%	81.7%	93.8%	85.0%	98.3%	90.2%	79.2%	83.1%
	PET	dist, non-brain	70	45	1	2	22	65.7%	97.8%	88.5%	99.9%	91.7%	73.0%	99.0%	95.7%	95.7%	95.7%
	Conv		70	38	8	5	19	65.7%	82.6%	68.6%	92.2%	79.2%	57.8%	92.9%	88.4%	70.4%	81.4%
	PET	brain	91	6	7	2	76	14.3%	46.2%	19.2%	74.9%	97.4%	91.0%	99.7%	75.0%	91.6%	90.1%
	Conv		91	13	0	0	78	14.3%	100%	75.3%	100%	100%	95.4%	100%	100%	100%	100%
Kamel, Zwahlen, Wyss, et al., 2003																	
Shen, Shiau, Wang, et al., 2002	PET	regl mets	18	20	0	2	0		100%	83.2%	100%						
		MD/HL LNs	9	9	0	2	0		100%	66.4%	100%						
		ips SC LNs	7	7	0	0	0		100%	59.0%	100%						
		ips lung	2	2	0	0	0		100%	15.8%	100%						
		distant	24	23	1	1	0		95.8%	78.9%	100%						
		contr SC LNs	5	5	0	0	0		100%	47.8%	100%						
		contr lung	3	3	0	1	0		100%	29.2%	100%						
		liver	3	3	0	0	0		100%	29.2%	100%						
		bone/marrow	6	6	0	0	0		100%	54.1%	100%						
		brain	2	1	1	0	0		50.0%	1.3%	99%						
		adrenal	2	2	0	0	0		100%	15.8%	100%						
		other extrathoracic	3	3	0	0	0		100%	29.2%	100%						
Schumacher, Brink, Mix, et al., 2001																	

Abbreviations table available at the end of the Report.

Distant Sites, Non-Brain. Among 70 patients, Brink, Schumacher, Mix et al. (2004) found that PET's sensitivity for distant non-brain sites was 97.8 percent, compared with 82.6 percent for conventional staging. Specificity was 91.7 percent for PET and 79.2 percent for conventional staging. In the Shen, Shiau, Wang, et al. (2002) study, PET had 100 percent sensitivity in 19 patients. Sites in this study included contralateral lung (1 false positive), liver, bone/marrow, adrenal and other extrathoracic.

Brain Metastases. In the Brink, Schumacher, Mix et al. (2004) study, PET's sensitivity was 46.2 percent, compared with 100 percent for conventional staging, among 13 patients. Specificities were 97.4 percent for PET and 100 percent for conventional staging. Shen, Shiau, Wang, et al. (2002) included 2 patients with brain metastases and PET detected 1 (50 percent sensitivity).

Staging Accuracy

All 6 studies reported on instances in which PET correctly upstaged disease among those undergoing initial staging (Table 41). The proportions were: 3 of 15 (20 percent) in Blum, MacManus, Rischin, et al. (2004); 1 of 24 (4.2 percent) in Bradley, Dehdashti, Mintun et al. (2004); 10 of 120 (8.3 percent) in Brink, Schumacher, Mix et al. (2004); 3 of 24 (12.5 percent) in Kamel, Zwahlen, Wyss, et al. (2003); 1 of 25 (4 percent) in Shen, Shiau, Wang, et al. (2002); and 5 of 30 (19.2 percent) in Schumacher, Brink, Mix, et al. (2001). Three studies mentioned examples of PET correctly downstaging disease. Brink, Schumacher, Mix et al. (2004) found 3 cases in 24 (12.5 percent), Kamel, Zwahlen, Wyss, et al. (2003) observed 1 in 24 (4.2 percent) and Shen, Shiau, Wang, et al. (2002) saw 1 in 25 (4 percent). Among patients being restaged, Schumacher, Brink, Mix, et al. (2001) reported that PET correctly upstaged disease in 1 of 6 patients (16.7 percent).

In two studies, PET was found to correctly rule in disease at various sites. In the Bradley, Dehdashti, Mintun et al. (2004) study the site was lung in 1 patient (4.2 percent) and regional lymph nodes in 6 (25 percent). In the Kamel, Zwahlen, Wyss, et al. (2003) study, the sites were: visceral/soft tissue in 1 patient undergoing initial staging (4.2 percent); lung in 1 restaged patient (5 percent); and breast/axilla in 1 restaged patient. PET was shown to correctly rule out disease in selected sites in the Kamel, Zwahlen, Wyss, et al. (2003)study, including: adrenal gland in 1 patient who was initially staged (4.2 percent); bone in 1 who was restaged (5 percent); and lymph node in 2 restaged patients (10 percent).

Only Kamel, Zwahlen, Wyss, et al. (2003) and Shen, Shiau, Wang, et al. (2002) reported the frequency of incorrect staging by PET; it is unclear from the other studies how often restaging by PET was incorrect. Both Kamel, Zwahlen, Wyss, et al. (2003) and Shen, Shiau, Wang, et al. (2002) found no cases incorrectly upstaged or downstaged by PET at initial staging, but Kamel, Zwahlen, Wyss, et al. (2003)reported 1 case being restaged that was incorrectly upstaged.

Changes in Patient Management

Four studies reported on instances in which patient management was changed based on PET results. The total proportions were: 41.7 percent in Blum, MacManus, Rischin, et al. (2004); 58.3 percent in Brink, Schumacher, Mix et al. (2004); 29.2 percent in Bradley, Dehdashti, Mintun, et al. (2004) and 28.6 percent in Kamel, Zwahlen, Wyss, et al. (2003). Specific changes

Summary Table41. Staging Accuracy Results/Changes in Patient Management: Positron Emission Tomography for Staging of Small-Cell Lung Cancer

Study	Test	Use	PET Correctly Changed Stage	#	%	PET Ruled-in (R/I) or Ruled-out (R/O) Metastases	Site	#	%	PET Missed Metastases	Site	#	%	PET Changed Patient Management	#	%	Changes
Blum, MacManus, Rischin, et al., 2004	PET	staging	up	3	20										4	26.7	forgone RTx for ED
															1	6.7	ED, received palliative CTx/RTx
															2	13.3	RTx target volume changed
															3	12	PCI omitted
															3	12	PCI selected
															2	8	forgone CTx, observation for NED
Bradley, Dehdashti, Mintun et al., 2004	PET	staging	up	1	4.2	R/I	lung	1	4.2						7	29.2	RTx target volume changed
						R/I	regl LNs	6	25								
Brink, Schumacher, Mix et al., 2004	PET	staging	up	10	8.3						brain	1	0.8		10	8.3	forgone RTx for ED
			down	3	2.5										3	2.5	selected CTx/RTx
															1	0.8	missed brain metastasis, affected treatment
Kamel, Zwahlen, Wyss, et al., 2003	PET	staging	up	3	12.5	R/I	visceral/ soft tissue	1	4.2		brain	2	8.3		12	29	
			down	1	4.2	R/O	adrenal	1	4.2						9	37	forgone RTx for ED (3)
																	altered radiation field (5)
											LN	1	5				selected surgery (1)
		restaging				R/I	lung	1	5						3	15	CTx reinstituted (1)
						R/I	breast/ axilla	1	5								CTx discontinued (2)
						R/O	LN	2	10								
						R/O	bone	1	5								
Shen, Shiau, Wang, et al., 2002	PET	staging	up	1	4												
			down	1	4												
Schumacher, Brink, Mix, et al., 2001	PET	staging	up	5	19.2												
		restaging	up	1	16.7												

included the following: forgoing of RTx for extensive disease; palliative CTx/RTx selected for extensive disease; change in RTx target volume; PCI selected; PCI omitted; forgoing of CTx for no evidence of disease; CTx/RTx selected for limited disease; surgery selected; CTx reinstituted; and CTx discontinued.

Study Quality. The quality assessment tool used for Key Question 6 includes 14 items, 8 of which focus on the reference standard (Appendix Table 4G).* A reference standard is the basis for estimating sensitivity and specificity. As noted, the quality of information about the reference standard was uniformly poor, undermining confidence in estimates of sensitivity and specificity. The ratings of study quality can be seen in Summary Table 42.

Given 14 items in the instrument and 6 studies, there were 84 data points, among which 51 percent were rated as unclear, underlining the prevalence of poor reporting in these articles.

In only 1 study (Bradley, Dehdashti, Mintun et al., 2004) was it clear if the sample was representative of population of interest. Conventional staging suggested that patients in the Bradley, Dehdashti, Mintun et al. (2004) study had limited disease, so PET was used to determine if any patients were understaged. In all of the other 5 studies, it is unclear why patients were referred for PET and no study clearly stated that an intact group of patients newly diagnosed with SCLC were enrolled. Selection criteria were clear only in the Bradley, Dehdashti, Mintun et al. (2004) study. For all other studies, criteria were unclear. Articles by Brink, Schumacher, Mix et al. (2004) and Shen, Shiau, Wang, et al. (2002) suggest that PET results influenced performance of the reference standard. In the other 4 studies, it is unclear if PET results influenced performance of the reference standard. The Bradley, Dehdashti, Mintun et al. (2004) study did not incorporate PET into the reference standard, while in all other studies, it was unclear whether PET and the reference standard were independent. Only the Bradley, Dehdashti, Mintun et al. (2004) study stated that PET was interpreted blind to the reference standard; all others were unclear.

Conclusions

Six studies reporting on a total of 277 patients (range 20-120) provided data on the diagnostic accuracy of PET in SCLC. The evidence suggests that, except for detection of brain metastases, the PET added to conventional staging is more sensitive in detecting disease than conventional staging alone. Upstaging was reported in 4–20 percent of patients and downstaging in 4–13 percent of patients. Three studies reported very high occurrence of patient management changes that were attributed to PET (29–58 percent).

However, the quality of these studies is consistently poor and insufficient detail in reporting was the norm. There is such a high degree of uncertainty about the execution and interpretation of the reference standard in all of these studies that confidence is quite low in estimates of diagnostic and staging accuracy. Although these studies report that PET has correctly upstaged or downstaged the extent of disease, the frequency of incorrect changes in stage attributable to PET is unknown due to incomplete reporting. It is not possible to determine the frequency with which management changes, based on PET results, were actually beneficial or harmful.

Thus it is not possible from the limited and poor quality evidence that is available to determine whether the use of PET adds value relative to conventional staging tests for SCLC.

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf.

Summary Table 42. Ratings of Study Quality for Key Question 6

Item	Blum	Bradley	Brink	Kamel	Shen	Schumacher
Representative sample?	?	+	?	?	?	?
Clear patient selection criteria?	?	+	?	?	?	?
Correct reference standard classification of target?	?	?	?	?	?	?
Short period between test and reference standard?	?	?	?	?	?	?
Random/whole sample received reference standard?	+	+	+	+	+	+
Received reference standard regardless of test results?	?	?	-	?	-	-
Reference standard independent of test?	?	+	+	?	?	?
Test execution sufficiently described?	+	+	+	+	-	+
Reference standard execution sufficiently described?	-	-	-	-	-	-
Test interpreted blind to reference standard?	?	?	+	?	?	?
Reference standard interpreted blind to test?	?	?	?	?	?	?
Clinical data available?	+	+/-	-	+	-	-
Uninterpretable/indeterminate results?	-	-	-	-	-	+
Withdrawals explained?	+	+	+	+	+	+

Key Question 7

What are the outcomes (survival, toxicity and quality of life) of treatments used to manage patients with mixed small cell/non-small cell lung cancers?

Overview

Two types of studies were sought: RCTs that compared alternative chemotherapy regimens for mixed small cell/non-small cell cancers; and phase II prospective trials reporting on at least 25 patients treated with a single regimen that reported at least one health outcome of interest. Health outcomes included: duration of survival; disease-free survival and/or progression-free

survival; quality of life; treatment-related adverse effects; objective tumor response rates; and response durations.

Results

No studies meet selection criteria for this question. Very few references from the literature search represented studies of any kind that included patients with mixed histology. Several studies are described below, along with reasons for exclusion.

- The single-arm study by Ruffini, Rena, Oliaro, et al. (2002) was excluded because it could not be confirmed as a prospective phase II multicenter trial. It was clearly conducted as a single-center case series of patients with mixed histologic pattern who underwent surgery. The article does not mention that it was prospective and is likely to be retrospective. Between 1993 and 1999, 1158 patients underwent surgery for lung tumors. Among these were 59 patients with a mixed histologic pattern, separated into 3 main subgroups: 1) adenosquamous carcinoma, n=33, 2) combined neuroendocrine + non-neuroendocrine carcinoma (NNEC), n=21, and 3) biphasic tumors, n=5. The second subgroup included 14 patients with SCLC: 10 who had SCLC + squamous cell carcinoma and 4 who had SCLC + adenocarcinoma. The article provides survival data for 19 of the patients in the second subgroup.

- SmytheEstrera, Swisher, et al. (2001) was excluded because it was not prospective or multicenter and it did not enroll the minimum of 25 patients. These authors reported a single-center retrospective study of 11 patients who underwent surgery for NSCLC after treatment for SCLC. The study period spanned 1978 to 1998. Survival results for the mixed histology patients were compared with 3 control groups: 1) 23 patients with stage I NSCLC undergoing any resection; 2) 46 patients with stage I NSCLC undergoing wedge resection; and 3) 17 patients undergoing wedge resection who had NSCLC and a prior malignancy.

- A subset of patients with mixed histology from an RCT is discussed by Aisner, Finkelstein, Ettinger, et al. (1990). This study is excluded because outcomes are not presented according to treatment group. Patients with extensive stage SCLC received one of 2 induction chemotherapy regimens and complete responders were further randomized to maintenance chemotherapy or observation after whole brain irradiation. A pathologist reviewed the tumor specimens according to a revised classification scheme that includes a variant-morphology category characterized as the small-cell/large-cell (SC/LC) subtype. An initial review of 577 patients identified 24 with the SC/LC subtype. Subsequent review with a second pathologist confirmed only 11 patients in this category. Of these 11 patients, 3 achieved a complete response and 4 achieved a partial response.

- The paper by Johnson, Ihde, Bunn, et al. (1985) is excluded because it presents outcome data for only a single patient with mixed histology. This article summarized data from a series of intramural NCI clinical trials that included 252 patients with newly diagnosed SCLC. Of these, 19 patients were of SC/LC subtype. The article focuses on 19 patients

who achieved long-term survival (≥30 months). Only 1 SC/LC patient was a member of this group.

Conclusions

No studies meet selection criteria for this question. Very few references from the literature search represented studies of any kind that included patients with mixed histology. No conclusions can be drawn on outcomes of treatment for patients with mixed small cell/non-small cell lung cancers.

Key Question 8

What is the role of surgery and what is its impact on survival in patients with very early stage SCLC? How do available studies define very early stage SCLC?

Overview

Very early limited SCLC is defined as no preoperative evidence of involved nodes (clinically N0). In a retrospective analysis of 264 limited stage SCLC patients treated with chemotherapy and radiation from 1976 through 1985, Shepherd, Ginsberg, Haddad et al. (1993) found significantly (p=0.02) better survival for patients clinically staged with negative mediastinal nodes, compared to those with positive mediastinal nodes and also to those with pneumonic consolidation, pleural effusion, atelectasis, or supraclavicular adenopathy. About half the patients classified node negative underwent mediastinoscopy and half were staged by thoracic CT or X-ray only. Unfortunately, retrospective analyses of resected SCLC patients show that clinical (preoperative) staging frequently underestimates pathologic stage (Shepherd, Ginsberg, Patterson et al. 1989; Shepherd, Ginsberg, Feld et al. 1991; Inoue, Miyoshi, Yasumitsu et al. 2000) and inadequately separates limited stage patients by prognosis (Waddell and Shepherd, 2004). Moreover, detection of involved nodes depends on the methods used for staging.

For this question, randomized, controlled trials that compared surgery to no surgery in patients with very early limited SCLC were sought. Two randomized, controlled trials were identified (Lad, Piantadosi, Thomas, et al., 1994; Liao, Zhao, Zhou, et al., 1995), but each had serious limitations for purposes of this review (Summary Table 43). First, neither used platinum based chemotherapy, and thus had limited relevance to contemporary treatment settings. Second, neither RCT studied a homogeneous group with respect to nodal status at randomization (Summary Table 44). The larger RCT (Lad, Piantadosi, Thomas, et al., 1994; N=146) included patients with involved mediastinal nodes, and it is uncertain whether Liao, Zhao, Zhou, et al. (1995; N=40) excluded such patients. Neither study reported outcomes separately for a subgroup without nodal involvement. Since relevant RCT data were lacking, we also sought data from non-randomized comparative studies, both prospective and retrospective (see Summary Table 43 and Appendix Tables 8A-D).[*] Eight studies were identified:

[*] Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf.

- one case-control study (Badzio, Kurowski, Karnicka-Mlodkowska, et al., 2004/Badzio, Jassem, Kurowski, et al., 2005);

- a prospective study of surgery with a comparison group of surgical candidates who did not undergo thoracotomy (Shepherd, Ginsberg, Patterson, et al. 1989);

- four retrospective analyses (Namikawa, Den, Kimura, et al., 1994; Hara, Ohta, Ichinose, et al., 1991/Hara, Ichinose, Kuda et al., 1991; Friess, McCracken, Troxell, et al., 1985; Osterlind, Hansen, Hansen, et al., 1985); and

- two registry analyses (Rostad, Naalsund, Jacobsen, et al., 2004; George, Fitzgerald, Brown, et al., 1986).

These studies had similar limitations with respect to treatment regimens and included patients (Summary Tables 43 and 45). Three studies used platinum-based regimens (Badzio, Kurowski, Karnicka-Mlodkowska, et al., 2004/Badzio, Jassem, Kurowski, et al., 2005; Shepherd, Ginsberg, Patterson, et al. 1989; Hara, Ohta, Ichinose, et al., 1991/Hara, Ichinose, Kuda et al., 1991), but not for all included patients. Only the Rostad, Naalsund, Jacobsen, et al. (2004) registry analysis restricted their study population to patients with very early limited stage disease (N0 patients clinically staged Ia or Ib).

Summary Table 43. Studies Comparing Surgery versus No Surgery for Early Limited Stage SCLC

Study	N evaluated		Pt?	ChemoTx regimen	TRTx?	PCI?	resections		response status[3]	study type	# centers	quality rating
	+surg	-surg					types[1]	timing[2]				
Lad, Piantadosi, Thomas, et al., 1994	70	76	no	CAV	all	all	54 c, 4 p, 12 T	after	40% CR 60% PR	RCT	multi	fair
Liao, Zhao, Zhou, et al., 1995	20	20	no	IMAV	-surg only	NR	NR	mid	70-80% CR	RCT	one	poor
Badzio, Kurowski, Karnicka-Mlodkowska, et al., 2004/Badzio, Jassem, Kurowski, et al., 2005	67	67	some[4]	various	58% of -surg	34% of +surg	30 P 37 L	before	not relevant	case-control	one	poor
Shepherd, Ginsberg, Patterson et al. 1989	38	19	~5%	various	all	all	8 P, 25 L 5 T	after	45% CR 50% PR	non-random.	multi	fair
Namikawa, Den, Kimura, et al., 1994	58	43	NR	NR	NR	NR	NR	NR	?	retro-spect.	one	poor
Hara, Ohta, Ichinose, et al., 1991/Hara, Ichinose, Kuda et al., 1991	36	45	~33%	various	all	NR	4 P, 27 L 5 B	19 before 17 after	24% CR 59% CR	retro-spect.	one	poor
Friess, McCracken, Troxell, et al., 1985	15	246	no	COMF or CAV	all	all	3 P 12L	before	not relevant	retro-spect.	multi	fair
Osterlind, Hansen, Hansen, et al., 1985	33	46	no	CCM±V±A±E	33% each	7-12%	11c, 13p 9<p	before	not relevant	retro-spect.	two	fair
Rostad, Naalsund, Jacobsen, et al., 2004	29	96	NR	NR	NR	NR	3P, 15L 3B, 5<p	before	not relevant	registry	multi	poor
George, Fitzgerald, Brown, et al., 1986	13	88	no	various	NR	NR	NR	before	not relevant	registry	multi	poor

[1] resection types: c=complete; p=partial; <p=less than a partial resection; T=thoracotomy only (open and close); P=pneumonectomy; L=lobectomy; B=bilobectomy; [2] resection timing: after = after all chemotherapy cycles; before = before any chemotherapy; mid = between cycles; [3] at the time of randomization or resection; [4] proportion treated with platinum not reported.

Summary Table44. Sample and Methods: Surgery versus No Surgery for Very Early Limited Stage Disease

Study	N	Age	% Female	% Performance Status	+Surg: Type of Resections	CTX Regimen	RTx Regimen
Lad et al. 1994 RCT multi-center late 1983 - 10/1989	Total 146 +surg 70 -surg 76	md (rng) 59 (35-72); arms pooled, but "well matched"	35 arms pooled but "well matched"	82% with KPS ≥90 arms pooled but "well matched"	54 complete 4 partial 12 open & close	CAV same	Dose / Schedule / PCI? 50 Gy / 25 x 2 Gy / 30 Gy 15 x 2 Gy
Liao et al. 1995 single center RCT (Shanghai) 1/90-12/91	Total 40 +surg 20 -surg 20	mn (rng) 50 (33-74) 54 (31-66)	10 10	NOT REPORTED	not reported	same for all: ifosfamide, Mesna, doxorubicin, vincristine	Dose / Schedule / PCI? only for -surg arm; dose, schedule not reported / not reported
Badzio et al. 2004, 2005; pair-matched case/control one center 1984-96	Total 134 +surg 67 -surg 67 in CR 23	mn (rng) 57 (29-70) 54 (36-71) (p=0.03)	15 22 (p=0.27)	0 1 2 3 60 36 4 58 33 9 WHO	30 pneumonectomy; 37 lobectomy	CAV, CDE, PE or MCCC/CAV/VI CCMV or ACOM	Dose / Schedule / PCI? 30-50 Gy / 10, 20, or 25 fracs; n=39 -surg only / n=23, +surg only; dose, fractionation not reported
Shepherd et al. 1989; adjuv. surgery post chemoTx; non-randomized multi-center	Total 57 +surg 38 -surg 19	md (rng) 60 (39-77) 59 (44-75)	32 47	NOT REPORTED	8 pneumonectomy; 25 lobectomy; 5 thoracotomy only	CAV±etoposide or PE	Dose / Schedule / PCI? 25-35 Gy / 10-20 fracs / 20 Gy in 5 fracs same
Namikawa et al. 1994 retrospective series; single center 1960-86	Total 101 +surg 58 -surg 43	NOT REPORTED	NOT REPORTED	NOT REPORTED	NOT REPORTED	NOT REPORTED	Dose / Schedule / PCI? NOT REPORTED
Hara et al. 1991 retrospective series; single center 1972-89	Total 81 +surg 36 -surg 45	mn (rng) 64 (44-76) 63 (45-83)	17 16	0 1 2 3 50 44 6 18 78 4 ECOG	4 pneumonectomy; 27 lobectomy; 5 bilobectomy	various regimens same	Dose / Schedule / PCI? 30-70 Gy (mn 46 Gy) / 1.4-2 Gy, 25-36 fracs, 1/d / NOT REPORTED
Friess et al. 1985 retrospective analysis of SWOG 7628 patients; 1977-9	Total 261 +surg 15 -surg 246	NOT REPORTED	NOT REPORTED	NOT REPORTED	3 pneumonectomy; 12 lobectomy	4 different regimens	Dose / Schedule / PCI? 2 x 30 Gy ± 15 Gy boost / NOT REPORTED / dose, fracs not reported

Summary Table44. Sample and Methods: Surgery versus No Surgery for Very Early Limited Stage Disease (continued)

Study	N	Age	% Female	% Performance Status	+Surg: Type of Resections	CTX Regimen	RTx Regimen
Osterlind et al. 1985; retrospective analysis of patients from 6 trials, 2 Danish institutions, 3/73-9/81	Total 79 +surg 33 -surg 46	mn (sd) 55 (±8) 60 (±6)	 18 28	AJC[1] 0-1 2 3-4 83 17 0 91 6 3	11 complete, 13 partial, 9 <partial resections	CCM ± vincristine ± (doxorubicin + etoposide)	Dose Schedule PCI? 33% of each group, but dose, schedule not reported 12% 7% but regimen details not reported
Rostad et al. 2004 registry analysis all cases in Norway, 1993-9	Total 125 +surg 29 -surg 96	"no age difference" between groups	NOT REPORTED	NOT REPORTED	3 pneumonectomy; 15 lobectomy; 3 bilobectomy; 5 minor resection	NOT REPORTED	Dose Schedule PCI? no details provided not specified
George et al. 1986 registry analysis all cases in Rochester, NY 1975-81	Total 101 +surg 13 -surg 88	14% 31-50 29% 51-60 38% 61-70 19% ≥71 (groups pooled)	35 (groups pooled)	NOT REPORTED	NOT REPORTED	CCM, CMVP, CC, or CAV same	Dose Schedule PCI? no details provided not specified

[1] American Joint Committee for Cancer Staging, 1979
Abbreviations table provided at the end of this Report.

Summary Table 45. Eligibility criteria and staging procedures used in studies of surgery for very early limited stage SCLC

Study	eligibility criteria for inclusion by clinical staging evaluation											staging procedures utilized						
	diagnosis before thoracotomy?	solitary peripheral nodules?	T2 tumors	T3 tumors	involved mediastinal nodes	involved supraclavic-ular nodes	involved hilar nodes	pleural effusion	pericardial effusion	superior vena cava syndrome	stage II disease	stage III disease	chest imaging	abdominal imaging	brain imaging	bone imaging	bone marrow evaluation	bronchos-copy	medistin-oscopy
Lad et al., 1994	yes	no	yes	yes	yes	?	?	?	no	no	yes	yes	?	yes; method unknown	CT	yes; method unknown	yes	yes	?
Liao et al., 1995	yes	no	yes	yes	?	?	?	?	?	?	yes	yes	CT	CT & US	CT	RNS	yes	?	?
Badzio et al., 2004	no	?	yes	no	yes	no	?	no	?	?	yes	yes	CT	CT or US	CT	RNS	no	yes	not routinely
Shepherd et al., 1989	yes	no	yes	yes if N0	yes	?	?	?	?	?	yes	yes	some CT	RNS	CT or RNS	RNS	yes	?	yes if no CT
Namikawa et al., 1994	most	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Hara et al., 1991	yes	?	yes	?	yes	?	?	?	?	?	yes	yes	CT	CT or RNS	CT or RNS	CT or RNS	yes	yes	?
Friess et al., 1985	yes	?	?	?	yes	yes	?	?	?	?	?	?	X ray	RNS	RNS	RNS	yes	?	?
Osterlind et al., 1985	yes	?	?	?	no	no	no	?	?	?	no	no	?	?	?	?	yes	in most	in most
Rostad et al., 2004	?	?	yes	no	no	no	no	?	?	?	no	no	CT for some	?	?	?	?	?	?
George et al., 1986	?	?	yes	yes	yes	yes	yes	no	?	?	yes	yes	CT for some	CT, US or RNS in 75%	CT or RNS in 77%	?	yes in 58%	?	?

yes=eligible for inclusion, or procedure was used for staging ; no=not eligible for inclusion or not used or evaluated for staging ; ?= cannot be determined from information in published report;
Abbreviations table provided at the end of this Report.

Summary Table 46. Survival Outcomes: Surgery versus No Surgery for Very Early Limited Stage Disease

Study	N	OS Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr (%)	TTP Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr (%)
Lad et al., 1994	+surg 70	15.4	~60	20	~20	~20	~20						
multi-center RCT	-surg 76	18.6	~65	20	~20	~20	~20						
									NOT REPORTED				
	Difference	-3.2	-5	0									
		log rank p=0.78											
Liao et al., 1995 single-center RCT (Shanghai) 1/90-12/91	+surg 20		79	52	24								
	-surg 20		63	18	18								
									NOT REPORTED				
	Difference		16	34	6								
		(log rank p=0.12; t-test at 2 yr, p<0.05)											
Badzio et al., 2004, 2005	+surg 67	22.3	70	43	~35	~30	27	20.9					
									(time to relapse or progression)				
	-surg 67	11.2	45	17	~12	~4	4	7					
single center	(in CR 23)	(22)		(36)			(26)						
case-control	Difference	11.1	25	26	~23	~26	23	13.9					
		p < 0.001; HR = 0.42; 95% CI: 0.28, 0.61						p < 0.001					
Shepherd et al., 1989	+surg 38	22.8	~63	~47	~36	~36	36						
	-surg 19	11.8	~48	~10	~10	~10							
non-randomized multi-center									NOT REPORTED				
	Difference	10	~15	~37	~26	~26							
		p = 0.049											
Namikawa et al., 1994	resected 43	8.1											
	explored[1] 15	5.1											
single center case series	-surg 43	5.2							NOT REPORTED				
	Difference	2.9 (statistical test result not reported)											
Hara et al., 1991	+surg 36	33					38						
single center case series	-surg[2]: CR 19	24.5					21						
	PR 20	12.5					0		NOT REPORTED				
	Difference	8.5 (+surg – CR)											
		20.5 (+surg – PR) (statistical test result not reported)											

[1] patients found intra-operatively to have unresectable disease

[2] results for unresected patients reported separately for complete (CR) and partial (PR) responders to chemotherapy ± TRTx

Summary Table 46. Survival Outcomes: Surgery versus No Surgery for Very Early Limited Stage Disease (continued)

Study	N	OS Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr (%)	TTP Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr (%)
Friess et al., 1985	+surg 15	25		44									
	-surg 246	10.5 (p=0.0037)		13.7 (p<0.05)									
4-arm RCT	33[3]	10 (range, 1-46+; p=0.03)						NOT REPORTED					
subgroup analysis	Difference	15		30.3									
Osterlind et al., 1985; retrospec-	+surg 33		~37	~16	~14	~14		DFS:	15% at 1.5 yr, 12% at 2 yr				
tive analysis, patients from 6	-surg 46		~50	~16	~10	~8			15% at 1.5 yr, 13% at 2 yr				
trials, 2 Danish	Difference		~(-13)	0	~4	~6			none				
institutions, 3/73-9/81			(p=0.35 by life table analysis)										
Rostad et al., 2004	+surg 29						44.9 (95% CI: 23.9, 65.9)						
	-surg 96						11.3 (95% CI: 4.2, 18.4)						
registry analysis	Difference						33.6	NOT REPORTED					
George et al., 1986	+surg 13	30.8	~70	~56	~46	~40	~40						
	-surg (all) 88	12.4											
registry analysis	CTx 43	11.9	~43	~15	~10	~4	0	NOT REPORTED					
	RTx 20	13.4	~58	~20	~20	~20	18						
	both 25	14.1											
	Difference	18.4 [+surg – (all -surg)]; (p=0.009 versus all –surg)											

[3] subgroup of unresected patients selected for "similar initial presentation" as those resected

Summary Table 47. Adverse Events: Surgery versus No Surgery for Very Early Limited Stage Disease

Toxicity Type	Study	Severity or Grade	Early n	%	Late n	%	p	Not Reporting
Treatment-related or operative mortality	Lad 1994		70	2.9	76	NR		Badzio 2004; Namikawa 1994; Friess 1985; Osterlind 1985; Rostad 2004
	Liao 1995		20	0	20	0		
	Shepherd[1] 1989		38	0	19	NR[1]		
	Hara 1991		36	0	45	NR		
	George 1986		13	0	88	1[2]		

[1] 2 of 72 patients (3%) died after the first course of chemotherapy.
[2] given chemotherapy plus TRTx

Only Shepherd, Ginsberg, Patterson, et al. (1989) reported post-operative complications other than mortality. Among 38 resected patients, they observed:

1 severe bronchospasm (2.6%)
1 prolonged atelectasis (2.6%)
1 pulmonary edema (2.6%)
2 transient arrhythmias (5.3%)
1 assisted ventilation for 6 weeks (2.6%)

Randomized, Controlled Trials

Interventions. Although two RCTs compared outcomes for limited stage SCLC patients managed with versus without surgery, neither trial fully adhered to a contemporary management strategy (Lad, Piantadosi, Thomas, et al., 1994; Liao, Zhao, Zhou, et al., 1995; see Table 43, Table 44, Appendix Tables 8A-D). Only the Lad, Piantadosi, Thomas, et al., (1994) trial used TRTx (and PCI) for all patients, while the Liao, Zhao, Zhou, et al. (1995) trial only gave TRTx to those randomized to no surgery. Patients in the Lad, Piantadosi, Thomas, et al. (1994) trial received TRTx sequentially after completing chemotherapy (and post-operative recovery if randomized to surgery). The Liao, Zhao, Zhou, et al. (1995) trial scheduled operations (and TRTx for the other arm) after chemotherapy cycles 2 or 3 (of up to 7). Each treatment regimen lacked platinum.

Study Populations. Published information suggests that neither RCT studied a homogeneous group of patients with respect to nodal status at randomization (Table 44). Lad, Piantadosi, Thomas, et al. (1994) randomized limited stage patients in CR or PR after five cycles of induction (neoadjuvant) chemotherapy. They did not report nodal status by clinical staging after chemotherapy for either arm. However, of 70 patients randomized to surgery, 15 were clinically N0 at registration (before induction), and 16 were pathologically N0 after resection. Ninety to 95 percent of those Liao, Zhao, Zhou, et al. (1995) randomized were in stage III. They reported 70–80 percent in CR, but it is uncertain when in the course of therapy these remissions were achieved. Liao, Zhao, Zhou, et al. (1995) also did not report nodal status before chemotherapy or after cycles 2-3, when surgery or radiation therapy took place.

Neither trial required mediastinoscopy or other invasive staging. Noninvasive staging was inadequately described in both RCTs.

Results. By log rank analysis, neither RCT found a statistically significant difference between Kaplan-Meier survival curves for those managed with versus without surgery (Lad, Piantadosi, Thomas, et al., 1994, $p=0.78$; Liao, Zhao, Zhou, et al., 1995, $p=0.12$; see Table 46, Appendix Table 8E). However, Liao, Zhao, Zhou, et al. (1995) reported a significant difference in percent survival at two years that favored the arm randomized to surgery (52 percent versus 18 percent; $p<0.05$ by t-test). Neither RCT reported time to relapse or progression, disease-free survival, or quality of life outcomes.

Nonrandomized Comparisons

Interventions. Only three of the eight studies reported that all patients received TRTx (Shepherd, Ginsberg, Patterson, et al., 1989; Hara, Ohta, Ichinose, et al., 1991/Hara, Ichinose, Kuda et al., 1991; Friess, McCracken, Troxell, et al., 1985), and only two used PCI (Shepherd, Ginsberg, Patterson, et al. 1989; Friess, McCracken, Troxell, et al., 1985). Only the Shepherd, Ginsberg, Patterson, et al. (1989) study resected patients after chemotherapy was completed. Three studies used platinum-based regimens (Badzio, Kurowski, Karnicka-Mlodkowska, et al., 2004/Badzio, Jassem, Kurowski, et al., 2005; Shepherd, Ginsberg, Patterson, et al., 1989; Hara, Ohta, Ichinose, et al., 1991/Hara, Ichinose, Kuda et al., 1991), but not for all included patients.

Study Populations. Inclusion and exclusion criteria (Summary Table 43, Appendix Table 8A)* showed that only the Rostad, Naalsund, Jacobsen, et al. (2004) registry analysis restricted their study population to patients with very early limited stage disease (N0 patients clinically staged Ia or Ib). However, Rostad, Naalsund, Jacobsen, et al. (2004) did not report TRTx or PCI use, and excluded 18 patients who received adjuvant chemotherapy after surgery from their analysis. Thus, none of the eight non-randomized comparisons addressed the population of interest given contemporary treatment with versus without surgery.

Results. Four of eight nonrandomized studies reported significantly longer survival for the group given surgery than for the comparison group managed without surgery (Badzio, Kurowski, Karnicka-Mlodkowska, et al., 2004/Badzio, Jassem, Kurowski, et al., 2005; Shepherd, Ginsberg, Patterson, et al., 1989; Friess, McCracken, Troxell, et al., 1985; George, Fitzgerald, Brown, et al., 1986; see Summary Table 8B, Appendix Table 8E). The Badzio case-control study (Badzio, Kurowski, Karnicka-Mlodkowska, et al., 2004/Badzio, Jassem, Kurowski, et al., 2005) also reported a statistically significant increase in time to relapse or progression for those given surgery. No non-randomized comparison evaluated quality of life outcomes.

One cannot exclude the influence of patient selection and other biases in the survival results from non-randomized studies. Most did not report adequate details to evaluate the similarity of study groups with respect to baseline characteristics and prognostic factors (Table 44, Appendix Tables 8b and 8H). Information also was inadequate to determine whether patients in each group were managed similarly with respect to chemotherapy and radiation therapy regimens (Table 44, Appendix Table 8C).

Adverse Events

Perioperative mortality was 2.9 percent in the Lad, Piantadosi, Thomas, et al. (1994) RCT (Table 47, Appendix Table 8G).* It was zero in the Liao, Zhao, Zhou, et al. (1995) RCT and in three reporting non-randomized comparisons. Only two of these five studies reported treatment-related mortality in the comparison groups managed without surgery (Liao, Zhao, Zhou, et al., 1995; George, Fitzgerald, Brown, et al., 1986). Only the Shepherd, Ginsberg, Patterson, et al. (1989) study reported other adverse events, but did not report their rates in the comparison group.

Conclusions

For this question, we sought randomized and nonrandomized studies that compared surgery to no surgery in patients with very early limited SCLC, defined as no preoperative evidence of involved nodes (clinically N0). Two randomized controlled trials and 8 nonrandomized comparative studies were included in the review, but none provided evidence that directly address the question.

None of these comparisons studied a homogeneous group of patients with respect to nodal status; nor were separate outcomes reported for the subgroup of patients without nodal involvement. Moreover, the treatment regimens used had limited relevance to contemporary

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf.

treatment settings; for example, 5 studies did not use platinum based chemotherapy for any patients, and the remaining 3 used platinum based therapy only for some patients. Thus no conclusion can be drawn on the outcomes of management of very early limited SCLC with versus without surgery.

Key Question 9

What are the outcomes of second- or subsequent-line therapy in patients with relapsed or progressive SCLC? Where available data permit, patients with limited- and extensive-stage disease will be addressed separately, as will those with refractory disease (relapse or progression within 3 months of primary treatment).

Overview

Two types of studies were sought: randomized, controlled trials (RCTs) that compared alternative chemotherapy regimens for relapsed, progressive, or extensive-stage SCLC; and phase II multicenter, prospective trials reporting on at least 25 patients treated with a single regimen that reported at least one health outcome of interest. Health outcomes included: duration of survival; disease-free survival and/or progression-free survival; quality of life; treatment-related adverse effects; objective tumor response rates; and response durations.

The primary focus here is on RCTs (Summary Tables 48–51; Appendix Tables 9A–9G).* The main purpose of single-arm phase II trials is to assess responsiveness to a chemotherapy regimen and select treatments for further testing in RCTs. Phase II trials in Appendix Tables 9H-9M* are presented mainly to illustrate the regimens that have been tried on relapsed or progressive SCLC. The lack of comparisons between regimens within such trials limits their usefulness to this Review. Several recent studies that reported encouraging response data will be noted.

Randomized, Controlled Trials

Among 9 RCTs meeting selection criteria, sample sizes ranged from 32 to 610 and they collectively included 1,415 patients. As shown in Table 48, each of the 9 trials compared different sets of chemotherapy regimens. Seven trials compared 2 regimens and the Wolff, Birch, Sarma, et al. (1986) trial compared 3. Six studies specifically noted that second-line regimens were compared (von Pawel, Gatzemeier, Pujol, et al., 2001,; von Pawel, Schiller, Shepherd, et al., 1999; Postmus, Smit, Kirkpatrick, et al., 1993; Trillet-Lenoir, Lasset, Arpin, et al., 1992; O'Bryan, Crowley, Kim, et al., 1990; Spiro, Souhami, Geddes, et al. 1989). The study by Sculier, Lafitte, Lecomte, et al. (2002) stated that patients had previously undergone chemotherapy that did not include cisplatin and etoposide, but did not specify the distribution of number of previous regimens. It was also unspecified by O'Brien, Ciuleanu, Tsekov, et al.

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf.

(2005). Wolff, Birch, Sarma, et al. (1986) described this distribution: 80 percent had previously had 1 chemotherapy regimen, 14 percent had 2; and 6 percent had 3.

Data on age, gender and performance status were reported by all studies except von Pawel, Schiller, Shepherd, et al. (1999), which only give performance status. O'Brien, Ciuleanu, Tsekov, et al. (2005) did not provide separate gender distributions for the two groups. The study by Spiro, Souhami, Geddes, et al. (1989) was a 2-stage randomized trial. In the first stage, patients were randomized to either 4 or 8 cycles of primary chemotherapy consisting of cyclophosphamide, vincristine and etoposide. The second stage randomized patients at relapse to either methotrexate plus doxorubicin or supportive care. Two pairs of first stage groups were compared at the second stage and shown to be similar on age, gender, performance status and stage. Where information was available, groups appeared comparable on these characteristics.

Summary Table 48. RCTs Comparing Alternative Chemotherapy Regimens for Relapsed, Progressive, or Extensive-Stage SCLC

	N Grp1	N Grp2	N Grp3	Regimen 1	Regimen 2	Regimen 3	Previous Regimens	pub type	quality rating
O'Brien, Ciuleanu, Tsekov, et al., 2005	70	71		po T	BSC			Abstr	?
Sculier, Lafitte, Lecomte, et al., 2002	31	34		PE	CbPE		No PE; EVI, VAC, RTx, Surgery	Full	Fair
von Pawel, Gatzemeier, Pujol, et al., 2001	52	54		po T	iv T			Full	Fair
von Pawel, Schiller, Shepherd, et al., 1999	107	104		iv T	CAV		Platinum, CAV, PE+CAV, RTx, Immuno-therapy, Surgery	Full	Fair
Postmus, Smit, Kirkpatrick, et al., 1993	43	25		VIMP	CDE			Full	Fair
Trillet-Lenoir, Lasset, Arpin, et al., 1992	15	17		Low PE	High PE			Full	Poor
O'Bryan, Crowley, Kim, et al., 1990	45	58		BTOC	PE		CAV, E, other	Full	Poor
Spiro, Souhami, Geddes, et al., 1989	294	290		MA	BSC		CV	Full	Poor
Wolff, Birch, Sarma, et al., 1986	26	27	26	E100	E200	E300	1-3 CTx regimens, RTx, Surgery	Full	Poor

Abbreviations table provided at the end of the Report.

Summary Table 49. Sample and Treatments: Treatment of Recurrent/Progressive Disease

Study	Inclusion	Chemotherapy Agents	Age (yr)	Gender (%)	Performance Status (%)
O'Brien, Ciuleanu, Tsekov, et al., 2005	relapsed SCLC ineligible for further IV CTx	po T topotecan BSC best supportive care	po T / BSC mn md 60 / 59 rng sd	All M 73 F 27	PS / po T / BSC 0/1 / 73 / 67
Sculier, Lafitte, Lecomte, et al., 2002	proven SCLC prior CTx did not include PE	PE cisplatin etoposide CbPE carboplatin cisplatin etoposide	PE / CbPE mn md 58 / 59 rng 41-73 / 39-70 sd	PE / CbPE M 84 / 76 F 16 / 24	KPS / PE / CbPE 60-70 / 45 / 32 80-100 / 55 / 68
von Pawel, Gatzemeier, Pujol, et al., 2001	limited or extensive SCLC recurrence ≥ 3 mo after CR/PR to 1st-line CTx	po T topotecan iv T topotecan	po T / iv T mn 59.9 / 58.2 md rng 38-79 / 35-74 sd	po T / iv T M 75.0 / 79.6 F 25.0 / 20.4	PS / po T / iv T 0 / 19.2 / 33.3 1 / 65.4 / 38.9 2 / 15.4 / 27.8
von Pawel, Schiller, Shepherd, et al., 1999	progressive, limited or extensive SCLC PD ≥ 60 d after 1st-line CTx	iv T topotecan CAV cytoxan doxorubin vincristine			ECOG / iv T / CAV 0 / 16.8 / 19.2 1 / 59.8 / 61.5 2 / 23.4 / 19.2
Postmus, Smit, Kirkpatrick, et al., 1993	proven SCLC PD ≤ 3 mo of last CTx 1st-line CTx: IMP, VP or CDE; PD after IMP/VP has 2nd-line CDE; PD after CDE had VIMP	VIMP vincristine ifosfamide mesna carboplatin CDE cytoxan doxorubicin etoposide	IMP / VP / CDE mn md 57 / 58 / 55 rng 38-69 / 39-73 / 43-67 sd	MP / VP / CDE M 71 / 86 / 88 F 29 / 14 / 12	ECOG / IMP / VP / CDE 0 / 24 / 18 / 20 1 / 43 / 45 / 40 2 / 24 / 32 / 20 3 / 10 / 5 / 20
Trillet-Lenoir, Lasset, Arpin, et al., 1992	relapsed SCLC after 1st-line CTx	PE1 cisplatin 20 etoposide 60 PE2 cisplatin 40 etoposide 100	PE1 / PE2 mn 56.73 / 52.47 md rng sd 8.7 / 5.95	PE1 / PE2 M 100 / 88 F 0 / 12	KPS / PE1 / PE2 mn / 79.17 / 74.71 sd / 13.82 / 10.06
O'Bryan, Crowley, Kim, et al., 1990	failed or relapsed SCLC after 1st-line CTx	BTOC vincristine thiotepa cytoxan carmustine PE cisplatin etoposide	BTOC / PE mn md 58 / 61 rng 41-75 / 38-76 sd	BTOC / PE M 80 / 64 F 20 / 36	KPS / BTOC / PE 0-1 / 53 / 39 2-3 / 47 / 61

Abbreviations table provided at the end of the Report.

Summary Table 49. Sample and Treatments: Treatment of Recurrent/Progressive Disease (continued)

Study	Inclusion	Chemotherapy Agents	Age (yr)	Gender (%)	Performance Status (%)
Spiro, Souhami, Geddes, et al., 1989	histologically, cytologically proven SCLC; < 75;	MA methotrexate doxorubicin BSC best supportive care			
Wolff, Birch, Sarma, et al., 1986	recurrent SCLC, prior CTx did not include E	E100 etoposide 100 E200 etoposide 200 E300 etoposide 300	100 200 300 < 50 19 11 15 50-60 38 56 46 > 60 42 33 31	100 200 300 M 58 93 81 F 42 7 19	KPS 100 200 300 60 0 15 0 70 46 33 46 80 27 41 31 90 19 7 12 100 8 4 12

Summary Table 50. Efficacy Outcomes: Treatment of Recurrent/Progressive Disease

Study	Overall Survival (%)	N	Med	1 yr	Test	Tumor Response (%)	N	CR	PR	SD	PD	NE	Test	Med Dur (wks)
O'Brien, Ciuleanu, Tsekov, et al., 2005		N	Med	1 yr		po T	71	7		44				
	po T	71	26 wks	49 (6 mo)		BSC	70							
	BSC	70	14 wks	26										
	HR=0.64 (95% CI: 0.45, 0.90, p=0.0104)													
Sculier, Lafitte, Lecomte, et al., 2002	PE	31	18.9 wks	18	Log-rank,	PE	31	0	29					22.6
	CbPE	34	33.0 wks	19	p=0.11	CbPE	34	9	38					33.9
von Pawel, Gatzemeier, Pujol, et al., 2001	po T	52	32.3 wks	~25	adjusted	po T	52	1.9	21.2	19.2	30.8	26.9	Difference in ORR=	18.1
	iv T	54	25.1 wks	~8	RR=0.90 (95% CI 0.55, 1.47)	iv T	54	3.7	11.1	29.6	42.6	13.0	8.3% (95% CI -6.6%, 23.1%, NS)	13.9
von Pawel, Schiller, Shepherd, et al., 1999	iv T	107	25.0 wks	14.2	Log-rank,	iv T	107	0.0	24.3	19.6	45.8	10.3	Difference in ORR,	14.4
	CAV	104	24.7 wks	14.4	p=0.772, Adjusted RR=1.17 (p=0.322)	CAV	104	1.0	17.3	11.5	52.9	17.3	P=0.285	15.3 (p=0.300)
Postmus, Smit, Kirkpatrick, et al., 1993	VIMP	43	19 wks			VIMP	25	4	56	8	24	8		16
	CDE	25	22 wks			CDE	43	14	37	19	23	7		19
Trillet-Lenoir, Lasset, Arpin, et al., 1992	PE1	15	13 wks			PE1	15	6.6	20	13.3	60			
	PE2	17	16.5 wks			PE2	17	11.8	23.5	11.8	52.9			
O'Bryan, Crowley, Kim, et al., 1990	BTOC	45	13 wks		RR 1.3	BTOC	45	0	13					
	PE	58	16 wks		(95%CI 0.9, 2.0)	PE	58	2	10				(p=0.91)	
						BTOCgood	11	27						
	BTOCgood	11	10 wks		RR 3.3	PEgood	16	27						
	PEgood	16	35 wks		(95%CI 0.2, 9.1)	BTOCpoor	34	9						
						PEpoor	68	9						
	BTOCpoor	34	14 wks		RR1.1									
	PEpoor	68	12 wks		(95%CI 0.7, 1.8)									

Summary Table 50. Efficacy Outcomes: Treatment of Recurrent/Progressive Disease (continued)

Study	Overall Survival (%)	N	Med	1 yr	Test	Tumor Response (%)	N	CR	PR	SD	PD	NE	Test	Med Dur (wks)
Spiro, Souhami, Geddes, et al., 1989	MA					MA	170	4	19	45	32	1		
Wolff, Birch, Sarma, et al., 1986	E100 E200 E300	26 27 26	12.6 wks 20.0 wks 22.5 wks	~4 ~12 ~24	Log-rank, Gehan-Wilcoxon (p=NS)	E100 E200 E300	26 27 26		4 7 4					

Summary Table 51. Adverse Events: Treatment of Recurrent/Progressive Disease

Toxicity Type	Study	Description	Group	n	Gr 3 %	Gr 4 %	p value[18]
Treatment-related mortality	O'Bryan 1990	Drug-related deaths	BTOC	45	4		0.28
			PE	84	1		
Alopecia	Sculier 2002		PE	28		21 (3/4)	0.15
			CbPE	31		39	
	von Pawel 2001		po T	52	1.9	0.0	0.06
			iv T	54	13.0	0.0	
	von Pawel 1999		iv T	107		0.0 (3/4)	1.0
			CAV	104		0.0	
Fatigue	von Pawel 2001		po T	52	5.8	0.0	0.36
			iv T	54	1.9	0.0	
	von Pawel 1999		iv T	107		4.7 (3/4)	0.28
			CAV	104		8.7	
Diarrhea	von Pawel 2001		po T	52	7.7	0.0	0.054
			iv T	54	0.0	0.0	
	von Pawel 1999		iv T	107		0.9 (3/4)	1.0
			CAV	104		0.0	
Nausea	O'Brien 2005		po T	71	1		1.0
			BSC	70	0		
	von Pawel 1999		iv T	107		39.3 (3/4)	0.89
			CAV	104		40.4	
Vomiting	O'Brien 2005		po T	71	3		0.50
			BSC	70	0		
	Sculier 2002	Nausea/vomiting	PE	30		7 (3/4)	0.23
				32		0	
	von Pawel 2001		po T	52	11.5	0.0	0.16
			iv T	54	3.7	0.0	
	von Pawel 1999		iv T	107		2.9 (3/4)	1.0
			CAV	104		1.9	
	Wolf 1986	Nausea/vomiting/bloody diarrhea/ stomatitis	E100	26	5	0	0.44
			E200	27	4	0	
			E300	26	10	0	
Anorexia	von Pawel 1999		iv T	107		0.9 (3/4)	1.0
			CAV	104		0.0	
Diarrhea	O'Brien 2005		po T	71	6		0.12
			BSC	70	0		
Lethargy	O'Brien 2005	Fatigue	po T	71	4		1.0
			BSC	70	4		
Neurosensory	O'Brien 2005	Pain	po T	71	3		0.44
			BSC	70	6		
Neuromotor							
Hearing loss							
Esophagitis							

[18] Comparison of grade 3 and above versus others Fisher's exact test.

Summary Table 51. Adverse Events: Treatment of Recurrent/Progressive Disease (continued)

Toxicity Type	Study	Description	Group	n	Gr 3 %	Gr 4 %	p value[19]
Bronchopulmonary	O'Brien 2005	Dyspnea	po T	71	3		0.32
			BSC	70	9		
	von Pawel 2001	Dyspnea	po T	52	9.6	0	1.0
			iv T	54	9.3	0 (5:1.9)	
			po T	52	1.9	0 (5: 3.8)	0.36
		Pulmonary embolism	iv T	54	0	0 (5: 1.9)	
Pneumonitis	von Pawel 2001	Pneumonia	po T	52	5.8	1.9	0.054
			iv T	54	0.0	0.0	
Hepatic							
Kidney							
Hemorrhage							
Anemia	O'Brien 2005		po T	71	25 (3/4)		
	von Pawel 2001		po T	52	27.5	3.9	1.0
			iv T	54	26.4	3.8	
	von Pawel 1999		iv T	104	39.4	2.9	0.001
			CAV	101	17.8	2.0	
Thrombocytopenia	O'Brien 2005		po T	71		7	
	Sculier 2002		PE	30	17 (3/4)		0.07
			CbPE	32	38		
	von Pawel 2001		po T	52	25.5	27.5	0.85
			iv T	54	24.5	24.5	
	von Pawel 1999		iv T	104	28.8	28.8	<0.001
			CAV	101	9.9	5.0	
	Postmus 1993		VIMP	25	8	45	<0.001
			CDE	43	6	3	
	Trillet-Lenoir 1992		PE1	15	0	7	0.041
			PE2	17	18	24	
	Wolff 1986	Neutropenia	E100	26	0	15	<0.001
			E200	27	0	13	
			E300	26	24	33	
Leukopenia or neutropenia	O'Brien 2005	Neutropenia	po T	71		33	
	Sculier 2002	Leukopenia	PE	30	60 (3/4)		0.76
			CbPE	32	56		
	von Pawel 2001	Leukopenia	po T	52	27.5	17.6	0.006
			iv T	54	45.3	28.3	
		Neutropenia	po T	52	21.6	35.3	<0.001
			iv T	54	25.9	67.3	

[19] Comparison of grade 3 and above versus others Fisher's exact test.

Summary Table 51. Adverse Events: Treatment of Recurrent/Progressive Disease (continued)

Toxicity Type	Study	Description	Group	n	Gr 3 %	Gr 4 %	p value
Leukopenia or neutropenia	von Pawel 1999	Leukopenia	iv T	104	54.8	31.7	0.34
			CAV	101	37.6	43.6	
		Neutropenia	iv T	104	18.3	70.2	0.83
			CAV	99	15.2	71.7	
	Postmus 1993	Leukopenia	VIMP	25	26	40	1.0
			CDE	43	38	25	
	Trillet-Lenoir 1992	Leukopenia	PE1	15	33	13	0.021
			PE2	17	12	76	
	Wolff 1986		E100	26	5	0	<0.001
			E200	27	25	54	
			E300	26	0	86	
Infection	O'Brien 2005	Febrile neutropenia	po T	71		3	
		Neutropenic infections	po T	71		1	
		Sepsis	po T	71		4	
	Sculier 2002		PE	30	3 (3/4)		0.96
			CbPE	33	3		
	von Pawel 2001	Fever	po T	52	3.8	1.9 (5:1.9)	0.20
			iv T	54	1.9	0.0	
Other							

Study Quality. Of the nine RCTs meeting selection criteria, four were rated as being of fair quality (Sculier, Lafitte, Lecomte, et al., 2002; von Pawel, Gatzemeier, Pujol, et al., 2001; von Pawel, Schiller, Shepherd, et al., 1999; Postmus, Smit, Kirkpatrick, et al., 1993, 4 were rated as poor (Trillet-Lenoir, Lasset, Arpin, et al., 1992; O'Bryan, Crowley, Kim, et al., 1990; Spiro, Souhami, Geddes et al. 1989; Wolff, Birch, Sarma, et al. 1986), and one could not be rated because it has only been reported as a conference abstract (O'Brien, Ciuleanu, Tsekov, et al., 2005). The fair trials had moderate flaws mainly in the initial assembly of comparable groups: either the randomization method was inadequately described or insufficient information was available about group baseline characteristics. The 4 poor trials had multiple problems, but 3 failed to define interventions clearly enough. Specifically, the number of intended cycles of chemotherapy was unspecified in these articles.

Overview of Outcomes

Overall Survival. Eight of nine trials reported data on overall survival, but only the study by O'Brien, Ciuleanu, Tsekov, et al. (2005) found a statistically significant difference between groups, in this case favoring oral topotecan over best supportive care.

Time to Progression. Neither of the two studies reporting on time to progression (von Pawel, Gatzemeier, Pujol, et al., 2001; von Pawel, Schiller, Shepherd, et al., 1999) found statistically significant differences between groups.

Quality of Life. The two studies by von Pawel et al. both reported data from a symptom scale that includes 9 domains. Only the earlier study, comparing intravenous topotecan and CAV, mentioned statistically significant differences between treatment groups.

Adverse Events. Specific risks of adverse events varied as expected given that these studies used a variety of treatments. Higher risks of grade 3 and 4 toxicity may be acceptable if a treatment yields a substantial survival advantage. O'Brien, Ciuleanu, Tsekov, et al. (2005) found significantly greater survival for oral topotecan over best supportive care, while toxicities were low. The 2001 trial by von Pawel, Gatzemeier, Pujol, et al. found no difference in survival between oral and intravenous topotecan, but the intravenous route was associated with higher rates of leukopenia and neutropenia. The 1999 study by von Pawel, Schiller, Shepherd, et al. reported no survival difference between intravenous topotecan and CAV, but the topotecan group had higher risks of anemia and thrombocytopenia. Trillet-Lenoir, Lasset, Arpin, et al. (1992) observed similar survival for low and high dose PE, but the high dose group experienced more leukopenia. The small study conducted by Wolf did not find significant differences in survival for 3 doses of etoposide, but there was a trend toward better survival with higher dose, as well as more thrombocytopenia and neutropenia.

Tumor Response. Excluding the O'Brien, Ciuleanu, Tsekov, et al. (2005) and Spiro, Souhami, Geddes, et al. (1989) studies that did not actively treat the control group, none of the other 7 studies found significant differences in tumor response or duration between treatment groups.

O'Brien, Ciuleanu, Tsekov, et al. (2005). Oral Topotecan (po T) vs. Best Supportive Care (BSC).

Study Quality. Since there is insufficient information about this study's methods, study quality could not be rated.

Overall Survival. This study, available only as a conference abstract, randomized 71 patients to oral topotecan and 70 patients to best supportive care. There was a 36 percent reduction in the risk of death for those receiving topotecan (hazard ratio=0.64, 95 percent CI: 0.45–0.90, p=0.0104). Median survival was longer for the topotecan patients (26 weeks vs. 14 wks) and 6-month survival was increased (49 percent vs. 26 percent).

Time to Progression. No data.

Quality of Life. This study administered the EQ-5D health-related quality of life questionnaire and found a significantly faster rate of deterioration in the BSC group.

Adverse Events. No significant differences were found in the incidence of these adverse events: vomiting, diarrhea, fatigue, pain and dyspnea. No hematologic toxicity was noted in the abstract for the BSC group, but in the topotecan group 7 percent had grade 3 or 4 anemia, 7 percent had grade 4 thrombocytopenia and 33 percent had grade 4 neutropenia. In the topotecan group, the risk of febrile neutropenia was 3 percent, while 1 percent had neutropenic infections and 4 percent developed sepsis.

Tumor Response. The abstract noted that the response rate for topotecan was 7 percent, but it was unclear what proportions had complete or partial responses. A further 44 percent experienced a stable disease after topotecan.

Summary. Compared with best supportive care, oral topotecan significantly improves survival in patients with relapsed SCLC. The decline in quality of life is faster in patients receiving best supportive care. Neutropenia is the most common major adverse event. Careful assessment of the methodologic quality of this study awaits full publication beyond a conference abstract.

Sculier, Lafitte, Lecomte, et al. (2002). Cisplatin/Etoposide (PE) vs. Carboplatin/Cisplatin/Etoposide (CbPE).

Study Quality. This study was rated as fair, its main shortcoming concerned its lack of detail about the randomization method and lack of blinded interpretation of tumor response, which was the primary outcome.

Overall Survival. This trial reported on 31 patients who received cisplatin and etoposide and 34 patients who received that regimen plus carboplatin. These investigators found a median survival advantage of 14.1 weeks for the CbPE group relative to the PE group, although the difference was not statistically significant (p=0.11).

Time to Progression. No data.

Quality of Life. No data.

Adverse Events. Although nearly twice as CbPE patients as PE patients had grade 3 or 4 alopecia (39 percent vs. 20 percent), the difference was not statistically significant. The authors reported that 19 percent of patients receiving PE experienced grade 3 or 4 thrombocytopenia, compared with 12 percent receiving CbPE, a nonsignificant difference. Grade 3 or 4 leukopenia occurred in 60 percent given PE and 56 percent given CbPE (p=0.97). The same percentage of patients (3 percent) in both groups developed infections.

Tumor Response. Thie trial found an ORR of 47 percent for CbPE and an ORR of 29 percent for PE. Median response duration was 33.9 weeks for CbPE and 22.6 weeks for PE. No statistical test results for these outcomes were provided.

Summary. The data from this trial suggested slightly improved survival and tumor response in adding carboplatin to the combination of cisplatin and etoposide. This small underpowered study did not find significant differences between groups on any outcome. It is important to remember that this trial enrolled only patients who did not have previous therapy with platinum and etoposide.

von Pawel, Gatzemeier, Pujol, et al. (2001). Oral Topotecan (po T) vs. Intravenous Topotecan (iv T).

Study Quality. This trial was rated as fair; the principal problem was lack of detail about the randomization method.

Overall Survival. These authors randomized 52 patients to oral topotecan and 54 patients to intravenous topotecan. They reported that median survival using oral topotecan was 32.3 weeks, compared with 25.1 weeks for intravenous topotecan. The difference was not statistically significant.

Time to Progression. These authors found that median time to disease progression was similar in the oral (14.9 weeks) and intravenous (13.1 weeks) topotecan groups. The difference was not statistically significant.

Quality of Life. This article stated that both oral and intravenous topotecan were associated with symptom improvement, but specific results of statistical tests were not given.

Adverse Events. Significant differences were not observed between groups on the following grade 3 and grade 4 outcomes: alopecia, vomiting, dyspnea, pulmonary embolism, pneumonia, anemia, thrombocytopenia and fever. Grade 3 diarrhea was significantly more common in the group receiving oral topotecan (7.7 percent vs. 0 percent). Grade 3 leukopenia was significantly more frequent in the intravenous group (45.3 percent vs. 27.5 percent). Grade 4 neutropenia occurred significantly more often among intravenous topotecan patients (67.3 percent vs. 35.3 percent).

Tumor Response. The ORR for oral topotecan was 23.1 percent and the proportion for intravenous topotecan was 14.8 percent. The difference was not statistically significant.

Summary. This study observed no significant difference in survival between those give oral or intravenous topotecan. The difference in overall response was not significant, but favored the oral route. Some hematologic toxicities were more common for intravenous, but most other adverse events occurred at similar rates.

von Pawel, Schiller, Shepherd, et al. (1999). Intravenous Topotecan (iv T) vs. Cyclophosphamide/Doxorubin/Vincristine (CAV).

Study Quality. This study was rated as fair. While the randomization method was sufficiently described and seemed adequate, age and gender distributions were not specified, co it could not be established if groups were comparable on these characteristics at baseline.

Overall Survival. The total assigned to intravenous topotecan was 107, while 104 received CAV. Median survival was nearly identical for intravenous topotecan (25 weeks) and CAV (24.7 weeks). The analysis that adjusted for covariates was not statistically significant.

Time to Progression. Median progression-free survival differed by only 1 week between the iv T and CAV groups in this trial.

Quality of Life. The percentage of patients improved on symptoms was greater for intravenous topotecan than CAV for all domains except hemoptysis, which showed a nonsignificant difference of 6.6 percent. Five domains significantly favored intravenous topotecan: dyspnea, anorexia, hoarseness, fatigue and impaired activities of daily living.

Adverse Events. Significant differences were not found between groups for these grade 3 or 4 outcomes: fatigue, nausea, vomiting and anorexia. The group receiving intravenous topotecan had a risk of grade 3 or 4 anemia that was twice that of the CAV group: 42.3 percent versus 19.8 percent ($p<0.001$). The rates of both grade 3 and grade 4 thrombocytopenia were significantly higher for the intravenous topotecan group, compared with the CAV group (grade 3: 28.8 percent vs. 9.9 percent; grade 4: 28.89 percent vs. 5 percent). Risks of grade 3 or 4 leukopenia were similar for intravenous topotecan (76.5 percent) and CAV (81.2 percent), as were grade 3 or 4 neutropenia (78.5 percent) and CAV (76.9 percent).

Tumor Response. Intravenous topotecan had an ORR of 24.3 percent, while CAV had an ORR of 18.3 percent, a difference that was not statistically significant.

Summary. Intravenous topotecan and CAV produced similar overall and progression-free survival. Five symptom domains showed significantly greater improvement in the intravenous topotecan group. Anemia and thrombocytopenia was more common among those receiving intravenous topotecan.

Postmus, Smit, Kirkpatrick, et al. (1993). Vincristine/Ifosfamide/Mesna/Carboplatin (VIMP) vs. Cyclophosphamide/Doxorubicin/Etoposide (CDE).

Study Quality. This study was rated as fair, due to missing information about the method of randomization.

Overall Survival. This study did not include the results of a statistical test on survival duration, but median survival differed between groups by only 3 weeks and given the small sample (n=68; 43 had VIMP and 25 had CDE), this is probably not statistically significant.

Time to Progression. No data.

Quality of Life. No data.

Adverse Events. In this study, there was a significantly higher incidence of grade 3 or 4 thrombocytopenia in the VIMP group (53 percent) compared with the CDE group (9 percent). Incidence of grade 3 or 4 leukopenia was similar for VIMP (66 percent) and CDE (63 percent).

Tumor Response. This study did not mention statistical test results. The ORR for the VIMP group was 60 percent and the figure for the CDE group was 51 percent.

Summary. The VIMP and CDE groups did not differ significantly on survival or tumor response. The only outcome that differed was the incidence of grade 3 or 4 thrombocytopenia, which was significantly more frequent in the VIMP group.

Trillet-Lenoir, Lasset, Arpin, et al. (1992). Cisplatin 20/Etoposide 60 (PE1) vs. Cisplatin 40/Etoposide 100 (PE2).

Study Quality. This study was rated as poor because the randomization method was not sufficiently described, no primary outcome was identified, interventions were incompletely described and it was unclear if outcome measurement was valid, reliable and equal.

Overall Survival. This study found that the high-dose PE2 group (n=15) had a longer median survival than the low-dose group (n=17) by 3.5 weeks. There was no mention of statistical test results on survival, but this trial was very small and the difference is unlikely to be statistically significant.

Time to Progression. No data.

Quality of Life. No data.

Adverse Events. This study showed that high-dose PE was associated with a significantly higher risk of grade 3 or 4 thrombocytopenia than low-dose PE (42 percent vs. 7 percent). Grade 4 leukopenia was much more frequent (76 percent vs. 13 percent) in the high-dose PE group.

Tumor Response. The high-dose PE group had an ORR of 26.6 percent while the low-dose group achieved an ORR of 35.3 percent. No statistical test findings were noted by the authors, but the small sample size of 32 patients would require a large difference to achieve statistical significance.

Summary. Survival and tumor response were roughly similar in the low-dose and high-dose PE groups, while there were higher rates of thrombocytopenia and leukopenia in the high-dose group.

O'Bryan, Crowley, Kim, et al. (1990).
Vincristine/Thiotepa/Cyclophosphamide/Carmustine (BTOC) vs. Cisplatin/Etoposide (PE).

Study Quality. This study's quality was rated as poor owing to lack of information about the randomization technique, lack of blinding for the primary outcome (tumor response), and lack of details about treatment.

Overall Survival. There were 45 patients in the BTOC group and 58 in the PE group. The authors presented 3 sets of results: all patients; good prognosis patients; and poor prognosis patients. None of the analyses demonstrated a statistically significant difference between BTOC and PE. Median survival nonsignificantly favored PE among all patients and good prognosis patients. The difference was large for good prognosis patients (25 weeks), but only 27 patients were in this subset. The relation between treatments was reversed for bad prognosis patients: median survival was better by 2 weeks for BTOC over PE.

Time to Progression. No data.

Quality of Life. No data.

Adverse Events. The trial reported that 4 percent of patients in the BTOC group experienced drug-related death, compared with 1 percent for PE, a difference that was not statistically significant.

Tumor Response. The trial found no statistically significant difference between the ORR for BTOC (13 percent) and PE (12 percent). Identical ORRs were obtained for treatment groups with both good and poor prognoses.

Summary. This trial found no significant differences between BTOC and PE in survival, tumor response or drug-related death.

Spiro, Souhami, Geddes, et al. (1989). Methotrexate/Doxorubicin vs. Supportive Care

Study Quality. Quality was rated as poor due to lack of details about the randomization technique and a high loss of patients in the second stage of the study (42 percent).

Overall Survival. This outcome was not reported on the basis of the second randomization (to second-line chemotherapy or supportive care), rather it was based on the first randomization to either 4 or 8 cycles of primary chemotherapy. Therefore, it is unclear how patients given chemotherapy or supportive care upon relapse compare in terms of survival.

Time to Progression. As above, this outcome was not presented based on treatment approach given at relapse.

Quality of Life. This outcome was not reported.

Adverse Events. Toxicity data were not provided for second-line chemotherapy.

Tumor Response. Of the 294 patients randomized to receive chemotherapy at relapse, 170 received it and were assessed for response. Complete response was achieved in 4 percent and partial response was observed in 19 percent.

Summary. Results were presented from this study mainly based on randomization for first-line chemotherapy. An overall response rate of 23 percent to second-line chemotherapy was observed, but other data are lacking on outcomes after randomization at relapse, comparing chemotherapy and supportive care.

Wolff, Birch, Sarma, et al. (1986). Etoposide 100 (E100) vs. Etoposide 200 (E200) vs. Etoposide 300 (E300).

Study Quality. The Wolff, Birch, Sarma, et al. (1986) trial received a poor quality rating due to uncertainty on the comparability of groups at baseline, lack of blinded assessment of tumor response, the primary outcome, lack of detail about treatments and inappropriate analysis of results.

Overall Survival. There were 26, 27 and 26 patients in the groups receiving 100 mg, 200 mg and 300 mg of etoposide, respectively. No statistically significant differences were found between etoposide dose groups. The 200 mg and 300 mg groups were similar in median survival (20 weeks and 22.5 weeks, respectively), while the median for 100 mg group was 12.6 weeks.

Time to Progression. No data.

Quality of Life. No data.

Adverse Events. There was a significant dose gradient for higher grade thrombocytopenia in 3 groups given single agent etoposide therapy: 5 percent for 100 mg; 79 percent for 200 mg; and 86 percent for 300 mg. The trial found that grade 3 or 4 neutropenia was much more likely in the etoposide 300 mg group (57 percent), compared with those receiving 100 mg (15 percent) or 200 mg (13 percent).

Tumor Response. Only PRs were achieved in each of the 3 etoposide groups: 4 percent for 100 mg; 7 percent for 200 mg; and 4 percent for 300 mg.

Summary. Significant differences in survival and tumor response were not observed between 3 different doses of single-agent etoposide. Thrombocytopenia and leukopenia were more common for higher dose etoposide

Phase II Trial Evidence

Among multicenter phase II trials published since 2000 (Summary Table 52; see Appendix Tables 9H–9M),[20] 5 deserve brief mention due to encouraging response data. While overall response rates of 20 percent or higher were reported by these trials, high rates of hematologic

[20] Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf.

toxicity were observed. Each used a different treatment regimen. The largest study was Ardizzoni, Manegold, Debruyne, et al. (2003, n=116); all others enrolled fewer than 50 patients.

Ando, Kobayashi, Yoshimura, et al. (2004) reported data for 25 patients who were given irinotecan plus cisplatin for refractory or relapsed SCLC after first-line etoposide therapy. Partial responses were observed in 81 percent of 16 relapsed patients and 78 percent of 9 refractory patients. Grade 3 thrombocytopenia was seen in 12 percent and 24 percent had grade 3 or 4 neutropenia.

Summary Table 52. Multicenter Phase II Trials of Note for Key Question 9

Study	Patient Selection	N	Regimen	Previous Treatment (%)
Ando, Kobayashi, Yoshimura, et al., 2004	refractory (off CTx < 2 mo) or relapsed (off CTx > 2 mo) after initial etoposide regimen	25	irinotecan+cisplatin	PE 16 CbP 84 TRTx 20 Surgery 4
Ardizzoni, Manegold, Debruyne, et al., 2003	relapsed after 1st-line CTX (except camptothecin analogues; cisplatin allowable if responsive, CTx ≥ 6 mo before	116	topotecan+cisplatin	Sen Ref TRTx 69 31 med # CTX 3 3 Cisplatin 22 5 Carbopl 24 36 Etopos 90 83
Kosmas, Tsavaris , Malamos, et al. et al. ,2001	relapsed after CbE CTx ± TRTx; not curable by other 2nd-line CTx or RTx	33	paclitaxel+ifosfamide+cisplatin	CTx 100 TRTx 42
Kakolyris, Mavroudis, Tsavaris, et al., 2001	refractory; had failed 1 prior 1st-line CTx	32	paclitaxel+carboplatin	EP 84 CAB 16 RTx 47 Surgery 6
Sonpavde, Ansari, Walker, et al., 2000	recurrent; 1 prior combination CTx regimen	46	doxorubicin+paclitaxel	Platinum-E ± VIP 100 RTx 59

Ardizzoni, Manegold, Debruyne, et al. (2003) collected outcomes for 110 patients who received topotecan plus cisplatin for either sensitive (n=68) or refractory (n=42) SCLC. Among sensitive patients, a CR was seen in 1.5 percent and PR in 27.9 percent. The incidence of grade 3 or 4 leukopenia was 80.9 percent and neutropenia occurred in 76.5 percent. At least 1 episode of febrile neutropenia happened in 19 percent. There was a PR rate of 23.8 percent in refractory patients. Grade 3 or 4 leukopenia was observed in 75.6 percent and the risk of neutropenia was the same. At least 1 instance of febrile neutropenia occurred in 15 percent.

Kosmas, Tsavaris, Malamos, et al. (2001) enrolled 33 patients who relapsed after initial treatment with carboplatin plus etoposide. Second-line therapy was paclitaxel, ifosfamide and cisplatin. The CR rate was 24.2 percent and the PR rate was 48.5 percent. Grade 3 anemia was seen in 18 percent. Grade 3 thrombocytopenia affected 36 percent. Grade 3 or 4 leukopenia occurred in 73 percent, the rate of neutropenia was 91 percent. Grade 3 febrile neutropenia was found in 18 percent.

Kakolyris, Mavroudis, Tsavaris, et al. (2001) gave data for 29 patients who were refractory after first-line chemotherapy and then were offered paclitaxel plus carboplatin. CR was achieved in 3 percent and PR in 22 percent. Grade 3 or 4 neutropenia was observed in 48 percent.

Sonpavde, Ansari, Walker, et al. (2000) recruited 46 patients who recurred after first-line therapy and were given doxorubicin plus carboplatin. CRs were measured in 7 percent and PRs in 35 percent. Grade 3 or 4 granulocytopenia occurred in 80 percent.

Conclusions

Nine randomized trials have made 9 different comparisons for second- or subsequent-line treatment of SCLC. Two randomized trials have directly compared chemotherapy with best supportive care for recurrent SCLC. The first studied second-line methotrexate plus doxorubicin and found an overall response rate of 23 percent for the chemotherapy arm. The second reported that oral topotecan resulted in a modest but significant improvement in survival, slower decline in quality of life and high grade neutropenia in one third. In another trial, oral topotecan had nonsignificantly higher median survival and overall response rate than intravenous topotecan, which had higher risks of leukopenia and neutropenia. A study that addressed the addition of carboplatin to cisplatin and etoposide is of limited use given that it in enrolled only those who did not receive first-line cisplatin and etoposide, which is the current standard regimen. One small study comparing 3 doses of monotherapy etoposide did not find significant survival differences, but a trend favored the highest dose, along with increased thrombocytopenia and neutropenia. Other studies found higher rates of adverse events for one treatment over another, but no associated survival advantage that would offset increased high grade toxicity. One example is a comparison of oral and intravenous topotecan which reported that the intravenous route was associated with higher rates of leukopenia and neutropenia. A study comparing intravenous topotecan and CAV showed that the topotecan group had higher risks of anemia and thrombocytopenia. High dose PE had more leukopenia than low dose PE.

Five multicenter phase II trials of note published since 2000 have reported overall response rates of 20 percent or more. Only one study, using topotecan plus cisplatin, enrolled more than 50 patients. Approximately one-fourth of both sensitive and refractory patients responded. Three-quarters or more of both patient groups had high grade leukopenia and neutropenia. A small study of irinotecan plus cisplatin found very high rates of partial response and low hematologic toxicity. The combination of paclitaxel, ifosfamide and cisplatin achieved a high ORR and high grade leukopenia in nearly all patients. One quarter of those given paclitaxel plus carboplatin had a response and about half had high grade neutropenia. In a study of doxorubicin plus carboplatin, nearly half responded, but 4 out of 5 had grade 3 or 4 granulocytopenia. Whether these regimens should be used in practice awaits randomized trials.

Chapter 4. Conclusions

1. For limited-stage SCLC, what are the relative benefits and harms of TRTx combined with chemotherapy either in alternating fashion, concurrently, or sequentially?

One multicenter trial and one single-center trial (n=307) compared concurrent and sequential TRTx. Results are not conclusive but suggest better outcomes for concurrent TRTx. Overall survival adjusted for confounders significantly favored concurrent TRTx in the Takada, Fukuoka, Kawahara, et al. trial (2002; n=228), although unadjusted results were not significant. Additionally, the Park, Kim, Jeong, et al. (1996) trial found significantly longer response duration for concurrent TRTx. Of 11 types of adverse events reported, only leukopenia occurred significantly more frequently in the concurrent TRTx group in both studies.

No conclusions could be drawn on the relative benefits and harms of TRTx combined with chemotherapy in alternating fashion. No significant differences in survival or progression-free survival were found in any of four trials. Two trials (n=458) compared alternating to sequential TRTx; one trial (n=156) compared alternating to concurrent TRTx; and one trial (n=199) compared early alternating and late alternating TRTx.

2. For limited-stage SCLC, do outcomes differ if concurrent TRTx is given in early versus late chemotherapy cycles?

Overall, the evidence is equivocal, either finding no difference or a small advantage for early TRTx. One multi-center trial of good quality significantly favored concurrent therapy given in an early cycle (Murray, Coy, Pater, et al., 1993/Coy, Hodson, Murray, et al., 1994/Feld, Payne, Hodson, et al., 1988), as did 2 smaller trials. Of the two larger multi-center trials that that found no significant difference in survival, one did not use platinum chemotherapy (Perry, Eaton, Propert, et al., 1987/Ahles, Silberfarb, Rundle, et al., 1994/Perry, Herndon, Eaton, et al., 1988) and the other has not been published in full-text (James, Spiro, O'Donnell, et al., 2003).

Leukopenia/neutropenia appeared to be more common with early concurrent TRTx, although differences were statistically significant in only two of six reporting trials. Other events do not appear to be more frequent with either early or late TRTx. However, evidence is limited as adverse events were not reported consistently across all trials

Meta-analysis was performed on survival outcome of early versus late TRTx in an attempt to obtain clearer results. For purposes of the meta-analysis, the studies selected for Key Questions 1 and 2 were viewed as comparing early and late TRTx. Therefore, these studies were pooled to give a more robust analysis of early versus late TRTx. Overall, we did not find significant reductions in 2- and 3-year mortality for early TRTx over late TRTx. The RR at 2 years was 0.921 (95 percent CI: 0.844–1.005) and the RR at 3 years was 0.991 (0.955–1.029). Although the overall analysis was not significant, sensitivity analysis suggests that if there is an advantage

favoring early TRTx it would accompany use of hyperfractionation and possibly use of platinum chemotherapy.

3. For limited-stage SCLC, do outcomes (survival, toxicity, quality of life) of primary therapy differ if one varies dose rate, treatment interval, or fractionation scheme for delivering radiotherapy? Comparisons of interest include:

- **accelerated regimens (>10 Gy per week completed over a short interval) versus standard duration regimens (≤10 Gy per week) versus split courses delivered over the standard interval; and**

- **single daily fractions versus hyperfractionated (two or more daily fractions or concomitant boost).**

Evidence to compare dose rates, treatment intervals, or fractionation schemes is limited. Two RCTs compared one versus two fractions a day for previously untreated SCLC. One compared an accelerated regimen versus the standard duration, while the other compared a split-course regimen versus the standard duration.

Compared to a single daily fraction, two daily fractions delivered concurrently with platinum chemotherapy improved overall survival in a large multicenter trial of good quality (Turrisi, Kim, Blum, et al., 1999/Yuen, Zou, Turrisi, et al., 2000; N=417). More specifically, this trial showed that starting TRTx with the first cycle of cisplatin-etoposide chemotherapy and giving it in two daily fractions over 3 weeks increased overall survival (23 vs. 19 months, log rank p=0.04) when compared with the same dose begun at the same time but given in one daily fraction over 5 weeks.

Evidence from the second trial is difficult to interpret, since multiple variables were studied simultaneously (Schild, Bonner, Shanahan, et al., 2004/Sloan, Bonner, Hillman, et al., 2002/Bonner, Sloan, Shanahan, et al., 1999; N=161). However, it found no difference in overall survival between treatment arms managed with one versus two fractions per day.

Neither trial reported data on quality of life. Esophagitis was the only adverse event reported more frequently with two fractions per day than with one fraction per day in both trials.

4. What are the relative benefits and harms (survival, toxicity, and quality of life) of adding thoracic radiation therapy to chemotherapy for primary treatment of extensive-stage SCLC?

Evidence from one single-center RCT (Jeremic, Shibamoto, Nikolic, et al., 1999; 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 outside the thorax and at least a partial response in the thorax. Uncontrolled data from the same trial suggest little to no benefit for patients who achieve no better than a partial response outside the thorax. With the regimens used in this trial, concurrent TRTx apparently increases grades 3 and 4 esophagitis.

No other trials have reproduced the results reported by Jeremic, Shibamoto, Nikolic, et al. (1999). Four earlier trials (N=129) are limited by small sample sizes and non- platinum chemotherapy regimens; none used concurrent TRTx.

5. What are the benefits and harms (survival, toxicity and quality of life) of prophylactic cranial irradiation?

Evidence from an individual patient data Cochrane review and meta-analysis on seven RCTs (N=987) conducted by the PCI Overview Collaborative Group shows that PCI modestly improves survival of SCLC patients in CR after primary therapy. PCI increases the proportion alive at 3 years from 15.3 percent to 20.7 percent (P=0.01), an absolute increase of 5.4 percent. PCI also significantly decreases the risk for brain metastasis and increases the likelihood of disease-free survival. The sole trial reported after the meta-analysis confirms effects of PCI on brain metastasis, and generally agrees with the modest effect on overall survival.

Subgroup analyses using individual patient data showed that PCI significantly decreases brain metastases for SCLC patients in CR regardless of age, disease stage or performance status at diagnosis, and whether or not TRTx is part of the induction regimen. Although PCI does not have significant effect on survival for most of these subgroups, it does not appear that any of these subgroups benefits more or less than others.

Additional subgroup analyses suggested that increasing the PCI dose from 8 to 40 Gy and starting PCI within the first 6 months after achieving CR may decrease the likelihood of brain metastasis. Patient gender also may interact with effects of PCI on survival. However, these hypotheses, derived from subgroup analyses, require formal testing in RCTs.

Data on acute toxicities of PCI are scant, but those available suggest they are tolerable at the doses used in these trials (8–40 Gy in 1.8 to 3 Gy fractions). Evidence from two trials suggests neuropsychological and cognitive deficits and structural abnormalities on brain CT scans are relatively common among SCLC patients in CR after primary therapy but before PCI. Available evidence on patients who survived 1–2 years, while limited, did not show greater deterioration of existing deficits or more frequent appearance of new abnormalities with PCI than among controls.

6. Does the addition of PET scanning improve the accuracy of staging for patients with SCLC over the use of other techniques, including CT and MRI, without PET?

It is not possible from the limited and poor quality evidence that is available to determine whether the use of PET adds value relative to conventional staging tests for SCLC.

Six studies reporting on a total of 277 patients (range 20–120) provided data on the diagnostic accuracy of PET in SCLC. The evidence suggests that, except for detection of brain metastases, PET added to conventional staging is more sensitive in detecting disease than conventional staging alone. Upstaging was reported in 4–20 percent of patients and downstaging in 4–13 percent of patients. Three studies reported very high occurrence of patient management changes that were attributed to PET (29–58 percent).

However, the quality of these studies is consistently poor and insufficient detail in reporting was the norm. There is such a high degree of uncertainty about the execution and interpretation of the reference standard in all of these studies that confidence is quite low in estimates of diagnostic and staging accuracy. Although these studies report that PET has correctly upstaged or downstaged the extent of disease, the frequency of incorrect changes in stage attributable to PET is unknown due to incomplete reporting. It is not possible to determine the frequency with which management changes based on PET results were actually beneficial or harmful.

7. What are the outcomes (survival, toxicity and quality of life) of treatments used to manage patients with mixed small cell/non-small cell lung cancers?

No studies meet selection criteria for this question. Very few references from the literature search represented studies of any kind that included patients with mixed histology. No conclusions can be drawn on outcomes of treatment for patients with mixed small cell/non-small cell lung cancers.

8. What is the role of surgery and what is its impact on survival in patients with early stage SCLC? How do available studies define early stage SCLC?

For this question, we sought randomized and nonrandomized studies that compared surgery to no surgery in patients with very early limited SCLC, defined as no preoperative evidence of involved nodes (clinically N0). Two randomized controlled trials and 8 nonrandomized comparative studies were included in the review, but none provided evidence that directly addresses the question.

None of these comparisons studied a homogeneous group of patients with respect to nodal status; nor were separate outcomes reported for a subgroup of patients without evidence of nodal involvement by current staging methods. Moreover, the treatment regimens used had limited relevance to contemporary treatment settings; for example, 5 studies did not use platinum-based chemotherapy for any patients, and the remaining 3 used platinum based therapy only for some patients. Thus no conclusion can be drawn on the outcomes of management of very early limited SCLC with versus without surgery.

9. What are the outcomes of second- or subsequent-line therapy in patients with relapsed or progressive SCLC? Where available data permit, patients with limited- and extensive-stage disease will be addressed separately, as will those with refractory disease.

Nine RCTs address second- or subsequent-line treatment of SCLC, each of which compared different sets of chemotherapy regimens. Two randomized trials directly compared chemotherapy with best supportive care for recurrent SCLC. The first studied second-line methotrexate plus doxorubicin and found an overall response rate of 23 percent for the chemotherapy arm. The second reported that oral topotecan resulted in a statistically significant increase in survival (26 weeks vs. 14 weeks) and slower decline in quality of life. High grade neutropenia occurred in one third of patients. Another trial compared oral versus intravenous topotecan; leukopenia and neutropenia were more frequent with the intravenous route, but survival and response were no greater.

A study that addressed the addition of carboplatin to cisplatin and etoposide is of limited use given that it enrolled only those who did not receive first-line cisplatin and etoposide, which is the current standard regimen. One small study comparing 3 doses of monotherapy etoposide did not find significant survival differences, but a trend favored the highest dose, along with increased thrombocytopenia and neutropenia. Other studies found higher rates of adverse events for one treatment over another, but no associated survival advantage that would offset increased high grade toxicity. A study comparing intravenous topotecan and CAV chemotherapy showed that the topotecan group had higher risks of anemia and thrombocytopenia. High-dose platinum/etoposide had more leukopenia than low-dose platinum/etoposide.

Five multicenter phase II trials of note published since 2000 have reported overall response rates of 20% or more. Only one study, using topotecan plus cisplatin, enrolled more than 50 patients. Approximately one fourth of both sensitive and refractory patients responded. Three-quarters or more of both patient groups had high grade leukopenia and neutropenia. A small study of irinotecan plus cisplatin found very high rates of partial response and low hematologic toxicity. The combination of paclitaxel, ifosfamide and cisplatin achieved a high ORR and high grade leukopenia in nearly all patients. One-quarter of those given paclitaxel plus carboplatin had a response and about half had high grade neutropenia. In a study of doxorubicin plus carboplatin, nearly half of patients responded; however, 4 out of 5 had grade 3 or 4 granulocytopenia. The clinical applicability of these regimens awaits the results of randomized trials.

Chapter 5. Discussion and Future Research

The majority of evidence reviewed for this report addresses treatments added to primary chemotherapy for small cell lung cancer (SCLC). The main objective is to improve survival by increasing the rate and durability of complete response (CR) resulting from primary treatment; and, for those who do not achieve CR, to delay progression. Questions focus on whether outcomes can be optimized by manipulating variables of adjunctive treatments and their combination.

The strongest evidence available for this report shows that prophylactic cranial irradiation (PCI) improves survival of SCLC patients who achieved CR following primary therapy. Although the benefit is modest, an absolute increase of 5.4 percent in 3-year survival, the evidence is robust and convincing. For this knowledge, clinicians and their patients are the beneficiaries of the PCI Overview Cochrane Collaborative Group, which conducted an individual patient-level meta-analysis, a laborious undertaking. Thus seven discrete randomized, controlled trials were transformed into a rich source of data on almost one-thousand patients, adequate to support clinically relevant subgroup analyses. The results are encouraging in that it appears that all subgroups of eligible patients can potentially benefit from PCI, regardless of age, disease stage, performance status at diagnosis, and whether or not thoracic radiotherapy (TRTx) is part of the induction regimen. Two trials comparing alternative doses and schedules for PCI are in progress, one in the U.S. (RTOG-0212) and one in Europe (FRE-IGR-PCI-99). Targeted accrual for the two trials together is over 900 patients. These trials will provide additional data on neurotoxicity and quality of life.

Patient level meta-analysis was not available for any other key question considered in this evidence report. No other question yielded a body of evidence so robust. Where we attempted to draw conclusions, we typically relied on a single trial showing treatment effects that were modest at best, and sometimes equivocal. This was apparent in our review of evidence for the sequence, timing, dosing and fractionation of TRTx. For some questions (i.e., management of mixed-histology disease; surgery for early limited SCLC) comparative trials were nonexistent.

Perhaps the most vexing questions are those regarding the delivery of TRTx. Strategies for sequencing, timing, dosing, and fractionation are not well supported by a strong evidence base; each rests largely on a single study that shows significant findings. The case for concurrent over sequential delivery rests largely on a single multi-center trial (Takada 2002) supplemented by a smaller study judged to be of poor quality (Park 1996). We found the results to be suggestive, but not conclusive, of better outcomes for concurrent over sequential TRTx. No studies show an advantage for alternating TRTx, but none show it to be inferior. Support for early concurrent therapy comes largely from the results of the multicenter trial by Murray-Coy-Feld (Murray, Coy, Pater, et al., 1993/Coy, Hodson, Murray, et al., 1994/Feld, Payne, Hodson, et al., 1988); but two other multicenter trials, one using non-platinum chemotherapy (Perry, Eaton, Propert, et al., 1987/Ahles, Silberfarb, Rundle, et al., 1994/Perry, Herndon, Eaton, et al., 1988) and the other not yet published in full text (James, Spiro, O'Donnell, et al., 2003), found no advantage. We conducted a meta-analysis of 11 studies, which did not find significant reductions in 2- and 3-year mortality for early TRTx over late TRTx.

Compared to a single daily fraction, two fractions per day of accelerated TRTx delivered concurrently with platinum chemotherapy improved overall survival in a large multicenter trial of good quality (Turrisi, Kim, Blum, et al., 1999/Yuen, Zou, Turrisi, et al., 2000). In contrast to

a subsequent study comparing single to twice-daily fractionation (Schild, Bonner, Shanahan, et al., 2004/Sloan, Bonner, Hillman, et al., 2002/Bonner, Sloan, Shanahan, et al., 1999), which is difficult to interpret because multiple variables were studied simultaneously, the Turrisi study compared only the variable of fractionation. An approach to comparing early- versus late-concurrent TRTx, would be to reproduce this twice daily fractionation regimen varying only the element of timing. In concept, late-concurrent TRTx could be advantageous if better tolerated, thus permitting more patients to complete their full course and intensity of chemotherapy. In contrast, our meta-analytic sensitivity analysis suggests that an advantage for early TRTx depends on use of hyperfractionation, a finding that is hypothesis-generating only.

With respect to treatment for extensive-stage disease, results reported by Jeremic, Shibamoto, Nikolic et al. (1999) on the addition of TRTx to chemotherapy need replication in a multicenter setting. This applies both to the evidence suggesting benefit from TRTx for those with complete disappearance of extrathoracic lesions after three cycles of platinum/etoposide, and to the uncontrolled evidence suggesting little or no benefit if extra-thoracic lesions only partially respond.

Use of positron emission tomography (PET) as an adjunct to conventional tests is relevant to initial staging and restaging after treatment. Because PET may be more sensitive in detecting disease outside the brain than conventional staging modalities, and has been suggested to correctly upstage or downstage disease, it should be investigated in better quality studies to confirm these results and determine if it improves clinical management of SCLC. Currently available studies are limited primarily by inadequate quality, especially failure to define an adequate reference standard. An informative design would compare the frequency of correct upstaging, correct downstaging, incorrect overstaging and incorrect understaging for PET plus conventional staging tests in relation to conventional staging tests alone. The use of PET/CT is becoming more common and should be addressed in future studies. Future studies should be conducted according to standards described by the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) and reported according to the Standards for Reporting of Diagnostic Accuracy (STARD) statement.

Authors of a systematic review will rarely be proven wrong in calling for more rigorous evidence from well-conducted, randomized, controlled trials. However, it is also fair to acknowledge that some diseases and treatments pose greater difficulties in conducting trials to evaluate the effectiveness of interventions. A central challenge in evaluating treatments for SCLC is that overall disease outcome is poor and, at this time, the potential for an intervention to change the course of disease is limited. Because treatment effect sizes are small, large numbers of patients are needed in trials to test effectiveness. Complicating this is the multimodal nature of interventions and, as exemplified by TRTx, the multiplicity of variables that might contribute to the effectiveness of a single component of a multimodal intervention. And for some populations of interest (i.e., mixed histology disease; early limited disease), the number of affected individuals is small, making prospective study difficult.

The very circumstances that comprise the challenges to research in SCLC highlight the necessity of setting a systematic and rigorous research agenda to accumulate findings that can improve clinical care and outcomes. To this end, we make the following recommendations for future research.

- In assessing strategies for the delivery of multimodality interventions, such as TRTx, design trials to clearly test a single variable (e.g., early concurrent vs. late concurrent). Multi-arm trials could permit testing of more than one variable simultaneously. Given

the potential complexity of variables and combinations, there should be a consensus on the priority of strategies and elements to be tested.

- Trials that are poorly designed, conducted, or reported waste limited resources. To advance clinical knowledge and practice, the field should adhere to standards of research quality, as well as setting an agenda for research priorities.

- Quality of life assessment should be an integral to clinical trials. Given modest gains in survival, it is important to assess the quality of the survival. Quality of life research poses intrinsic difficulties, including missing data as disease progresses. Studies should adhere to recommended methods for quality of life research and handling of missing data.

- Future trials should use consensus definitions for patient enrollment criteria, subgroup characteristics and trial endpoints. Adverse events data should be consistently reported and collected. The use of consistent definitions and end-points can produce a more robust body of cumulative evidence improving the ability to compare results among trials and increasing the potential for combined analyses.

Finally, clinicians and investigators would be well-served by improved indexing and search terms so that electronic literature databases would better distinguish records on SCLC from those on non-small cell lung cancer.

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List of Acronyms/Abbreviations

-	without
#	number
#	number
∆	change
?	unknown, unclear
+	with
<p	less than a partial resection
1°	primary
18-FDG	18-fluorodeoxyglucose
95% CIL	lower limit 95% confidence interval
95% CIU	upper limit 95% confidence interval
A	Asian
A	doxorubicin (Adriamycin®)
abstr	abstract
ACCP	American College of Chest Physicians
AHRQ	Agency for Healthcare Research and Quality
ALT	alanine transaminase
Alt	alternating
AP	anterioposterior
ASCO	American Society of Clinical Oncology
AST	aspartate transaminases
ASTRO	American Society for Therapeutic Radiology and Oncology
B	bilobectomy
B	Black
BSC	best supportive care
c	complete
C	cyclophosphamide
CALGB	Cancer and Leukemia Group B
Cb	carboplatin
CCNU	lomustine
CD	cyclophosphamide- and/or doxorubicin-based chemotherapy
chemoTx	chemotherapy
CI	confidence interval
CNS	central nervous system
Conc	concurrent
cont'd	continued
contr	contralateral
Conv	conventional
CPHM	Cox proportional hazard model
CR	complete response
CT	computed tomography
Ctrl	control
CTx	chemotherapy
d	day
DA	diagnostic accuracy
dist	distant
Dx	diagnosis
E Alt	early alternating
E	etoposide
E	etoposide
ea	each
ECOG	Eastern Cooperative Oncology Group
endosc	endoscopic
EORTC LCCG	European Organization for the Research and

	Treatment of Cancer Lung Cancer Cooperative Group
EPC	Evidence-based Practice Center
EQ-5D	EuroQOL 5-dimension health-related quality of life instrument
ES	extensive stage
ESD	extensive-stage disease
F	female
F	fractions
F/d	fractions per day
F/U	follow-up
FDA	Food and Drug Administration
FE	fixed effects
FEV1	forced expiratory volume in 1 second
FN	false negative
FNA	fine-needle aspiration
FP	false positive
Frac(s)	fraction(s)
FWHM	full width, half maximum
GQ	good quality
Gy	Gray
H	Hispanic
HL	hilar
HR	hazard ratio
hr	hour
Hyper	hyperfractionated
ips	ipsilateral
IV	intravenous
K-M	Kaplan-Meier
KPS	Karnofsky Performance Status
L Alt	late alternating
L	lobectomy
L	lomustine
L95	upper limit 95% confidence interval
LCSG	Lung Cancer Study Group
LDH	lactic dehydrogenase
LINAC	linear accelerator
LN	lymph node
LRFS	local recurrence-free survival
LRFS	local recurrence-free survival
LS	limited stage
LSD	limited-stage disease
M	male
M	methotrexate
MBq	megabecquerel
mCi	milliCurie
md	median
MD	mediastinal
mets	metastases
MeV	megaelectron volt
mg	milligram
M-H	Mantel-Haenszel
MI	myocardial infarction
mn	mean
mo(s).	month(s)
MR	meta regression
MRI	magnetic resonance imaging
MS	mediastinal
N	no
n	number
N	pooled number
NCI	National Cancer Institute

NE	not evaluable
NED	no evidence of disease
neg	negative
NNEC	non-neuroendocrine carcinoma
NNT	number needed to treat
nonrandom.	nonrandomized
NOS	not otherwise specified
NR	not reported
NS	nonsignificant
NSCLC	non-small-cell lung cancer
O	other
OR	odds ratio
ORR	overall response rate
OS	overall survival
P	cisplatin
p	partial
P	pneumonectomy
PA	posterioanterior
PCI	prophylactic cranial radiation
PD	progressive disease
PE	platinum/etoposide chemotherapy
PET	positron emission tomography
PFS	progression-free survival
PI	primary investigator
po	oral
P-OR	Peto odds ratio
pos	positive
PR	partial response
PS	performance status
Pt	platinum
pub	publication
PWIFR	percent/proportion with in-field recurrence
Q	heterogeneity statistic
QoL	quality of life
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
R/I	ruled in
R/O	ruled out
radiol	radiologic
RadioTx	radiotherapy
RCT	randomized, controlled trial
RD	risk difference
RE	random effects
reg	regimen
regl	regional
retrospect	retrospective
RFS	recurrence-free survival
rng	range
RNS	radionuclide scan
ROC	receiver operating characteristic
RR	relative risk
RR	risk ratio
SC	supraclavicular
SC/LC	small-cell/large-cell subtype
SCLC	small cell lung cancer
SD	stable disease
SE	standard error
Sens	sensitivity
Seq	sequential
Spec	specificity
STARD	Standards for Reporting of Diagnostic Accuracy
sup-clav	supraclavicular
supraclav	supraclavicular

surg	surgery
SWOG	Southwest Oncology Group
T	thoracotomy only (open and close)
TN	true negative
TNM	Tumor, Node, Metastasis (staging system)
TP	true positive
TRTx	thoracic radiotherapy
TTF	time to failure
Tx	treatment; therapy
U.S.	United States
U95	upper limit 95% confidence interval
ULN	upper limit of normal
US	ultrasound
V	vincristine
VC	vital capacity
Ve	vindesine
W	White
WBC	white blood cell
WHO	World Health Organization
wk(s)	week(s)
Wt	weight
XRT	radiotherapy
Y	yes
yr	year

Abbreviations of Combination Chemotherapy Regimens

ACO	doxorubicin, cyclophosphamide, and vincristine
ACOM	doxorubicin, lomustine, methotrexate, vincristine
BTOC	vincristine, thiotepa, cyclophosphamide, carmustine
CAE	cyclophosphamide, doxorubicin, etoposide
CAV	cyclophosphamide, doxorubicin, vincristine
CbE	carboplatin, etoposide
CbPE	carboplatin, cisplatin, etoposide
CC	cyclophosphamide, lomustine
CCM	cyclophosphamide, lomustine, methotrexate
CCMV	cyclophosphamide, lomustine, methotrexate, vincristine
CDE	cyclophosphamide, doxorubicin, etoposide
CE-CAP	cyclophosphamide, doxorubicin, cisplatin
COME	cyclophosphamide, vincristine, methotrexate, etoposide
COMF	cyclophosphamide, vincristine, methotrexate, fluorouracil
CVMP	cyclophosphamide, vincristine, methotrexate, cisplatin
EP	etoposide, platinum compound
LCAE	lomustine, cyclophosphamide, doxorubicin, etoposide
M-CAV	methotrexate, cyclophosphamide, doxorubicin, vincristine
MCCC/VI	methotrexate, cyclophosphamide, lomustine, ifosfamide, etoposide
PE	cisplatin, etoposide
PEVe	platinum, epirubicin, etoposide
PMP	cisplatin, methotrexate, procarbazine
VCMV	vincristine, cyclophosphamide, mitomycin, chromomycin
VIC-E/VICE	vincristine, ifosfamide, carboplatin, etoposide
VIMP	vincristine, ifosfamide, mesna, carboplatin
VIP-E	etoposide, ifosfamide, cisplatin, and epirubicin

Appendix A. Exact Search Strings

MEDLINE search (performed through 12/21/04)

EMBASE search (performed through 03/04/05)

Cochrane Controlled Clinical Trials Register (performed through 03/11/05)

Database Search Strategies: Key Questions 1–5, 7–9

- (lung neoplasms [mh] AND ("small cell" [tw] OR "small-cell" [tw])) OR
- carcinoma, small cell [mh] OR
- (("small cell" [tw] OR "small-cell" [tw]) AND (lung [tw] OR pulmonary [tw] OR bronchial [tw] OR bronchogenic [tw]))

Results of this search will be limited to citations also identified by the Cochrane Handbook search strategy for controlled trials (Alderson et al. 2004):

- randomized controlled trial [pt] OR
- controlled clinical trial [pt] OR
- randomized controlled trials [mh] OR
- random allocation [mh] OR
- double-blind method [mh] OR
- single-blind method [mh] OR
- clinical trial [pt] OR
- clinical trials [mh] OR
- "clinical trial" [tw] OR
- ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR
- placebos [mh] OR
- placebo* [tw] OR
- random* [tw] OR
- research design [mh:noexp] OR
- comparative study [mh] OR
- evaluation studies [mh] OR
- follow-up studies [mh] OR
- prospective studies [mh] OR
- control* [tw] OR
- prospectiv* [tw] OR
- volunteer* [tw])

For Key Question 6 (PET Imaging), the following search terms were used:

(carcinoma, small cell [mh] OR (("small cell" [tw] OR "small-cell" [tw]) AND (lung [tw] OR pulmonary [tw] OR bronchial [tw] OR bronchogenic [tw]))) AND (positron* [tw] OR pet [tw] OR "PET-CT" OR "PET/CT" OR FDG*)

Appendix B. Sample Data Abstraction Forms

Question #
Table A: Sample Selection

Study	Inclusion	Exclusion	n, Randomized			n, Withdrawn			n, Evaluated for Primary Outcome		
			Total	Grp1	Grp2	Total	Grp1	Grp2	Total	Grp1	Grp2
			Total	Grp1	Grp2	Total	Grp1	Grp2	Total	Grp1	Grp2
			Total	Grp1	Grp2	Total	Grp1	Grp2	Total	Grp1	Grp2
			Total	Grp1	Grp2	Total	Grp1	Grp2	Total	Grp1	Grp2
			Total	Grp1	Grp2	Total	Grp1	Grp2	Total	Grp1	Grp2
			Total	Grp1	Grp2	Total	Grp1	Grp2	Total	Grp1	Grp2

Question #
Table B: Patient Characteristics

Study	Age	Gender (%)	Race (%)	Performance Status	Comorbidities or Prognostic Factors
	Grp1 Grp2 mn md rng sd	Grp1 Grp2 M F	Grp1 Grp2 B W H A O	ECOG Grp1 Grp2 0 1 2 3	Grp1 Grp2
	Grp1 Grp2 mn md rng sd	Grp1 Grp2 M F	Grp1 Grp2 B W H A O	ECOG Grp1 Grp2 0 1 2 3	Grp1 Grp2
	Grp1 Grp2 mn md rng sd	Grp1 Grp2 M F	Grp1 Grp2 B W H A O	ECOG Grp1 Grp2 0 1 2 3	Grp1 Grp2
	Grp1 Grp2 mn md rng sd	Grp1 Grp2 M F	Grp1 Grp2 B W H A O	ECOG Grp1 Grp2 0 1 2 3	Grp1 Grp2
	Grp1 Grp2 mn md rng sd	Grp1 Grp2 M F	Grp1 Grp2 B W H A O	ECOG Grp1 Grp2 0 1 2 3	Grp1 Grp2
	Grp1 Grp2 mn md rng sd	Grp1 Grp2 M F	Grp1 Grp2 B W H A O	ECOG Grp1 Grp2 0 1 2 3	Grp1 Grp2

Question #
Table C: Treatments

Study	Chemotherapy regimen, per protocol	Group 1 XRT	Group 2 XRT	PCI
	Agent Dose Schedule	Dose Schedule	Dose Schedule	
	Agent Dose Schedule	Dose Schedule	Dose Schedule	
	Agent Dose Schedule	Dose Schedule	Dose Schedule	
	Agent Dose Schedule	Dose Schedule	Dose Schedule	
	Agent Dose Schedule	Dose Schedule	Dose Schedule	
	Agent Dose Schedule	Dose Schedule	Dose Schedule	

Question #
Table D: Outcome Assessment

Study	Primary Outcomes	Secondary Outcomes	Response Criteria	Observer	F/U
					Total Grp1 Grp2 mn md rng sd
					Total Grp1 Grp2 mn md rng sd
					Total Grp1 Grp2 mn md rng sd
					Total Grp1 Grp2 mn md rng sd
					Total Grp1 Grp2 mn md rng sd
					Total Grp1 Grp2 mn md rng sd

Question #
Table E: Survival Outcomes

Study	Overall Survival								Progression-Free Survival							
		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
	Grp1								Grp1							
	Grp2								Grp2							
	Statistical Test Results								Statistical Test Results							
		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
	Grp1								Grp1							
	Grp2								Grp2							
	Statistical Test Results								Statistical Test Results							
		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
	Grp1								Grp1							
	Grp2								Grp2							
	Statistical Test Results								Statistical Test Results							
		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
	Grp1								Grp1							
	Grp2								Grp2							
	Statistical Test Results								Statistical Test Results							
		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
	Grp1								Grp1							
	Grp2								Grp2							
	Statistical Test Results								Statistical Test Results							
		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
	Grp1								Grp1							
	Grp2								Grp2							
	Statistical Test Results								Statistical Test Results							

Question #
Table F: Tumor Response and Quality of Life

Study	**Tumor Response**							**Quality of Life**						
		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	Grp1 n	Grp2 n	Grp1 mn±sd	Grp2 mn±sd
	Grp1													
	Grp2													
	Statistical Test Results													
		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	Grp1 n	Grp2 n	Grp1 mn+sd	Grp2 mn+sd
	Grp1													
	Grp2													
	Statistical Test Results													
		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	Grp1 n	Grp2 n	Grp1 mn+sd	Grp2 mn+sd
	Grp1													
	Grp2													
	Statistical Test Results													
		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	Grp1 n	Grp2 n	Grp1 mn+sd	Grp2 mn+sd
	Grp1													
	Grp2													
	Statistical Test Results													
		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	Grp1 n	Grp2 n	Grp1 mn+sd	Grp2 mn+sd
	Grp1													
	Grp2													
	Statistical Test Results													
		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	Grp1 n	Grp2 n	Grp1 mn+sd	Grp2 mn+sd
	Grp1													
	Grp2													
	Statistical Test Results													

Question #
Table G: Adverse Events

Toxicity Type	Study	Severity or Grade	Results
Treatment-related mortality			F/U (yr) Grp1 n % Grp2 n % p
Nausea			F/U (yr) Grp1 n % Grp2 n % p
Vomiting			F/U (yr) Grp1 n % Grp2 n % p
Anorexia			F/U (yr) Grp1 n % Grp2 n % p
Lethargy			F/U (yr) Grp1 n % Grp2 n % p
Neurosensory			F/U (yr) Grp1 n % Grp2 n % p
Hearing loss			F/U (yr) Grp1 n % Grp2 n % p
Esophagitis			F/U (yr) Grp1 n % Grp2 n % p
Bronchopulmonary			F/U (yr) Grp1 n % Grp2 n % p
Pneumonitis			F/U (yr) Grp1 n % Grp2 n % p
Kidney			F/U (yr) Grp1 n % Grp2 n % p
Anemia			F/U (yr) Grp1 n % Grp2 n % p
Thrombocytopenia			F/U (yr) Grp1 n % Grp2 n % p
Leukopenia or neutropenia			F/U (yr) Grp1 n % Grp2 n % p
Infection			F/U (yr) Grp1 n % Grp2 n % p
Other			F/U (yr) Grp1 n % Grp2 n % p

Question #
Table H: Study Quality Ratings

Study	Initial Assembly of Comparable Groups	Low Loss to Followup, Maintenance of Comparable Groups	Measurements Reliable, Valid, Equal*	Interventions Comparable/ Clearly Defined	Appropriate Analysis of Results	Overall Rating

Question 6: Positron Emission Tomography for Staging of Small-Cell Lung Cancer
Table 6A: Sample Selection

Study	Design	Inclusion	Exclusion	n, Enrolled	n, Withdrawn or Excluded	n, Evaluated

Question 6: Positron Emission Tomography for Staging of Small-Cell Lung Cancer
Table 6B: Patient Characteristics

Study	Age (yr)	Gender (%)	Stage		Race	Performance Status (%)	Comorbidities or Prognostic Factors (%)
			Limited %	Extensive %			
	med	M F					
	med	M F					
	med	M F					
	med	M F					
	med	M F					
	med	M F					

Question 6: Positron Emission Tomography for Staging of Small-Cell Lung Cancer
Table 6C: Test Procedure and Interpretation

Study	PET Procedure	PET Interpretation	Conventional Staging Procedure	Conventonal Staging Interpretation

Question 6: Positron Emission Tomography for Staging of Small-Cell Lung Cancer
Table 6D: Reference Standard Procedure and Interpretation, Management Decisions

Study	Decision Rules for Receiving Reference Standard	Reference Standard Procedure	Reference Standard Interpretation	Management Decisions

Question 6: Positron Emission Tomography for Staging of Small-Cell Lung Cancer
Table 6E: Diagnostic Accuracy Results

Study	Test	Focus	n	TP	FN	FP	TN	Prev	Sens	Sens 95% CIL	Sens 95% CIU	Spec	Spec 95% CIL	Spec 95% CIU	PPV	NPV	DA

Question 6: Positron Emission Tomography for Staging of Small-Cell Lung Cancer
Table 6F: Staging Accuracy Results

Study	Test	Use	Correctly Upstaged #	Correctly Upstaged %	Incorrectly Upstaged #	Incorrectly Upstaged %	Correctly Downstaged #	Correctly Downstaged %	Incorrectly Downstaged #	Incorrectly Downstaged %	Identified Unsuspected Metastases Site	Identified Unsuspected Metastases #	Identified Unsuspected Metastases %	Ruled Out Suspected Metastases Site	Ruled Out Suspected Metastases #	Ruled Out Suspected Metastases %	Missed Metastases Site	Missed Metastases #	Missed Metastases %

Question 6: Positron Emission Tomography for Staging of Small-Cell Lung Cancer
Table 6G: Patient Management and Other Results

Study	Test	Use	PET Changed Patient Management #	%	Changes	Other Findings

Question 6: Positron Emission Tomography for Staging of Small-Cell Lung Cancer
Table 4G: Study Quality Ratings

Study	Representative sample?	Clear Selection Criteria?	Reference standard correctly classifies target condition?	Period between test, reference standard short enough?	Whole sample or random selection received reference standard?

Study	Patients received reference standard regardless of test results?	Reference standard independent of test?	Test execution sufficiently described?	Reference standard execution sufficiently described?

Study	Test results interpreted blind to reference standard?	Reference standard results interpreted blind to test?	Clinical practice data available for test interpretation?	Uninterpretable/ indeterminate results reported?	Withdrawals explained?

Appendix C
Evidence Tables

Question 1. Alternating, Concurrent and Sequential Radiotherapy
Table 1A: Sample Selection

Study	Inclusion	Exclusion	n, Randomized			n, Withdrawn			n, Evaluated for Primary Outcome		
Gregor 1997 EORTC LCCG Multiple European institutions, accrual 3/89 through 1/95	Previously untreated, confirmed SCLC, age < 75, ECOG PS 0-3, limited disease with adequate hematologic and biochemical function	Serious preexisting disease, T1N0M0 disease suitable for resection, bulky mediastinal disease (> 50% of max transverse diameter of thorax on PA X-ray before CTx), pleural effusion obscuring extent of pretreatment disease	Total 349	Seq 174	Alt 175	Total 14	Seq 9	Alt 5 (ineligible; 3 incorrect histology, 8 extensive disease, 3 preexisting thrombocytopenia)	Total 335	Seq 165	Alt 170
Lebeau 1999 26 French institutions, accrual 5/88 through 5/94	Confirmed SCLC; limited stage; no previous RTx,, CTx or surgery; ECOG PS 0-3, no history pf previous neoplasm in last 5 yrs	Age > 70; renal, hepatic, respiratory failure, serious cardiac disease	Total 164	Alt	Conc	Total 8 (ineligible: 5 extensive disease, 2 NSCLC, 1 inadequate pulmonary function tests)	Alt	Conc	Total 156	Alt 74	Conc 82
Takada 2002 15 Japanese institutions, accrual 5/91 through 1/95	Confirmed SCLS, limited state, measurable/assessable disease, age < 75, ECOG PS $\leq$ 2, adequate organ function, leukocytes > 4K/mm^3, hemoglobin > 11 g/dL, platelets > 100K/mm^3, serum creatinine < 1.5 mg/dL, serum AST/ALT < 2xULN, serum bilirubin < 2.0 mg/dL, 24 hr creatinine clearance > 60 mL/min/m^2, arterial oxygen > 70 mmHg.	Malignant pleural effusions or stage I by TNM, symptomatic cardiac disease, history of MI in previous 3 mo	Total 231	Seq 117	Conc 114	Total 3	Seq 3	Conc 0 (ineligible: 2 extensive disease, 1 malignant lymphoma)	Total 228	Seq 114	Conc 114
Sun 1995 15 Chinese institutions, accrual 1983 through 1989	Localized disease	Not specified	Total	Seq	Alt	Total	Seq	Conc	Total 123	Seq 59	Conc 64

Question 1. Alternating, Concurrent and Sequential Radiotherapy
Table 1A: Sample Selection (continued)

Study	Inclusion	Exclusion	n, Randomized			n, Withdrawn			n, Evaluated for Primary Outcome		
Work 1997 Work 1996 single-center study accrual 3/81-9/89	confirmed SCLC; age≤70 yr; limited stage (unilateral disease w/wo mediastinal involvement, + ipsilateral supraclavicular nodes, or invasion of trachea or contralateral main bronchus); no prior chemoTx, radioTx; or surgery for 1° tumor; KPS ≥40%	age>70y; extensive stage disease (disease outside one lung, mediastinum and ipselateral supraclav. nodes, or pleural effusion); prior malignancy	Total 199	L Alt 100	E Alt 99	Total 0	L Alt 0	E Alt 0	Total 199	L Alt 100	E Alt 99
Park 1996 Accrual 5/91 – 5/96 Korean Center	Diagnosed with limited stage SCLC; age < 80 yrs; ECOG PS ≤ 2; normal liver, hematologic and adrenal function; FEV1 > 1 L; VC > 45%		Total 79	Seq 47	Conc 32	Total	Seq	Conc	Total 79	Seq 47	Conc 32

Question 1. Alternating, Concurrent and Sequential Radiotherapy
Table 1B: Patient Characteristics

Study	Age		Gender (%)		Race (%)		Performance Status			Comorbidities or Prognostic Factors		
Gregor 1997		Seq Alt		Seq Alt		Seq Alt	ECOG	Seq	Alt		Seq	Alt
							0	46.1	47.1			
	mn		M	67.9 65.9	B		1	47.9	44.7	Wt ↓ ≤ 10%	76.4	75.3
	md	61 61	F	32.1 34.1	W		2	4.2	5.9	Wt ↓ ≥ 10%	9.7	11.8
	rng	33-75 34-74			H		3	1.8	2.4	NR	13.9	12.9
	sd				A							
					O							
Lebeau 1999		Alt Conc		Alt Conc		Alt Conc	ECOG	Alt	Conc		Alt	Conc
							0	50.0	51.2			
	mn	58 57	M	85.1 79.3	B		1	44.6	46.3	Mn vital cap	86%	86%
	md		F	14.9 20.7	W		2-3	4.1	2.4			
	rng				H		NR	1.4	0.0	Supraclav LN	12.2%	8.5%
	sd				A							
					O							
Takada 2002		Seq Conc		Seq Conc		Seq Conc	ECOG	Seq	Conc		Seq	Conc
							0	28.9	21.9	Wt ↓ < 10%	89.5	91.2
	mn		M	81.6 79.8	B		1	65.8	72.8	Wt ↓ ≥ 10%	7.0	5.3
	md	64 65	F	18.4 20.2	W		2	5.3	5.3	NR	3.5	3.5
	rng	30-74 39-74			H							
	sd				A					Stage II	8.8	6.1
					O					Stage IIIA	50.0	57.0
										Stage IIIB	41.2	36.8
Sun 1995		All Seq Alt		All Seq Alt		Seq Alt	ECOG	Seq	Alt		Seq	Alt
							0					
	mn		M	72.4	B		1					
	md		F	27.6	W		2					
	rng	29-71			H		3					
	sd				A							
					O							
Work 1997 Work 1996		L Alt E Alt		L Alt E Alt		L Alt E Alt	KPS	L Alt	E Alt		L Alt	E Alt
	mn				B		100	10.1	13.1			
	md	59 61	M	71 55	W	not	90-80	70.0	68.7			
	rng	36-69 36-70	F	29 45	H	reported	70-60	15.0	14.1		none	
	sd				A		50-40	5.0	4.0		reported	
					O							
Park 1996		Seq Conc		Seq Conc		Seq Conc	ECOG	Seq	Conc		Seq	Conc
							0	25.0	14.8	Smoking pack-	31	35
	mn	60.6 57.4	M	79.2 85.2	B		1	45.8	63.0	yrs (mn±sd)	±20.6	±19.8
	md		F	20.8 14.8	W		2	29.2	22.2			
	rng				H							
	sd	8.9 8.8			A							
					O							

Question 1. Alternating, Concurrent and Sequential Radiotherapy
Table 1C: Treatments

Study	Chemotherapy regimen, per protocol	Control XRT	Treatment XRT	PCI
Gregor 1997	Sequential: Agent / Dose / Schedule cytoxan 1 g/m^2 d 1, wks 1,4,7,10,13 doxorubicin 45 mg/ m^2 d 1, wks 1,4,7,10,13 etoposide 100 mg/ m^2 d 1,3,5, wks 1,4,7,10,13 Alternating: same agents, doses, days, wks 1,5,9,13,17,19	Sequential Dose / Schedule 50 Gy 20 fractions, 1 fraction/d, 5 d/wk, wks 15-18, 1st 15 fractions wider field, last 5 fractions narrower field, > 4 MeV	Alternating Dose / Schedule 50 Gy 20 fractions, 1 fraction/d, 5 d/wk, wks 7, 11, 15, 19, 1st 15 fractions wider field, last 5 fractions narrower field, > 4 MeV	Not formal part of treatment, but patients with CR eligible for UKCCCR/ EORTC trial UK02
Lebeau 1999	Agent / Dose / Schedule cytoxan 1 g/m^2 d 1, wks 1,5,9,13,17,22 doxorubicin 45 mg/ m^2 d 1, wks 1,13,17,22 vindesine 3 mg/ m^2 d 1, wks 5,9, etoposide 150 mg/ m^2 d 1,2, wks 1,5,9,13,17,22	Alternating Dose / Schedule 55 Gy 1st and 2nd courses: 20 Gy in 8 fractions over 12 d, wks 6-7, 10-11, 3rd course: 15 Gy in 6 fractions over 10 d, wks 14-15, ≥ 8 MeV linac	Concurrent Dose / Schedule 50 Gy 40 Gy 16 fractions over 28 d, then 10 Gy in 4 fractions over 7 d, wks 5-9, ≥ 8 MeV linac	Recommend-ed only if CR induced at dose of 30 Gy in 10 fractions over 16 d using 2 lateral fields
Takada 2002	Agent / Dose / Schedule Sequential cisplatin 80 mg/ m^2 d 1, wks 1,4,7,10 etoposide 100 mg/ m^2 d 1,2,3, wks 1,4,7,10 Concurrent cisplatin 80 mg/ m^2 d 1, wks 1,5,9,13 etoposide 100 mg/ m^2 d 1,2,3, wks 1,5,9,13	Sequential Dose / Schedule 45 Gy 30 fractions, 2 fractions/d, 5d/wk, wks 13-15	Concurrent Dose / Schedule 45 Gy 30 fractions, 2 fractions/d, 5d/wk, wks 1-3	CR or near CR, scar-like shadow on on chest films, no positive cytology and/ or broncho-scopic biopsy, 24 Gy in 16 fractions 2/d, 5/wk
Sun 1995	Agent / Dose / Schedule 1983-1988 ea 3 wks, 2-3 cycles cytoxan 600 mg/m^2 d 1,8 vincristine 1 mg/m^2 d 1,8 methotrexate 20 mg d 2,5,8,11 etoposide 100 mg d 1-5 1989 ea 2-3 wks, 2-3 cycles carboplatin 300 mg/m^2 d 1 etoposide 100 mg/ m^2 d 1-5 cytoxan 600 mg/m^2 d 1,8 doxorubicin 40 mg/ m^2 d 1, cisplatin 50 mg d 3-5	Sequential Dose / Schedule Local disease 45-60Gy 6 wks, after 2 cycles of CTx Mediastinum/supraclavicular nodes 30-45 Gy 3-4 wks	Alternating Dose / Schedule Local disease 45-60Gy 6 wks, between 2 cylces of CTx Mediastinum/supraclavicular nodes 30-45 Gy 3-4 wks	Not specified

Question 1. Alternating, Concurrent and Sequential Radiotherapy
Table 1C: Treatments (continued)

Study	Chemotherapy regimen, per protocol			Control XRT	Treatment XRT	PCI
Work 1997 Work 1996	Agent cisplatin etoposide cytoxan doxorubicin vincristine	Dose 60 mg/m^2 120 mg/m^2 1 g/m^2 45 mg/m^2 1.4 mg/m^2	Schedule d1; cycles 2, 4, 9 (early) or cycles 1, 2, 8 (late) d4,6,8; cycles 2, 4, 9 (early) or cycles 1, 2, 8 (late) d1; cycles 5-8, 10, 11 (early) or 3-6, 10,11 (late) d1; same as cytoxan d1; same as cytoxan	Later Alternating Dose Schedule 40 Gy n=41; 45 Gy n=59 wk 18-19 & 23-24 (cycles 7&9); split-course; 1 frac/d, 5 d/wk; 11 frac/course; 20 or 22.5 Gy/course; 8-16 MV photons; chemoTx (dose given between courses; change, 10/84)	Early Alternating Dose Schedule 40 Gy n=45; 45 Gy n=54 wk 1-2 & 6-7 (cycles 1&3); split-course; 1 frac/d, 5 d/wk; 11 frac/course; 20 or 22.5 Gy/course; 8-16 MV photons; chemoTx given (dose between courses; change, 10/84)	33 Gy in 11 fracs, for those in early arm until 10/84; 25 Gy in 11 fracs for all in both arms post 10/84; whole-brain PCI with ^{60}Co
Park 1996	Agent cytoxan doxorubicin vincristine etoposide cisplatin carboplatin	Dose 1 g/m^2 40 mg/m^2 1 mg/m^2 500 ml 60 mg/m^2 324 mg/m^2	Schedule every 21 d, cycles 1, 3, 5 every 21 d, cycles 1, 3, 5 every 21 d, cycles 1, 3, 5 every 21 d, cycles 2, 4, 6 every 21 d, cycles 2, 4, 6 every 21 d, cycles 2, 4, 6	Sequential Dose Schedule 40-50 Gy wk 19-24, 1 frac/d, 1.8-2 Gy/frac	Concurrent Dose Schedule 45 Gy wk 1-3, 2 frac/d, 30 frac 1.5 Gy/frac	Only if CR maintained

Question 1. Alternating, Concurrent and Sequential Radiotherapy
Table 1D: Outcome Assessment

Study	Primary Outcomes	Secondary Outcomes	Response Criteria	Observer	F/U
Gregor 1997	Overall survival	Time to progression, toxicity, first site of failure	Not specified	Not specified	Total Seq Alt mn md 43 mo rng sd
Lebeau 1999	Overall survival	Tumor response, toxicity, toxicity-related mortality	CR= no clinical, radiol, endosc evidence of tumor, ≥1 mo PR= ↓ by ≥50%, all measureable lesions, ≥1 mo SD= ↓ by < 50%, measurable lesions PD= ↑ by >25%, cross sectional area, ≥1 lesion, or any new lesion irrespective of response elsewhere NE= did not receive ≥ 2 courses CTx or refused RTx	Not blinded	Total Alt Conc mn md 66 mo rng ≥ 19 mo or until death sd
Takada 2002	Overall survival	Tumor response, progression-free survival, toxicity	WHO criteria	Not specified	Total Seq Conc mn md rng sd
Sun 1995	Not specified	Not Specified	Not specified	Not specified	Total Seq Alt mn md rng sd
Work 1997 Work 1996	overall survival no formal power calculation	in-field recurrence rate; CNS recurrence rate; response rates; adverse events	WHO criteria	unspecified; blinding not mentioned	Total L Alt E Alt mn md rng sd planned 5 yr post-diagnosis, but actual duration not reported
Park 1996	Not specified	Tumor response, survival, local control, adverse events	CR= no signs of tumor, > 4 wks PR= ↓ by ≥50%, any accountable lesion, no new symptoms, > 4 wks SD= ↓ by < 50%, any accountable lesion, > 4 wks PD= ↑ by >25%, any accountable lesion, > 4 wks	Not specified	Total Seq Conc mn md rng sd

Question 1. Alternating, Concurrent and Sequential Radiotherapy
Table 1E: Survival Outcomes

Study	Overall Survival							Progression-Free Survival						
Gregor 1997		N	Md (mos)	1 yr	2 yr	3 yr	4 yr	5 yr		N	Md (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
	Seq	165	15	64%	23%	15%	~14%	~12%	Seq	165	12	~50%	~22%	~17%	~15%	~5%
	Alt	170	14	60%	26%	12%	~10%	~4%	Alt	170	10	~43%	~16%	~10%	~8%	~8%
	(CPHM: RR 0.88, 95% CI 0.68, 1.1, p=0.237; p=0.288, log-rank)								(Log-rank p=0.07)							
Lebeau 1999		N	Md (mos)	1 yr	2 yr	3 yr	4 yr	5 yr		N	Md (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
	Alt	74	14.0	63%	17%	11%	6%	6%	Alt							
	Conc	82	13.5	54%	13%	6%	4%	4%	Conc							
	(p=0.15, log-rank, 66 Alt deaths, 77 Conc deaths)															
Takada 2002		N	Md (mos)	1 yr	2 yr	3 yr	4 yr	5 yr		N	Md (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
	Seq	114	19.7	~80%	35.1%	20.2%	~20%	18.3%	Seq	114	~10	~38%	~19%	~15%	~14%	~14%
	Conc	114	27.2	~80%	54.4%	29.8%	~25%	23.7%	Conc	114	~12	~50%	~28%	~25%	~20%	~17%
	(p=0.097 eligible patients, p=0.086 all randomized, log-rank; CPMH: HR 0.70, 95% CI 0.52, 0.94, p=0.02)								(p=0.084, log-rank))							
Sun 1995		N	Md (mos)	1 yr	2 yr	3 yr	4 yr	5 yr		N	Md (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
	Seq	59		64.0%	13.6%	12.0%			Seq							
	Alt	64		62.5%	28%	16.0%			Alt							
Work 1997 Work 1996		N	Md (mos)	1 yr	2 yr	3 yr	4 yr	5 yr	PWIFR:	N	Md (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
	L Alt	100	12.0	~55%	18.8%	~12%	~12%	12.0%	L Alt	100	~15	~58%	31.7%	~27%	~27%	27%
	E Alt	99	10.5	~43%	20.2%	~13%	~12%	10.8%	E Alt	99	~9	~40%	27.7%	~25%	~23%	23%
	(p=0.41, not significant)															
Park 1996		N	Mn (mos)	1 yr	2 yr	3 yr	4 yr	5 yr		N	Md (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
	Seq	47	16.0	74.4%	27.7%	8.8%	4.4%	2.2%	Seq							
	Conc	32	18.4	81.3%	29.0%	13.8%	10.7%	7.4%	Conc							
	(p=0.11)															

Question 1. Alternating, Concurrent and Sequential Radiotherapy
Table 1F: Tumor Response and Quality of Life

Study	Tumor Response							Quality of Life							
Gregor 1997		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	Seq n	Conc n	Seq mn±sd	Conc mn±sd
	Seq									NOT MEASURED				
	Alt													
Lebeau 1999		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	Seq n	Conc n	Seq mn±sd	Conc mn±sd
	Alt	74	49%	46%		4%	1%			NOT MEASURED				
	Conc (p=0.26)	82	53%	37%		7%	3%							
Takada 2002		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	Seq n	Conc n	Seq mn±sd	Conc mn±sd
	Seq	114	27.2%	64.9%	2.6%	3.5%	1.8%			NOT MEASURED				
	Conc	114	39.5%	57.0%	0.9%	0.9%	1.8%							
	(CR p=0.07, ORR p=0.25)													
Sun 1995		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	Seq n	Conc n	Seq mn±sd	Conc mn±sd
	Seq									NOT MEASURED				
	Conc													
Work 1997 Work 1996		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	Early n	Late n	Early mn+sd	Late mn+sd
	Seq	100	61.2%	23.5%	10.2%	5.1%				NOT MEASURED				
	Conc (NS)	99	59%	30%	5%	6%								
Park 1996		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	Seq n	Conc n	Seq mn±sd	Conc mn±sd
	Seq	24	13%	50%	29%	4%	4%			NOT MEASURED				
	Conc	27	30%	48%	4%	11%	7%							
	(response, p=0.13, response duration, mn±sd, Conc 395 d ±61.1, Seq 180 d ±43.9, p=0.03)													

Question 1. Alternating, Concurrent and Sequential Radiotherapy
Table 1G: Adverse Events

Toxicity Type	Study	Severity or Grade	Group	n	%	Group	n	%	p	Not Reporting
Treatment-related mortality	Lebeau 1999	Deaths from aplasia	Alt	74	2.7	Conc	82	3.7	0.67	Gregor 1997; Sun 1995; Work 1997; 1996; Park, 1996
		Deaths from pulmonary fibrosis	Alt	74	1.4	Conc	82	7.3	0.05	
	Takada 2002		Seql	110	3.6	Conc	112	2.7	0.72	
	Work 1997		L Alt	100	0	E Alt	99	0	1.00	
Nausea/Vomiting	Gregor 1997	Nausea or vomiting, acute (WHO grade)								Lebeau 1999; Sun 1995; Work 1997; 1996; Park, 1996
		0	Seql	165	25.5	Alt	169	36.1	0.129	
		1			21.8			21.3		
		2			37.6			25.4		
		3			13.3			15.4		
		4			0.6			1.2		
		NR			1.2			0.6		
	Takada 2002	Nausea or vomiting (WHO grade ≥ 3)	Seql	110	19.1	Conc	112	10.7	0.09	
Anorexia										Lebeau 1999; Gregor 1997; Takada 2002; Sun 1995; Work 1997; 1996; Park, 1996
Lethargy										Lebeau 1999; Gregor 1997; Takada 2002; Sun 1995; Work 1997; 1996; Park, 1996
Neurosensory	Work 1997; 1996	Moderate neurotoxicity (grade ≤ 3)	in 11 (of 199); no difference between groups							Lebeau 1999; Gregor 1997; Takada 2002; Sun 1995; Park, 1996
Hearing loss										Lebeau 1999; Gregor 1997; Takada 2002; Sun 1995; Work 1997; 1996; Park, 1996
Esophagitis	Gregor 1997	Acute (WHO grade)								Lebeau 1999; Sun 1995; Work 1997; 1996; Park, 1996
		0	Seql	165	83.0	Alt	169	75.7	0.198	
		1			7.9			11.8		
		2			6.1			9.5		
		3			3.0			3.0		
		Late esophageal stenosis (WHO grade)								
		0	Seql	143	82.5	Alt	135	94.1	0.010	
		1			11.2			3.0		
		2			2.8			1.5		
		3			2.1			0.7		
		NR			1.4			0.7		
	Takada 2002	WHO grade ≥ 3	Seql	110	3.6	Conc	112	8.9	0.17	

Question 1. Alternating, Concurrent and Sequential Radiotherapy
Table 1G: Adverse Events (continued)

Toxicity Type	Study	Severity or Grade	Group	n	%	Group	n	%	p	Not Reporting
Bronchopulmonary	Gregor 1997	Late Lung fibrosis (RTOG grade) 0 1 2 3 4 NR	Seql	143	19.6 19.6 21.7 18.2 18.9 2.1	Alt	135	11.1 20.0 27.4 14.8 24.4 2.2	0.135	Takada 2002; Sun 1995; Work 1997; 1996; Park, 1996
	Lebeau 1999	Pulmonary fibrosis	Alt	74	2.7	Conc	82	8.5	0.17	
Pneumonitis										Lebeau 1999; Gregor 1997; Takada 2002; Sun 1995; Work 1997; 1996; Park, 1996
Kidney	Work 1997; 1996		quantified by chromium-edathamil clearance; did not differ between groups							Lebeau 1999; Gregor 1997; Takada 2002; Sun 1995
	Park 1996	ECOG grade 3 ECOG grade 4	Seql	24	0 0	Conc	27	0 0	1.00	
Anemia	Takada 2002	WHO grade 3	Seql	110	41.8	Conc	112	53.6	0.08	Lebeau 1999; Gregor 1997; Sun 1995; Work 1997; 1996
	Park 1996	ECOG grade 3 ECOG grade 4	Seql	24	0 0	Conc	27	3.7 0	1.00	
Thrombocytopenia	Gregor 1997	Acute (WHO grade) 0 1 2 3 4 NR	Seql	165	55.2 13.9 10.9 12.7 6.7 0.6	Alt	169	24.9 17.2 23.1 11.8 20.7 2.4	<0.001	Lebeau 1999; Sun 1995;
	Takada 2002	(WHO grade) 3 4 $\geq$ 3	Seql	110	12.7 13.6 26.4	Conc	112	29.5 7.1 36.6	0.11	
	Work 1997; 1996	WHO grades 3 & 4	L Alt	100	13	E Alt	99	13	1.00	
	Park 1996	ECOG grade 3 ECOG grade 4	Seql	24	0 0	Conc	27	0 3.7	1.00	

Question 1. Alternating, Concurrent and Sequential Radiotherapy
Table 1G: Adverse Events (continued)

Toxicity Type	Study	Severity or Grade	Group	n	%	Group	n	%	p	Not Reporting
Leukopenia or neutropenia	Gregor 1997	Acute Leukopenia (WHO grade) 0 1 2 3 4 NR	Seql	165	6.7 5.5 10.9 34.5 41.8 0.6	Alt	169	4.1 1.2 3.6 17.8 71.6 1.8	<0.001	Sun 1995
	Lebeau 1999	Neutropenia (grade 3 or 4)	Alt	74	60.8	Conc	82	58.5	0.87	
	Takada 2002	Leukopenia (WHO grade) 3 4 3 or 4	Seql	110	44.5 9.1 53.6	Conc	112	50.9 37.5 88.4	0.001	
	Work 1997; 1996	WHO grades 3 & 4 leukopenia WHO grade 4 leukopenia	L Alt	100	39 6	E Alt	99	67 23	<0.001 0.0006	
	Park 1996	Leukopenia ECOG grade 3 ECOG grade 4	Seql	24	12.5 4.2	Conc	27	40.7 11.1	0.0176	
Infection	Takada 2002	WHO grade ≥ 3	Seql	110	0.9	Conc	112	5.4	0.12	Lebeau 1999; Gregor 1997; Sun 1995
	Work 1997; 1996		neutropenic fever in 8 patients; no difference between groups							
	Park 1996	ECOG grade 3 ECOG grade 4	Seql	24	0 0	Conc	27	3.7 0	1.00	
Other	Takada 2002	Alopecia (WHO grade ≥ 3)	Seql	109	12.7	Conc	109	11.6	0.99	
	Takada 2002	Fever (WHO grade ≥ 3)	Seql	110	1.8	Conc	112	1.8	0.99	
	Takada 2002	Arrhythmias (WHO grade ≥ 3)	Seql	110	0.0	Conc	112	1.8	0.50	
	Park 1996	Hepatic ECOG grade 3 Hepatic ECOG grade 4	Seql	24 0	0	Conc 0	27	0	1.00	

Question 1. Alternating, Concurrent and Sequential Radiotherapy
Table 1H: Study Quality Ratings

Study	Initial Assembly of Comparable Groups	Low Loss to Followup, Maintenance of Comparable Groups	Measurements Reliable, Valid, Equal*	Interventions Comparable/ Clearly Defined	Appropriate Analysis of Results	Overall Rating
Gregor 1997	Yes	Yes	Yes	Yes	Yes	Good
Lebeau 1999	Yes	Yes	Yes	Yes	Yes	Good
Takada 2002	Yes	Yes	Yes	Yes	Yes	Good
Sun 1995	?	?	?	?	?	Poor
Work 1997 Work 1996	Partial (arms balanced but "Randomization… based on a table of random numbers.")	yes	yes	yes	yes	Fair
Park 1996	?	?	Yes	Yes	?	Poor

Question 2. Early versus Late Radiotherapy
Table 2A: Sample Selection

Study	Inclusion	Exclusion	n, Randomized	n, Withdrawn or Excluded	n, Evaluated for Primary Outcome
Murray 1993 Coy 1994 Feld 1988 22 centers accrual 1/85 through 12/88	confirmed SCLC; limited stage (unilateral disease w/wo vena cava syndrome, mediastinal involvement, or + ipsilateral supraclavicular nodes); no prior chemoTx or radioTx; ECOG PS 0-3; adequate renal, hepatic, hematologic function; vital capacity ≥45%; FEV_1≥40%	age>80y; extensive stage disease (disease outside one lung, mediastinum and supraclav. nodes, or pleural effusion); tumor size > pre-specified limit of TRTx field size; serious cardiac disease; prior malignancy <5 years ago	Total Early Late 332 168 164	Total Early Late 24 (7%) 13 11 exclusions: extensive stage 5 not SCLC 10 poor lung func 3 tumor>RTx field 4 non-assessable lesion 2	Total Early Late 308 155 153
Perry 1987 Ahles 1994 Perry 1998 22 centers accrual 1/81 through 6/84	confirmed SCLC; limited stage (unilateral disease w/wo vena cava syndrome, mediastinal involvement, or + supraclavic-ular nodes); no prior chemoTx or radioTx; CALGB PS 0-3	MI within prior 6 mos; extensive stage disease (disease outside one lung, mediastinum and supraclav. nodes, or pleural effusion)	Total Early Late 426 3-arm study; data on regimen III (no TRTx) not abstracted	Total Early Late 27 (6%) exclusions: extensive stage 7 not SCLC 5 contraindications 3 wrong Tx: 1 withdrew consent 11	Total Early Late 270 125 145 (evaluated for OS; no 1° outcome specified)
Jeremic 1997 single center accrual 1/88-12/92; closed early since PI moved	confirmed SCLC; limited stage (unilateral disease w/wo vena cava syndrome, mediastinal involvement, or + ipsilateral supraclavicular nodes); no prior therapy; KPS ≥50%; adequate hematologic, renal, hepatic function	age≥70y; extensive stage disease (disease outside one lung, mediastinum and supraclav. nodes, or pleural effusion); serious cardiac or renal disease; prior malignancy <5 years ago	Total Early Late 107 54 53	Total Early Late 4 (4%) 2 2 exclusions: extensive stage 3 concurrent bladder cancer 1	Total Early Late 103 52 51
Qiao 2004 single center accrual 3/93-1/98	limited stage SCLC (unilateral disease), previously untreated, could bear comprehensive treatment, KPS >60, age <70, normal liver and kidney function	metastasis beyond homo-lateral hilus, mediastinum, and supraclavicular lymph nodes	Total Early Late 90 45 45	Total Early Late	Total Early Late 90 45 45
Skarlos 2001 multicenter accrual 12/93 to 11/99	confirmed SCLC; limited stage (unilateral disease w/wo vena cava syndrome, mediastinal involvement, or + ipsilateral supraclavicular nodes); no prior chemoTx or radioTx; ECOG PS 0-2; adequate renal, hepatic, hematologic function	extensive stage disease (disease outside one lung, mediastinum and ipsilateral supraclav. nodes, or pleural effusion); prior malignancy	Total Early Late 86	Total Early Late 5 (6%) exclusions: pleural effusion 4 adrenal mets 1	Total Early Late 81 42 39

Question 2. Early versus Late Radiotherapy
Table 2A: Sample Selection (continued)

Study	Inclusion	Exclusion	n, Randomized			n, Withdrawn or Excluded			n, Evaluated for Primary Outcome		
			Total	Early	Late	Total	Early	Late	Total	Early	Late
James 2003 (abstract only) multicenter; accrual 1/1993 through 1/2002	limited stage disease (definition not reported)	extensive stage disease (definition not reported)	325	159	166	0	0	0	325	159	166

Question 2. Early versus Late Radiotherapy
Table 2B: Patient Characteristics

Study	Age (yr)		Gender (%)		Race		Performance Status (%)			Comorbidities or Prognostic Factors (%)		
Murray 1993 Coy 1994 Feld 1988		Early 61.8 y	Late 61.6 y		Early 59.4 40.6	Late 65.4 34.6		Early not reported	Late	ECOG 0 1 2 3	Early 21.9 65.2 12.3 0.6	Late 22.2 68.0 9.2 0.7		Early 25.1% 16.2% 38.7% 53.5% 7.8%	Late 25.5% 15.7% 39.2% 56.2% 4.6%
Perry 1987 Ahles 1994 Perry 1998	<50 50-9 60-9 70-9	Early 14% 32% 41% 13%	Late 12% 33% 43% 12%		Early 62 38	Late 63 37		Early not reported	Late	CALGB 0 1 2 or 3	Early 38 48 13	Late 42 45 9		Early 14	Late 11
Jeremic 1997	mn md rng sd	Early 57 59 40-67	Late 57 59 44-66		Early 59.6 40.4	Late 60.8 39.2		Early not reported	Late	KPS 90, 100 50-80	Early 52 48	Late 47 53		Early 52	Late 53
Qiao 2004	mn md rng sd	Early 57 36-68	Late 56 38-69		Early 75.6 24.4	Late 66.7 33.3		Early not reported	Late	KPS ≥70 for all; excluded if KPS ≤60	Early	Late		Early 28.9 60 11.1	Late 24.4 60 15.6
Skarlos 2001	mn md rng sd	Early 61 40-76	Late 60 37-76		Early 93 7	Late 90 10		Early not reported	Late	ECOG 0 1 2	Early 26 50 24	Late 41 44 15		Early 100 67 17 21	Late 93 69 8 18
James 2003 (abstract only)	mn md rng sd	Early 62 34-74	Late 62 33-74		Early 60 40	Late 57 43		Early not reported	Late	ECOG 0-1 2-3	Early 91 9	Late 89 11		Early none reported	Late

Question 2. Early versus Late Radiotherapy
Table 2C: Treatments

Study	Chemotherapy regimen, per protocol			Early TRTx		Late TRTx		PCI
Murray 1993 Coy 1994 Feld 1988	Agent cytoxan doxorubicin vincristine etoposide cisplatin	Dose 1 g/m^2 50 mg/m^2 2 mg 100 mg/m^2 25 mg/m^2	Schedule d 1, wk 1, 8, 14 (early) wk 1, 7, 13 (late) d 1, as for cytoxan d 1, as for cytoxan d 1-3 wk 4, 11, 17 (early) wk 4, 10, 16 (late) d 1-3, as for etoposide	Dose 40 Gy	Schedule wks 4-6: 15 fracs, 2.67 Gy each, 1 frac/d, 5 d/wk; ^{60}Co or linac photons (4-25 MeV); 1 wk rest post TRTx before chemoTx cycles 3-6	Dose 40 Gy	Schedule wks 16-18: 15 fracs, 2.67 Gy each; 1 frac/d, 5 d/wk; ^{60}Co or linac photons (4-25 MeV)	25 Gy in 10 fracs; wks 20 & 21; if no PD post chemoTx and TRTx
Perry 1987 Ahles 1994 Perry 1998	Agent vincristine cytoxan etoposide doxorubicin (chemoTx for 18 months)	Dose 1.4 mg/m^2 1 g/m^2 80 mg/m^2 50 mg/m^2	Schedule d1; q21d d1; q21d d1,2,3; q21d (to cycle 7) d1; (replaced etoposide for odd cycles #7-17, to total dose of 350 mg/m^2)	Dose 50 Gy	Schedule wks 1-5: 40 Gy, then 10 Gy boost; source, # and size of fractions not specified (likely 2 Gy/d, 5 d/wk)	Dose 50 Gy	Schedule wks 10-14: 40 Gy, then 10 Gy boost; source, # and size of fractions not specified (likely 2 Gy/d, 5 d/wk)	30 Gy in 10 fractions concurrent with TRTx; all patients
Jeremic 1997	Agent carboplatin etoposide cisplatin etoposide	Dose 30 mg 30 mg 30 mg/m^2 120 mg/m^2	Schedule every RTx day every RTx day d 1-3; wk 6,9,12,15 (early) wk 1,4,11,14 (late) as for cisplatin	Dose 54 Gy	Schedule wks 1-4; 1.5 Gy fracs 2x/d 4.5-6 hr apart, 5x/wk; 36 fracs on 18 d over 3.6 wk; concurrent chemoTx given during interval between fracs	Dose 54 Gy	Schedule wks 6-9; 1.5 Gy fracs 2x/d 4.5-6 hr apart, 5x/wk; 36 fracs on 18 d over 3.6 wk; concurrent chemoTx given during interval between fracs	25 Gy in 10 fracs, wks 16 & 17; given to all with CR or PR
Qiao 2004	Agent carboplatin etoposide	Dose 100 mg 100 mg	Schedule d 1-5, wks 1,4,7,10,13,16 d 1-5, wks 1,4,7,10,13,16	Dose 50 or 60 Gy	Schedule started in first CTx cycle; given over 6 wks; 2 Gy fracs, 1x/d, 5d/wk, 40 Gy to front and back, 20 Gy from oblique angles/avoiding spinal cord; total 50 Gy if no LN metastasis	Dose 60 Gy	Schedule started after 4th CTx cycle same treatement plan radiation areas and dosages as early group	not mentioned
Skarlos 2001	Agent carboplatin etoposide	Dose AUC of 6 100 mg/m^2	Schedule d1, each of six 21-d cycles d 1-3, each of six 21-d cycles	Dose 45 Gy	Schedule wks 1-3; 1.5 Gy fracs 2 frac/d, 5 d/wk	Dose 45 Gy	Schedule wks 10-12; 1.5 Gy fracs, 2 frac/d, 5 d/wk	20 Gy; five daily 4 Gy fracs; only if achieved CR
James 2003 (abstract only)	Agent cytoxan doxorubicin vincristine etoposide cisplatin	Dose 1 g/m^2 50 mg/m^2 2 mg 100 mg/m^2 25 mg/m^2	Schedule d 1, wks 1, 7, 13 d 1, wks 1, 7, 13 d 1, wks 1, 7, 13 ds 1-3, wks 4, 10, 16 ds 1-3, wks 4, 10, 16	Dose 40 Gy	Schedule wks 4-6: 15 fracs, 2.67 Gy each, 1 frac/d, 5 d/wk; source not specified	Dose 40 Gy	Schedule wks 16-18: 15 fracs, 2.67 Gy each; 1 frac/d, 5 d/wk; source not specified	25 Gy in 10 fracs; wks 19 & 20; given to responders w neg, post Tx brain scan

Question 2. Early versus Late Radiotherapy
Table 2D: Outcome Assessment

Study	Primary Outcomes	Secondary Outcomes	Response Criteria	Observer	F/U
Murray 1993 Coy 1994 Feld 1988	overall survival 80% power to detect increase in 2-year survival from 20% to 35% at 2-sided p<0.05	progression-free survival; response rates; time to local recurrence; time to brain relapse; first relapse pattern (local versus distant versus both); adverse events	CR= no clinical, radiol evidence of tumor, ≥1 mo PR= ↓ by ≥50%, all measureable lesions, ≥1 mo SD= ↓ in lesion size by <50% or ↑ by <25%, ≥1 mo PD= ↑ by >25%, cross sectional area, ≥1 lesion, or any new lesion	unspecified; blinding not mentioned	Total Early Late mn md <5 y rng 2.7-? y sd
Perry 1987 Ahles 1994 Perry 1998	not specified; no power calculation	overall, disease-free and failure-free survival; time to failure in chest; response rates; adverse events	CR= no clinical, radiol evidence of tumor, ≥1 mo PR= ↓ by ≥50%, all measureable lesions, ≥1 mo SD= ↓ in lesion size by <50% ≥1 mo PD= any objective ↑ in lesion size	unspecified; blinding not mentioned	Total Early Late 10 yrs mn md rng sd
Jeremic 1997	survival at 2 yr planned 80% power to detect 20% Δ in 2 yr survival at p<0.05, assuming 25% baseline survival, but closed early	local recurrence-free and distant mets-free survival; response rates; adverse events	CR= disappearance of all measurable/assessable disease & no new lesions, ≥4 wk PR= ↓ by ≥50%, $\Sigma_{\text{all lesions}}$[products of cross-sectional diameters], no new lesions, ≥4 wk SD= ↓ by <50% or ↑ by <25% in above sum PD= ↑ by ≥25% in above sum	unspecified; blinding not mentioned	Total Early Late mn not reported md rng sd
Qiao 2004	not specified; no power calculation	overall survival; response rates at 4 months; adverse events; cause of death	CR= no clinical, radiol evidence of tumor, ≥4 wk PR= ≥50% ↓, $\Sigma_{\text{all lesions}}$[products, 2 greatest perpendicular diams.], no new lesions, ≥4 wk SD= did not meet criteria for CR, PR or PD PD= ↑ by ≥25% in above sum, without prior CR, PR or SD (WHO criteria)	unspecified; blinding not mentioned	Total Early Late 5 yrs mn md rng sd
Skarlos 2001	overall response rate (ORR = CR + PR) n=84 had 80% power to detect 25% ↑ in ORR at 5% level, if ORR=70% for late TRTx	overall survival; time to progression; adverse events	CR= no clinical, radiol evidence of tumor, ≥4 wk PR= ≥50% ↓, $\Sigma_{\text{all lesions}}$[products, 2 greatest perpendicular diams.], no new lesions, ≥4 wk SD= did not meet criteria for CR, PR or PD PD= ↑ by ≥25% in above sum, without prior CR, PR or SD (WHO criteria)	unspecified; blinding not mentioned	Total Early Late mn 35 mos md rng sd
James 2003 (abstract only)	overall survival (no power calculation)	adverse event; overall response rate (CR+PR)	CR= not provided PR= not provided SD= not provided PD= not provided	unspecified; blinding not mentioned	Total Early Late mn md not rng reported sd

Question 2. Early versus Late Radiotherapy
Table 2E: Survival Outcomes

Study	Overall Survival							Progression-Free Survival (PFS), Time to Failure (TTF), Local Recurrence-Free Survival (LRFS), or Proportion Without In-Field Recurrence (PWIFR)						
Murray 1993		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr	PFS:	N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
Coy 1994	Early	155	21.2	~77%	40%	29.7%	23.7%	20%	Early	155	15.4	~64%	~28%	26%	~23%	~23%
Feld 1988	Late	153	16.0	~63%	33.7%	21.5%	15.1%	11%	Late	153	11.8	~48%	~24%	19%	~17	~17%
	(p=0.008, log-rank; 0.005 Wilcoxon)								(p=0.036, log-rank; 0.014 Wilcoxon)							
Perry 1987		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr	TTF:	N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
Ahles 1994	Early	125	13.0	~53%	~24%	~10%			Early	125	11.0	~48%	15%	~9%	~7%	~6%
Perry 1998	Late	145	14.5	~62%	~30%	~20%			Late	145	11.2	~52%	21%	~14%	~12%	~11%
	(p=0.144; not significant)								(p=0.238; not significant)							
Jeremic 1997		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr	LRFS:	N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
	Early	52	34	90%	71%	48%	35%	30%	Early	52		94%	90%	73%	63%	58%
	Late	51	26	71%	53%	39%	25%	15%	Late	51		74%	69%	61%	46%	37%
				(p=0.052)									(p=0.011)			
Qiao 2004		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
	Early	45	26	78%		33%		27%	Early							
	Late	45	19	53%		22%		16%	Late							
	(log-rank, p<0.05)															
Skarlos 2001		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr	TTF:	N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
	Early	42	17.5	~65%	36%	22%			Early	42	9.5	~40%	~25%	~20%		
	Late	39	17	~80%	29%	13%			Late	39	10.5	~35%	~15%	~15%		
	(p=0.65, not significant)								(p=0.6, not significant)							
James 2003		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
(abstract only)	Early	159	13.5			16%			Early							
	Late	166	15.1			20%			Late			NOT REPORTED				
	(HR = 1.18; 95% CI: 0.93, 1.51; p=0.18)															

Question 2. Early versus Late Radiotherapy
Table 2F: Tumor Response and Quality of Life

Study	Tumor Response						Quality of Life						
Murray 1993		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	Early n	Late n	Early mn+sd	Late mn+sd
Coy 1994	Early	155	63.9%	20.6%	5.2%	9.7%	0.6%							
Feld 1988	Late	153	55.6%	25.5%	2.0%	15.0%	1.9%			NOT MEASURED				
	(not significantly different; p= 0.14)													
Perry 1987		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	Early n	Late n	Early mn+sd	Late mn+sd
Ahles 1994	Early	121	49%	30%	14%	2%	4%	Profile of	total score	pre-Tx	16	12	20.2±28.5	21.7±34.4
Perry 1998	Late	141	58%	25%	9%	3%	5%	Mood States		post RTx			35.3±30.3	39.1±33.4
	(not significantly different; p=0.13)							Handicap	total score	pre-Tx	14	10	4.5±3.2	2.7±2.3
								Rating Scale		post RTx			6.6±2.7	6.4±2.9
								Trails B	time to	pre Tx	17	11	186±97	171±113
								Test	complete	post RTx			193±97	161±91
Jeremic 1997	wk 15:	N	CR	PR	SD	PD	NE	Scale	Domain	F/U	Early n	Late n	Early mn+sd	Late mn+sd
	Early	52	96%	2%		2%								
	Late	51	82%	2%		10%	6% (dead)			NOT MEASURED				
	(p=0.023)													
Qiao 2004		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	Early n	Late n	Early mn+sd	Late mn+sd
	Early	45	67%	31%	2%									
	Late	45	47%	44%	9%					NOT MEASURED				
	(p>0.05)													
Skarlos 2001		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	Early n	Late n	Early mn+sd	Late mn+sd
	Early	42	40.5%	35.5%	14%	5%	5%							
	Late	39	56.5%	36.0%	5%	2.5%	0			NOT MEASURED				
	(ORR: 76% early, 92.5% late; p=0.07)													
James 2003		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	Early n	Late n	Early mn+sd	Late mn+sd
(abstract only)	Early	159	ORR=79%											
	Late	166	ORR=78%							NOT MEASURED				

ORR = overall response rate (CR + PR)

Question 2. Early versus Late Radiotherapy
Table 2G: Adverse Events

Toxicity Type	Study	Severity or Grade	Results				
Treatment-related mortality	Murray 1993 Coy 1994 Feld 1988	not applicable	F/U (yr) 2.7-5+	Early n 155	% 1.3	Late n 153	% 1.3
	Perry 1987 Ahles 1994 Perry 1998	not applicable	F/U (yr) 1.44	Early n 125	% 4	Late n 145	% 1
	Jeremic 1997	not applicable	F/U (yr)	Early n NOT REPORTED	%	Late n	%
	Qiao 2004	not applicable	F/U (yr)	Early n	%	Late n	%
	Skarlos 2001	not applicable	F/U (yr) 2.9 (med)	Early n 42	% 0	Late n 39	% 0
	James 2003 (abstract only)	not applicable	F/U (yr)	Early n NOT REPORTED	%	Late n	%
Nausea	Murray 1993 Coy 1994 Feld 1988		F/U (yr)	Early n	%	Late n	%
	Perry 1987 Ahles 1994 Perry 1998		F/U (yr)	Early n	%	Late n	%
	Jeremic 1997		F/U (yr)	Early n	%	Late n	%
	Qiao 2004		F/U (yr)	Early n	%	Late n	%
	Skarlos 2001		F/U (yr)	Early n	%	Late n	%
	James 2003 (abstract only)		F/U (yr)	Early n	%	Late n	%

Question 2. Early versus Late Radiotherapy
Table 2G: Adverse Events (continued)

Toxicity Type	Study	Severity or Grade	Results				
Vomiting	Murray 1993 Coy 1994 Feld 1988	required IV fluids	F/U (yr) 2.7 – 5+	Early n 155	% 11.6	Late n 153	% 15.8
			(p not significant)				
	Perry 1987 Ahles 1994 Perry 1998	nausea and vomiting, NOS	F/U (yr) 1.44	Early n 122	% 18	Late n 140	% 10
	Jeremic 1997	acute nausea and vomiting grades 3 & 4	F/U (yr) not reported	Early n 52	% 9.6	Late n 51	% 7.8
	Qiao 2004		F/U (yr)	Early n	%	Late n	%
	Skarlos 2001	grade 3 nausea and vomiting	F/U (yr) 2.9 (med)	Early n 42	% 2.5	Late n 39	% 2.5
	James 2003 (abstract only)	nausea and vomiting grades 3 & 4	F/U (yr) ???	Early n 159	% 2	Late n 166	% 3
Anorexia	Murray 1993 Coy 1994 Feld 1988		F/U (yr)	Early n	%	Late n	%
	Perry 1987 Ahles 1994 Perry 1998	>10% weight loss	F/U (yr) 1.44	Early n ???	% 14	Late n not reported	%
	Jeremic 1997		F/U (yr)	Early n	%	Late n	%
	Qiao 2004	weight loss (% not specified)	F/U (yr) ???	Early n 45	% 20	Late n 45	% 33.3
	Skarlos 2001		F/U (yr)	Early n	%	Late n	%
	James 2003 (abstract only)		F/U (yr)	Early n	%	Late n	%

Question 2. Early versus Late Radiotherapy
Table 2G: Adverse Events (continued)

Toxicity Type	Study	Severity or Grade	Results				
Lethargy	Murray 1993 Coy 1994 Feld 1988		F/U (yr)	Early n	%	Late n	%
	Perry 1987 Ahles 1994 Perry 1998		F/U (yr)	Early n	%	Late n	%
	Jeremic 1997		F/U (yr)	Early n	%	Late n	%
	Qiao 2004		F/U (yr)	Early n	%	Late n	%
	Skarlos 2001		F/U (yr)	Early n	%	Late n	%
	James 2003 (abstract only)		F/U (yr)	Early n	%	Late n	%
Neurosensory	Murray 1993 Coy 1994 Feld 1988	 severe life-threatening lethal	F/U (yr) 2.7-5+	Early n 155	% 0.6 0 0.6	Late n 153	% 3.3 1.3 0
	Perry 1987 Ahles 1994 Perry 1998	"neuromuscular effects"	F/U (yr) 1.44	Early n 124	% 17	Late n 144	% 16
	Jeremic 1997		F/U (yr)	Early n	%	Late n	%
	Qiao 2004		F/U (yr)	Early n	%	Late n	%
	Skarlos 2001	grade 2 & 3 neurotoxicity	F/U (yr) 2.9 (med)	Early n 42	% 0	Late n 39	% 0
	James 2003 (abstract only)		F/U (yr)	Early n	%	Late n	%

Question 2. Early versus Late Radiotherapy
Table 2G: Adverse Events (continued)

Toxicity Type	Study	Severity or Grade	Results				
Hearing loss	Murray 1993 Coy 1994 Feld 1988		F/U (yr)	Early n	%	Late n	%
	Perry 1987 Ahles 1994 Perry 1998		F/U (yr)	Early n	%	Late n	%
	Jeremic 1997		F/U (yr)	Early n	%	Late n	%
	Qiao 2004		F/U (yr)	Early n	%	Late n	%
	Skarlos 2001		F/U (yr)	Early n	%	Late n	%
	James 2003 (abstract only)		F/U (yr)	Early n	%	Late n	%
Esophagitis	Murray 1993 Coy 1994 Feld 1988	fluids only IV fluids	F/U (yr) 2.7-5+	Early n 149	% 11.4 3.4	Late n 133	% 6.8 0.8
	Perry 1987 Ahles 1994 Perry 1998	not specified	F/U (yr) 1.44	Early n ???	% 10	Late n ???	% 8
	Jeremic 1997	acute, grades 3 & 4	F/U (yr) not reported	Early n 52	% 28.9	Late n 51	% 25.5
	Qiao 2004	radio-esophagitis	F/U (yr) (p>0.05)	Early n 45	% 42.2	Late n 45	% 28.9
	Skarlos 2001	grade 2 grade 3	F/U (yr) 2.9 (med)	Early n 42	% 16.5% 2.5%	Late n 39	% 2.5% 18%
			(p=0.82 for any grade, 0.03 for grade 3)				
	James 2003 (abstract only)	grades 3 & 4	F/U (yr) ???	Early n 159	% 7	Late n 166	% 4

Question 2. Early versus Late Radiotherapy
Table 2G: Adverse Events (continued)

Toxicity Type	Study	Severity or Grade	Results				
Bronchopulmonary	Murray 1993 Coy 1994 Feld 1988		F/U (yr)	Early n	%	Late n	%
	Perry 1987 Ahles 1994 Perry 1998	not specified	F/U (yr) 1.44	Early n 122	% 9	Late n 133	% 6
	Jeremic 1997	acute, grades 3 & 4	F/U (yr) not reported	Early n 52	% 1.9	Late n 51	% 0
	Qiao 2004		F/U (yr)	Early n	%	Late n	%
	Skarlos 2001	grade 3	F/U (yr) 2.9 (med)	Early n 42	% 5.0% p = 0.69	Late n 39	% 7.5%
	James 2003 (abstract only)		F/U (yr)	Early n	%	Late n	%
Pneumonitis	Murray 1993 Coy 1994 Feld 1988	any lethal	F/U (yr) 2.7-5+	Early n 149	% 3.2 0	Late n 133	% 0.7 0
	Perry 1987 Ahles 1994 Perry 1998	not specified	F/U (yr) 1.44	Early n 122	% 9	Late n 133	% 4.5
	Jeremic 1997		F/U (yr)	Early n	%	Late n	%
	Qiao 2004	radio-pneumonia	F/U (yr)	Early n 45	% 8.9	Late n 45	% 6.7
	Skarlos 2001		F/U (yr)	Early n	%	Late n	%
	James 2003 (abstract only)		F/U (yr)	Early n	%	Late n	%

Question 2. Early versus Late Radiotherapy
Table 2G: Adverse Events (continued)

Toxicity Type	Study	Severity or Grade	Results
Kidney	Murray 1993 Coy 1994 Feld 1988	creatinine > 354 μmol/L	F/U (yr) Early n % Late n % 2.7-5+ 155 0 153 0.7 (p not significant)
	Perry 1987 Ahles 1994 Perry 1998		F/U (yr) Early n % Late n %
	Jeremic 1997		F/U (yr) Early n % Late n %
	Qiao 2004		F/U (yr) Early n % Late n %
	Skarlos 2001	grade 2 or 3	F/U (yr) Early n % Late n % 2.9 (med) 42 0 39 0
	James 2003 (abstract only)		F/U (yr) Early n % Late n %
Anemia	Murray 1993 Coy 1994 Feld 1988	Hb <80 g/L	F/U (yr) Early n % Late n % 2.7-5+ 155 49 153 36.8 (p = 0.03)
	Perry 1987 Ahles 1994 Perry 1998		F/U (yr) Early n % Late n %
	Jeremic 1997	acute, grades 3 & 4	F/U (yr) Early n % Late n % not reported 52 13.5 51 7.8
	Qiao 2004		F/U (yr) Early n % Late n %
	Skarlos 2001	grades 3 & 4	F/U (yr) Early n % Late n % 2.9 (med) 42 19 39 12.8
	James 2003 (abstract only)	grades 3 & 4	F/U (yr) Early n % Late n % not reported 159 9 166 5

Question 2. Early versus Late Radiotherapy
Table 2G: Adverse Events (continued)

Toxicity Type	Study	Severity or Grade	Results
Thrombocytopenia	Murray 1993 Coy 1994 Feld 1988	<25 x 10^9/L	F/U (yr) Early n % Late n % 2.7-5+ 155 3.9 153 2.6 (p not significant)
	Perry 1987 Ahles 1994 Perry 1998	<25 x 10^9/L	F/U (yr) Early n % Late n % 1.44 122 1 140 2
	Jeremic 1997	acute, grades 3 & 4	F/U (yr) Early n % Late n % not reported 52 38.5 51 21.6
	Qiao 2004		F/U (yr) Early n % Late n %
	Skarlos 2001	grades 3 & 4	F/U (yr) Early n % Late n % 2.9 (med) 42 21.4% 39 23.1%
	James 2003 (abstract only)	grades 3 & 4	F/U (yr) Early n % Late n % not reported 159 9 166 9
Leukopenia or neutropenia	Murray 1993 Coy 1994 Feld 1988	neutrophils<0.5 x 10^9/L	F/U (yr) Early n % Late n % 2.7-5+ 155 70.3 153 61.4 (p not significant)
	Perry 1987 Ahles 1994 Perry 1998	WBC<1 x 10^9/L	F/U (yr) Early n % Late n % 1.44 117 35 118 25
	Jeremic 1997	acute leukopenia, grades 3 & 4	F/U (yr) Early n % Late n % not reported 52 32.7 51 41.2
	Qiao 2004	leukocyte decline grade 2 grade 3 grade 4	F/U (yr) Early n % Late n % NR 45 6.7 45 24.4 71.1 57.8 22.2 17.8 (grade 3 & 4, p<0.05)
	Skarlos 2001	grades 3 & 4 leukopenia	F/U (yr) Early n % Late n % 2.9 (med) 42 35.7 39 20.5
	James 2003 (abstract only)	grades 3-4 leucopenia	F/U (yr) Early n % Late n % not reported 159 74 166 55 (p=0.006)

Question 2. Early versus Late Radiotherapy
Table 2G: Adverse Events (continued)

Toxicity Type	Study	Severity or Grade	Results				
Infection	Murray 1993 Coy 1994 Feld 1988	 neutropenic fever septic shock lethal	F/U (yr) 2.7-5+	Early n 155	% 4.5 0.6 0	Late n 153	% 3.3 0.7 1.3
	Perry 1987 Ahles 1994 Perry 1998	 sepsis fatal sepsis	F/U (yr) 1.44	Early n 125	% 20 3	Late n 140	% 15 1
	Jeremeic 1997	acute grades 3 & 4	F/U (yr) not reported	Early n 52	% 13.5	Late n 51	% 13.7
	Qiao 2004		F/U (yr)	Early n	%	Late n	%
	Skarlos 2001	neutropenic fever	F/U (yr) 2.9 (med)	Early n 42	% 5	Late n 39	% 2.5
	James 2003 (abstract only)		F/U (yr)	Early n	%	Late n	%
Other	Murray 1993 Coy 1994 Feld 1988	 severe dermatitis blisters	F/U (yr) 2.7-5+	Early n 149	% 2.0 4.0	Late n 133	% 1.5 0.7
	Perry 1987 Ahles 1994 Perry 1998		F/U (yr)	Early n	%	Late n	%
	Jeremic 1997		F/U (yr)	Early n	%	Late n	%
	Qiao 2004	mild digestive tract reaction	F/U (yr)	Early n 45	% 73.3	Late n 45	% 55.6
	Skarlos 2001		F/U (yr)	Early n	%	Late n	%
	James 2003 (abstract only)		F/U (yr)	Early n	%	Late n	%

Question 2. Early versus Late Radiotherapy
Table 2H: Study Quality Ratings

Study	Initial Assembly of Comparable Groups	Low Loss to Followup, Maintenance of Comparable Groups	Measurements Reliable, Valid, Equal*	Interventions Comparable/ Clearly Defined	Appropriate Analysis of Results	Overall Rating
Murray 1993 Coy 1994 Feld 1988	partial (arms balanced but randomization method not described)	yes	yes	yes	yes	fair
Perry 1987 Ahles 1994 Perry 1998	partial (arms balanced but randomization method not described)	yes	yes	yes	yes	fair
Jeremic 1997	partial (arms balanced but randomization method not described)	yes	yes	yes	yes	fair
Qiao 2004	partial (arms balanced but randomization method not described)	yes	yes	yes	yes	fair
Skarlos 2001	yes	yes	partial (overall response rate was primary outcome)	yes	yes	fair
James 2003 (abstract only)	partial (arms balanced but randomization method not described)	yes	? (no mention of intent to treat or # included in analyses)	yes	yes	not rated since abstract only

***** Those who rated response or progression were not described as blinded or masked to patients' allocated treatment in any of these reports.

Question 3. Alternative Fractionation Schemes (once versus twice daily)
Table 3A: Sample Selection

Study	Inclusion	Exclusion	n, Randomized			n, Withdrawn			n, Evaluated for Primary Outcome		
Turrisi 1999 Yuen 2000 multicenter trial ECOG/Intergroup #0096 accrual 5/89-7/92	confirmed SCLC confined to one hemithorax, the ipselateral supraclavicular fossa, or both; no previous cancer; adequate organ function (WBC≥4x10^3/ mm^3; platelets≥1x10^5/ mm^3; serum creatinine<130μmol/L; serum aspartate and alanine aminotransferase levels <2 x upper limit of normal range; serum bilirubin < 8.6 μmol/L; $FEV_1 \geq 1.0$ L)	bilateral disease, pleural effusion, contralateral hilar or supraclavicular adeno-pathy; ECOG PS ≥3; symptomatic cardiac disease or MI within past 6 mos; prior chemotherapy or radiotherapy for any malignancy	Total	1 F/d	2 F/d	Total	1 F/d	2 F/d	Total	1 F/d	2 F/D
			417	206	211	36	21	15	381	185	196
						reasons:					
						withdrew from Tx		7			
						no preTx tumor size		8			
						extensive disease		6			
						NSCLC		6			
						incomplete staging		5			
						↑ serum AST		1			
						incorrect Dx		1			
						ECOG PS ≥3		1			
Schild 2004 Sloan 2002 Bonner 1999 NCCT 89-20-52 Multiple US institutions, accrual 9/90 through 11/96	Confirmed limited disease SCLC, WBC > 3,500/μL, platelets > 100K/ μL, hemoglobin ≥ 9.5 g/dL, serum creatinine ≤ 2 F/dULN, normal total bilirubin, AST/ALT < 3xULN, FEV-1 > 1 L, ECOG PS ≤ 2, met predefined restaging criteria after 3 cycles prerandomization EP CTx: thoracic disease still within RTx ports, ECOG PS ≤ 2, WBC > 3,500/μL, platelets > 100K/ μL, serum creatinine ≤ 2 F/dULN, FEV-1 > 1 L, other chemistry values < 3xULN, no distant mets other than brain	MI < 3 months, uncontrolled CHF, uncontrolled arrhythmia, more than minimal pleural effusion, recent malignancy, prior therapy for this malignancy, weight loss > 10% < 3 mo, pregnant, lactating	Total	1 F/d	2 F/d	Total	1 F/d	2 F/d	Total	1 F/d	2 F/d
			262	132	130	1	1	0	261	131	130
						(1 ineligible)					

Question 3. Alternative Fractionation Schemes (once versus twice daily)
Table 3B: Patient Characteristics

Study	Age (yr)		Gender (%)		Race (%)		Performance Status (%)			Comorbidities or Prognostic Factors (%)		
		1 F/d	2 F/d		1 F/d	2 F/d		1 F/d	2 F/d		1 F/d	2 F/d
Turrisi 1999 Yuen 2000							ECOG:			5-10% ↓ weight	15%	13%
	mn			M	59	58	B	7	8	0	43	39	>10% ↓ weight	5%	5%
	md	63	61	F	41	42	W	90	89	1	51	55	ipsilateral lung	49%	55%
	rng	34-80	30-82				O	3	3	2	5	5	mediastinum	59%	62%
	sd												ips SC nodes	3%	5%
	>65	40%	31%										variant morphol	2%	2%
		(p=0.07)													
Schild 2004 Sloan 2002		1 F/d	2 F/d		1 F/d	2 F/d		1 F/d	2 F/d	ECOG	1 F/d	2 F/d		1 F/d	2 F/d
Bonner 1999	mn	61.8	62.1	M	58.0	56.9	B			0-1	97.7	93.1	Measurable	38.9%	39.2%
	md	63.0	62.5	F	42.0	43.1	W			2	5.3	6.9	Assessable	61.1%	60.8%
	rng	38-81	37-79				H								
	sd						A						Wt ↓ ≤ 5%	87.8%	89.2%
							O						Wt ↓ 5-10%	11.5%	10.0%
													Wt ↓ > 10%	0.8%	0.8%
													CTx, > SD	93.1%	94.6%
													CTx, SD	5.3%	4.6%
													CTx, LPD	0.8%	0.8%
													CTx, BrM	0.8%	0.0%

Question 3. Alternative Fractionation Schemes (once versus twice daily)
Table 3C: Treatments

Study	Chemotherapy regimen, per protocol			One Daily Fraction of TRTx		Two Daily Fractions of TRTx		PCI
Turrisi 1999 Yuen 2000	Agent cisplatin etoposide	Dose 60 mg/m^2 120 mg/m^2	Schedule d1, 3-wk cycles x 4 d1-3, 3-wk cycles x 4	Dose 45 Gy	Schedule 1.8 Gy fracs, 5 d/wk for 5 wk; started in 1st wk of chemoTx; linac photons only	Dose 45 Gy	Schedule 1.5 Gy fracs, 2/d; 5 d/wk for 3 wk; started in 1st wk of chemoTx; linac photons only	25 Gy; 10 x 2.5 Gy fracs, 5 d/wk over 2 wk; for those with CR after 1^{o} therapy
Schild 2004 Sloan 2002 Bonner 1999	Agent Prerandomization cisplatin etoposide Postrandomization cisplatin etoposide	Dose 30 mg/m^2 130 mg/m^2 30 mg/m^2 100 mg/m^2	Schedule d 1-3, wks 1, 5, 9 d 1-3, wks 1, 5, 9 (4-wk cycles) d 1-3, wks 13, 17, 21 d 1-3, wks 13, 17, 21	Dose 50.4 Gy	Schedule 28 x 1.8 Gy frac, 38 d, 1st 39.6 Gy in AP-PA fields, last 10.8 Gy in oblique fields excluding spine, 4-10 MeV, wks 13-17	Dose 48 Gy	Schedule 32 x 1.5 Gy frac, ≥4 hrs apart; split course, start week 13: 16 fracs over 1.5 wks, 2.5 wk rest, 16 more fracs over 1.5 wks	30 Gy; 15 x 2 Gy fracs, 5 d/wk over 3 wk; for those with CR after 1^{o} therapy

Question 3. Alternative Fractionation Schemes (once versus twice daily)
Table 3D: Outcome Assessment

Study	Primary Outcomes	Secondary Outcomes	Response Criteria	Observer	F/U
Turrisi 1999 Yuen 2000	survival at 2 years 82% power to detect absolute Δ of 15% (25% 1/d; 40% 2/d) at 0.05 level (2 sided)	median overall survival; time to treatment failure; local failure rates; response rates; adverse events	CR= no clinical evidence of disease PR= ≥50%↓ in l x w product of any measurable tumor for at least 4 weeks SD= not reported PD= ≥10%↓ in body weight, ≥25%↑ in diameter of any tumor ≥2 cm diameter, ≥50%↑ in diameter of any tumor <2 cm diameter, or any new tumor	not specified blinding not mentioned	Total / 1 F/d / 2 F/d mn md ~8 yr rng ~5-? yr sd
Schild 2004 Sloan 2002 Bonner 1999	Overall survival	Local progression, distant progression, progression-free survival, toxicity	CR= total disappearance of tumor PR= ↓ by ≥50% in greatest perpendicular diameters, all measureable lesions, ≥1 mo SD= ↓ by < 50%, measurable lesions, ↑ by < 25%, no new lesions PD= ↑ by ≥25%, any 1 lesion, new lesion, ↓ in PS by ≥ 2 levels	Not specified	Total / 1 F/d / 2 F/d mn md 7.4 yrs rng 4.6-11.9 yrs sd

Question 3. Alternative Fractionation Schemes (once versus twice daily)
Table 3E: Survival Outcomes

Study	**Overall Survival (%)**							**Progression-Free or Failure-Free Survival (PFS; FFS)**						
Turrisi 1999		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr	FFS: N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
Yuen 2000	1 F/d	206	19	~75	41%	~32	~29	16%	1 F/d 206			24%			
	2 F/d	211	23	~70	47%	~28	~20	26%	2 F/d 211			29%			
	(log-rank p=0.04; HR 1.2, 95% CI: 1.0, 1.6)								(p=0.10)						
Schild 2004		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
Sloan 2002																
Bonner 1999	1 F/d	131	20.6	~74%	44%	~33%	~23%	20.4%	1 F/d	131	~14	~57%	31.3%	~25%	~23%	19.8%
	2 F/d	130	20.6	~74%	44%	~31%	~26%	22%	2 F/d	130	~14	~58%	30.8%	~27%	~21%	21%
	(p=0.68, log-rank)								(p=0.68, log-rank)							

Question 3. Alternative Fractionation Schemes (once versus twice daily)
Table 3F: Tumor Response and Quality of Life

Study	Tumor Response (%)							Quality of Life						
Turrisi 1999		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	1/d n	2/d n	1/d mn+sd	2/d mn+sd
Yuen 2000	1/d	185	49	38	4	8	2							
	2/d	196	56	31	4	6	4			NOT MEASURED				
			(P=0.23; no significant difference)											
Bonner 1999		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	1/d n	2/d n	1/d mn+sd	2/d mn+sd
Sloan 2002	1/d	132	55											
Schild 2004	2/d	130	69							NOT MEASURED				

Question 3. Alternative Fractionation Schemes (once versus twice daily)
Table 3G: Adverse Events

Toxicity Type	Study	Severity or Grade	Results				
Treatment-related mortality	Turrisi 1999 Yuen 2000	not applicable	F/U (yr) med ~8	1/d n 203	% 2	2/d n 206	% 3
	Bonner 1999 Sloan 2002 Schild 2004	not applicable	F/U (yr) med 7.4	1/d n 131	% 0	2/d n 130	% 3
Nausea	Turrisi 1999 Yuen 2000		F/U (yr)	1/d n	%	2/d n	%
	Bonner 1999 Sloan 2002 Schild 2004	≥ grade 3	F/U (yr)	1 F/d n 132	% 16.7	2 F/d n 130	% 16.9
Vomiting	Turrisi 1999 Yuen 2000	grade 3 grade 4	F/U (yr) med ~8	1/d n 203	% 8 2	2/d n 206	% 8 1
	Bonner 1999 Sloan 2002 Schild 2004	≥ grade 3	F/U (yr)	1 F/d n 132	% 12.1	2 F/d n 130	% 14.6
Anorexia	Turrisi 1999 Yuen 2000	grade 3 weight loss (grade 4=0, both arms)	F/U (yr) med ~8	1/d n 203	% 3	2/d n 206	% 2
	Bonner 1999 Sloan 2002 Schild 2004	≥ grade 3	F/U (yr)	1 F/d n 132	% 3.0	2 F/d n 130	% 2.3
Lethargy	Turrisi 1999 Yuen 2000		F/U (yr)	1/d n	%	2/d n	%
	Bonner 1999 Sloan 2002 Schild 2004	≥ grade 3	F/U (yr) p=0.09	1 F/d n 132	% 3.0	2 F/d n 130	% 7.7
Neurosensory	Turrisi 1999 Yuen 2000		F/U (yr)	1/d n	%	2/d n	%
	Bonner 1999 Sloan 2002 Schild 2004	≥ grade 3	F/U (yr)	1 F/d n 132	% 7.6	2 F/d n 130	% 11.5

Question 3. Alternative Fractionation Schemes (once versus twice daily)
Table 3G: Adverse Events (continued)

Toxicity Type	Study	Severity or Grade	Results				
Hearing loss	Turrisi 1999 Yuen 2000		F/U (yr)	1/d n	%	2/d n	%
	Bonner 1999 Sloan 2002 Schild 2004	≥ grade 3	F/U (yr)	1 F/d n 132	% 1.5	2 F/d n 130	% 3.8
Esophagitis	Turrisi 1999 Yuen 2000	grade 3 grade 4	F/U (yr) med ~ 8	1/d n 203	% 11 5 (p<0.001)	2/d n 206	% 27 5
	Bonner 1999 Sloan 2002 Schild 2004	≥ grade 3	F/U (yr) p=0.05	1 F/d n 132	% 5.3	2 F/d n 130	% 12.3
Bronchopulmonary	Turrisi 1999 Yuen 2000	grade 3 grades 4 & 5	F/U (yr) med 8 yr	1/d n 203	% 3 1	2/d n 206	% 4 2
	Bonner 1999 Sloan 2002 Schild 2004	≥ grade 3	F/U (yr)	1 F/d n 132	% 4.5	2 F/d n 130	% 6.2
Pneumonitis	Turrisi 1999 Yuen 2000		F/U (yr)	1/d n	%	2/d n	%
	Bonner 1999 Sloan 2002 Schild 2004	≥ grade 3	F/U (yr)	1 F/d n 132	% 4.5	2 F/d n 130	% 6.2
Kidney	Turrisi 1999 Yuen 2000		F/U (yr)	1/d n	%	2/d n	%
	Bonner 1999 Sloan 2002 Schild 2004		F/U (yr)	1/d n	%	2/d n	%
Anemia	Turrisi 1999 Yuen 2000	grade 3 grade 4	F/U (yr) med ~8	1/d n 203	% 23 3	2/d n 206	% 23 5
	Bonner 1999 Sloan 2002 Schild 2004	≥ grade 3	F/U (yr)	1/d n 132	% 3.0	2/d n 130	% 2.3

Question 3. Alternative Fractionation Schemes (once versus twice daily)
Table 3G: Adverse Events (continued)

Toxicity Type	Study	Severity or Grade	Results				
Thrombocytopenia	Turrisi 1999 Yuen 2000	 grade 3 grade 4	F/U (yr) med ~8	1/d n 203	% 16 8	2/d n 206	% 13 8
	Bonner 1999 Sloan 2002 Schild 2004	 ≥ grade 3 grade 4	F/U (yr)	1 F/d n 128	% 60.9 24.2	2 F/d n 127	% 45.7 20.5
Leukopenia or neutropenia	Turrisi 1999 Yuen 2000	 grade 3 leukopenia grade 4 leukopenia	F/U (yr) med ~8	1/d n 203	% 41 39	2/d n 206	% 38 44
	Bonner 1999 Sloan 2002 Schild 2004	leukopenia ≥ grade 3 grade 4	F/U (yr)	1 F/d n 128	% 88.3 37.5	2 F/d n 127	% 89.8 36.2
Hemoglobin	Turrisi 1999 Yuen 2000		F/U (yr)	1/d n	%	2/d n	%
	Bonner 1999 Sloan 2002 Schild 2004	 ≥ grade 3 grade 4	F/U (yr)	1 F/d n 128	% 5.3 0.0	2 F/d n 127	% 3.8 0.0
Infection	Turrisi 1999 Yuen 2000	 grade 3 grades 4 & 5	F/U (yr) med ~8	1/d n 203	% 6 2	2/d n 206	% 6 3
	Bonner 1999 Sloan 2002 Schild 2004	 ≥ grade 3	F/U (yr)	1 F/d n 132	% 2.3	2 F/d n 130	% 3.8

Question 3. Alternative Fractionation Schemes (once versus twice daily)
Table 3G: Adverse Events

Toxicity Type	Study	Severity or Grade	Results				
Other	Turrisi 1999 Yuen 2000		F/U (yr)	1/d n	%	2/d n	%
		one or more grade 3, no grade 4	med ~8	203	23	206	25
		one or more grade 4, no grade 5			63		62
	Bonner 1999 Sloan 2002 Schild 2004	Any hematologic	F/U (yr)	1 F/d n	%	2 F/d n	%
		≥ grade 3		131	90.1	130	89.2
			p=0.82				
		≥ grade 4			43.5		42.3
			p=0.84				
		Any nonhematologic	F/U (yr)	1 F/d n	%	2 F/d n	%
		≥ grade 3		131	38.9	130	54.6
			p=0.01				
		≥ grade 4			9.2		13.8
			p=0.24				
		grade 5			0.0		3.1
			p=0.04				
		Any toxicity	F/U (yr)	1 F/d n	%	2 F/d n	%
		≥ grade 3		131	91.6	130	92.3
			p=0.83				
		≥ grade 4			46.6		46.9
			p=0.95				
		grade 5			0.0		3.1
			p=0.04				

Question 3. Alternative Fractionation Schemes
Table 3H: Study Quality Ratings

Study	Initial Assembly of Comparable Groups	Low Loss to Followup, Maintenance of Comparable Groups	Measurements Reliable, Valid, Equal*	Interventions Comparable/ Clearly Defined	Appropriate Analysis of Results	Overall Rating
Turrisi 1999 Yuen 2000	Yes	Yes	Yes	Yes	Yes	Good
Bonner 1999 Sloan 2002 Schild 2004	Yes	Yes	Yes	Yes	Yes	Good

***** Those who rated response or progression were not described as blinded or masked to patients' allocated treatment in any of these reports.

Question 4. Chemotherapy with versus without Thoracic Radiation Therapy, Extensive-Stage Disease (ESD)
Table 4A: Sample Selection

Study	Inclusion	Exclusion	n, Randomized	n, Withdrawn or Excluded	n, Evaluated for Primary Outcome
Jeremic 1999 single center: Kragujevac Univ. Hospital, Yugoslavia accrual Jan. 1988 through June 1993	confirmed SCLC; extensive stage (disease outside one hemithorax, mediastinum and supraclav. nodes; tumor of >size than tolerable RTx field; or w cytology+ pleural effusion); no prior chemoTx or radioTx; KPS ≥70; adequate renal, hepatic, hematologic function; CR outside thorax and CR or PR in thorax after 3 cycles of PE chemoTx	age>70y; limited stage disease (unilateral disease, w/wo mediastinal involvement, + ipsilateral supraclavicular nodes or cytology-neg pleural effusion); recent or concurrent severe uncontrolled cardiovascular or pulmonary disease; CNS mets or substantially impaired mental status; prior cancer except non-melanoma skin	Total +TRTx -TRTx 109 55 54 unrandomized groups by post-3rd cycle response (thorax/ elsewhere): CR/PR: 34 PR/PR: 28 SD or PD: 35	Total +TRTx -TRTx 0 0 0 0 0 0	Total +TRTx -TRTx 109 55 54 unrandomized groups by post-3rd cycle response (thorax/ elsewhere): CR/PR: 34 PR/PR: 28 SD or PD: 35
Nou 1988 Univ. Hospital, Uppsala accrual 01/80 through 12/83	confirmed SCLC; any age, PS, or expected survival; LSD if one hemithorax ± ipselateral supraclavicular nodes; all others, ESD	surgically resected for uncertain tumor type subsequently found to be SCLC;	Total +TRTx -TRTx 54 28 26 (also randomized n=56 with LSD)	Total +TRTx -TRTx 0 0 0	Total +TRTx -TRTx 54 28 26
Lebeau 1993 27 centers in France accrual 10/85 through 04/88	confirmed SCLC; any age, gender, performance status, or disease extent; CR after 5 wks ±heparin then 8 cycles of sequential or alternating chemoTx regimens; some outcomes reported separately by treatment arm for ESD	renal failure; previous chemotherapy or radiation therapy; curative thoracic surgery; "patients who could not be followed up closely"	Total +TRTx -TRTx 18 10 8 (also randomized 35 pts w LSD; n=422 for two previous randomizations)	Total +TRTx -TRTx 0 0 0	Total +TRTx -TRTx 18 10 8
Rosenthal 1991 3 centers in Australia accrual 01/77 through 07/79	confirmed SCLC; evaluable or measurable disease (LSD or ESD); previously untreated; serum creatinine and liver function tests ≤1.5 X ULNR; response (CR or PR) after 3 cycles of chemotherapy	prior chemo- or radiation therapy; cerebral metastasis; advanced age (not defined) and senility; severe co-existent disease (not defined); non-response after 3 cycles of chemotherapy	Total +TRTx -TRTx 27 ? ? treated n=139 (91, LSD; 48, ESD); randomized responders (66, LSD; 27, ESD) to ±TRTx	Total +TRTx -TRTx 0 ? ?	Total +TRTx -TRTx 27 ? ?
Brincker 1987 Odense Univ. Hospital, Denmark accrual 03/81 through 01/84	confirmed SCLC; <70 years of age; WHO PS 0-2; no clinical signs of CNS metastasis; with or without prior thoracotomy or radical resection ESD defined as metastasis to soft tissue, vicera, or bone or malignant pleural effusion	age ≥ 70 years; WHO PS >2; clinical signs of CNS metastasis	Total +TRTx -TRTx 43 25 18	Total +TRTx -TRTx 13 9 4 (patients dead before day 100 not evaluable; didn't receive full RTx therapy)	Total +TRTx -TRTx 30 16 14

Question 4. Chemotherapy with versus without Thoracic Radiation Therapy, Extensive-Stage Disease
Table 4B: Patient Characteristics

Study	Age (yr)	Gender (%)	Race	Performance Status (%)	Comorbidities or Prognostic Factors (%)
Jeremic 1999	+TRTx -TRTx mn md 59 59 rng 38-70 39-71 sd md rng CR/PR: 58 41-70 PR/PR: 60 44-69 SD or PD: 59 41-69	+TRTx -TRTx M 60 59 F 40 41 M F CR/PR: 62 38 PR/PR: 61 39 SD or PD 60 40	+TRTx -TRTx B W not H reported A O	KPS +TRTx -TRTx 100 31 24 90 36 43 80 18 18 70 15 15 70/80 90/100 CR/PR 35 65 PR/PR 32 68 SD or PD 31 69	+TRTx -TRTx weight loss 45.5 43.0 ≥5% # metastatic sites: 1 41.8 46.3 2 49.1 42.6 ≥3 9.1 11.1
Nou 1988	+TRTx -TRTx mn md 65 60 rng 55-78 41-81 sd	+TRTx -TRTx M 75 69 F 25 31	+TRTx -TRTx B W not H reported A O	KPS +TRTx -TRTx med 60 60 range 30-90 30-90	+TRTx -TRTx cerebral mets 7 8 2 metastatic sites 36 38 ≥3 metastatic sites 14 15
Lebeau 1993 (only reported characteristics of combined LSD & ESD patients)	+TRTx -TRTx % <50 22 23 50-9 30 38.5 60-9 33 23 70-81 15 15.5	+TRTx -TRTx M 96 92 F 4 8	+TRTx -TRTx B W not H reported A O	KPS +TRTx -TRTx 90-100 63 46 70-80 22 50 60 15 4	+TRTx -TRTx + heparin 45 58 - heparin 30 21 not randomized 25 21 seq. chemoTx 67 69 alt. chemoTx 33 31
Rosenthal 1991 (only reported characteristics of all enrolled patients, LSD + ESD, w/wo TRTx)	+TRTx -TRTx mn md 60 rng 26-77 sd	+TRTx -TRTx M 76 F 24	+TRTx -TRTx B W not H reported A O	ECOG +TRTx -TRTx 0 1 1 88 2 3 unknown 8	+TRTx -TRTx
Brincker 1987 (only reported characteristics of evaluable combined LSD & ESD patients)	+TRTx -TRTx mn md 60 63 rng 42-69 46-69 sd	+TRTx -TRTx M 73 73 F 27 27	+TRTx -TRTx B W not H reported A O	WHO +TRTx -TRTx 0 34 24 1 51 57 2 15 19	+TRTx -TRTx

Question 4. Chemotherapy with versus without Thoracic Radiation Therapy, Extensive-Stage Disease
Table 4C: Treatments

Study	Chemotherapy regimen, per protocol			with Thoracic Radiotherapy		PCI
Jeremic 1999	Agent	Dose	Schedule	Dose	Schedule	25 Gy whole brain; 10 daily fracs, 2.5 Gy each, 5 days/wk, wks 14 & 15, both arms
	cisplatin	80 mg/m^2	day 1, wks 1, 4, 7, 16 & 19 (+TRTx); also wks 10 & 13, -TRTx and non-randomized CR/PR and PR/PR groups	54 Gy	24 fracs, 1.5 Gy ea, twice daily over 2.5 wks, then 12 fracs, 1.5Gy ea, twice daily on 6 days; wks 10-13; 4.5 to 6 hr between fracs; 6-10 MV linac photons	non-randomized CR/PR and PR/PR groups received same PCI regimen, wks 20-21, if distant CR by wk 20
	etoposide	80 mg/m^2	days 1-3, wks 1, 4, 7, 16 & 19 (+TRTx); also wks 10 & 13, -TRTx and non-randomized groups	non-randomized CR/PR and PR/PR groups received same concurrent TRTx and carboplatin/etoposide chemotherapy, wks 16-19		
	carboplatin	50 mg	each day of TRTx, between fracs			
	etoposide	50 mg	each day of TRTX, between fracs			
Nou 1988	Agent	Dose	Schedule (all cycles, 3 weeks)	Dose	Schedule	none given
	Cytoxan	250 mg/m^2	days 1, 2 and 3, A cycles			
	vincristine	2 mg	day 1, A cycles and B cycles	40 Gy	1 frac/day, 2 Gy each, 5 days/wk, over 4 weeks; beginning after 3 cycles of regimen A; -TRTx arm give 4th cycle of A regimen at same time; then both arms give 4 cycles each, B regimen, then A, then B, then A, then B; 8- or 16 mV linac photons	
	doxorubicin	50 mg/m^2	day 1, A cycles			
	methotrexate	100 mg/m^2	day 1, A and B cycles (leucovorin on day 2)			
	lomustine	40 mg/m^2	day 1, every other B cycle			
	Cytoxan	750 mg/m$_2$	day 1, all B cycles			
Lebeau 1993	Agent	Dose	Schedule	Dose	Schedule	"…all responder patients in certain centers or by randomization in other centers as part of a separate study." PCI given to 21 of 27 in +TRTx group and 17 of 26 in no TRTx group, but no information on LSD or ESD subgroups; also no information on PCI dose or schedule
	CCNU	80 mg	day 1, X8 4-wk cycles (sequential) cycles 1, 3, 5, 7 (alternating)	varied	started 4 wks after final chemotherapy cycle; dosage ranged from 32 Gy in 9 fracs over 11 or 18 days to 65 Gy in 33 fracs over 64 days; mean 46.5 Gy-equivalents (corresponds to 5 fracs/wk, 2 Gy each) per patient; range 41-65 Gy-equivalents; all used megavoltage X-rays, ≥4 MeV	
	Cytoxan	1 gm/m^2	day 1, X8 4-wk cycles (sequential) cycles 1, 3, 5, 7 (alternating)			
	doxorubicin	45 mg/m^2	day 1, X8 4-wk cycles (sequential) cycles 1, 3, 5, 7 (alternating)			
	etoposide	225 mg/m^2	day 1, X8 4-wk cycles (sequential) cycles 2, 4, 6, 8 (alternating)			
	cisplatin	80 mg/m^2	day 1 q4 wk, altern. cycles 2, 4, 6, 8			
	vindesine	3 mg/m^2	day 1 q4 wk, altern. cycles 2, 4, 6, 8			
Rosenthal 1991	Agent	Dose	Schedule	Dose	Schedule	not mentioned
	vincristine	1 mg/m^2	day 1, q3wk, for 10 cycles			
	Cytoxan	750 mg/m^2	day 1, q3wk, for 10 cycles	40 Gy	20 fracs, given between chemotherapy cycles 3 and 4 in +TRTx arm; other details not provided	
	doxorubicin	50 mg/m^2	day 1, q3wk, for 10 cycles			
	methotrexate	12 mg	intrathecal, with each chemo cycle			
	or	1 g/m^2	IV, with folinic acid, cycles 1-3 only (initial randomization)			
Brincker 1987	Agent	Dose	Schedule	Dose	Schedule	not mentioned
	vincristine	2 mg	day 1, odd cycles, 4 wk each	12 Gy	600 cGy hemi-body irradiation as single fraction, to upper body on day 60 in place of chemoTx cycle 3, and to lower body on day 100 in place of cycle 4; 8 MeV linac photons (alternating chemoTx cycles continued to death or progression for up to 18 months in both arms)	
	doxorubicin	50 mg/m^2	day 1, odd cycles, 4 wk each			
	Cytoxan	600 mg/m^2	day 1, odd cycles, 4 wk each			
	lomustine	60 mg/m^2	day 1, even cycles, 4 wk each			
	methotrexate	20 mg/m^2	days 1&3, even cycles, 4 wk each			
	etoposide	100 mg/m^2	days 1-4, even cycles, 4 wk each			

Question 4. Chemotherapy with versus without Thoracic Radiation Therapy, Extensive-Stage Disease
Table 4D: Outcome Assessment

Study	Primary Outcomes	Secondary Outcomes	Response Criteria	Observer	F/U
Jeremic 1999	CR rate 80% power to detect ↑ in CR rate from 25% to 50% at 1-sided 0.05 level	overall, local recurrence-free, distant metastasis-free, and relapse-free survival; objective response rates; adverse events	CR= disappearance of all measurable/assessable disease & no new lesions, ≥4 wk PR= ↓ by ≥50%, $\Sigma_{\text{all lesions}}$[products of cross-sectional diameters], no new lesions, ≥4 wk SD= ↓ by <50% or ↑ by <25% in above sum PD= ↑ by ≥25% in above sum	unspecified (blinding not mentioned)	Total +TRTx -TRTx mn md not specified rng but >5 years for the few sd patients still alive at the time of analysis
Nou 1988	survival duration	response rates and durations; first sites of recurrence or progression; adverse events; autopsy findings	CR= complete disappearance of all recognizable lesions PR= ↓ by ≥50% in longest X perpendicular diameter, Σ over all measurable lesions anything less than PR defined as "no response"	unspecified (blinding not mentioned)	Total +TRTx -TRTx mn md "minimal observation time rng of 4 years" for survivors sd (all were LSD patients)
Lebeau 1993	survival from TRTx randomization (the only outcome reported by treatment arm separately for ESD patients)	time and site of first recurrence; duration of disease-free and treatment-free survival; adverse events	CR= disappearance of all measurable and evaluable lesions PR= ↓ by ≥50% in longest and perpendicular diameter for all measurable lesions anything less than PR defined as "no response"	unspecified (blinding not mentioned)	Total +TRTx -TRTx mn md "…each patient…for at rng least 3 years." sd
Rosenthal 1991	median survival (the only outcome reported by treatment arm separately for ESD patients)	response rates; relapse rates; sites of failure; "non-tumor related" deaths (all pooled for LSD + ESD patients)	CR= not provided PR= not provided SD= not provided PD= not provided	unspecified (blinding not mentioned)	Total +TRTx -TRTx mn md "ten-year follow-up" rng sd
Brincker 1987	not specified	response rates; overall survival; time to progression	CR= total disappearance for ≥90 days of all disease manifestations PR= ↓ by ≥50% for ≥90 dys in product of longest perpendicular diameters of indicator lesion NC= response for <90 days or ↓ by <50% PD= ≥25% ↑ in size, measured as for PR (resected patients: CR if no new lesions by day 90)	"all case reviewed independently by two observers" (blinding not mentioned)	Total +TRTx -TRTx "Follow-up was complete with only 3 patients still alive at the time of analysis" (16.8, 18.9, and 47.7 months after randomization)

Question 4. Chemotherapy with versus without Thoracic Radiation Therapy, Extensive-Stage Disease
Table 4E: Survival Outcomes

Study	Overall Survival								Relapse-Free Survival (RFS) or Time to Progression (TTP)							
Jeremic 1999		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr	RFS	N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
	+TRTx	55	17	65	38	22	13	9.1	+TRTx	55	13	56	35	20	13	9.1
	-TRTx	54	11	46	28	13	5.6	3.7	-TRTx	54	9	41	22	9.3	5.6	1.9
			(p=0.041 by log-rank test)								(p=0.045 by log-rank test)					
	unrandomized groups by post-3rd cycle response (thorax/ elsewhere):								unrandomized groups by post-3rd cycle response (thorax/ elsewhere):							
	CR/PR	34	8	35	8.8	2.9	0	0	CR/PR	34	6	26	5.9	0	0	0
	PR/PR	28	6	21	3.6	0	0	0	PR/PR	28	5	18	0	0	0	0
	SD or PD	35	3	0	0	0	0	0	SD or PD	35	NR	0	0	0	0	0
Nou 1988		N	Med (mos)	1 yr	2 yr	3 yr	4 yr			N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
	+TRTx	28	9.2 (range, 3.8-19.3)	~32	0	0	0		+TRTx							
	-TRTx	26	7.6 (range, 2.2-22.7)	~26	0	0	0		-TRTx		not reported for ESD patients					
			(chi-square 0.045, 0.8<p<0.9, by life-table analysis)													
Lebeau 1993		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
	+TRTx	10	~6.3	~10	~10	0	0	0	+TRTx							
	-TRTx	8	~7.0	~25	~12	~12	0	0	-TRTx		not reported separately for ESD patients					
				(p = 0.43 by log-rank test)												
Rosenthal 1991		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
	+TRTx	?	5 (95% CI: 2-8)						+TRTx							
	-TRTx	?	7 (95% CI: 3-10)						-TRTx		not reported separately for ESD patients					
			(p=0.796)													
Brincker 1987		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr	TTP	N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
	+TRTx	16	7	~25	0	0	0	0	+TRTx	16	7	~23	0	0	0	0
	-TRTx	14	10	~30	0	0	0	0	-TRTx	14	8.5	~26	0	0	0	0
				(p = 0.44)								(p = 0.45)				

Question 4. Chemotherapy with versus without Thoracic Radiation Therapy, Extensive-Stage Disease
Table 4F: Tumor Response and Quality of Life

Study	Tumor Response (%)							Quality of Life				
Jeremic 1999		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	+TRT n -TRT n	+TRT mn+sd -TRT mn+sd
	+TRTx	55	96	(mean duration: 22 ± 26 mos)								
	-TRTx	53	66	(mean duration: 14 ± 16 mos)						NOT MEASURED		
	(local CR rates at wk 21, p = 0.00005; duration, p = 0.055)											
Nou 1988		N	CR	med duration	PR	med duration	NR	Scale	Domain	F/U	+TRT n -TRT n	+TRT mn+sd -TRT mn+sd
	+TRTx	28	11	12.4 mo	75	1.4 mo	14					
	-TRTx	26	8	12.5 mo	62	1.3 mo	31			NOT MEASURED		
Lebeau 1993		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	+TRT n -TRT n	+TRT mn+sd -TRT mn+sd
	+TRTx	10	100	(only randomized patients in CR								
	-TRTx	8	100	after 8 cycles of chemotherapy)						NOT MEASURED		
Rosenthal 1991		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	+TRT n -TRT n	+TRT mn+sd -TRT mn+sd
	+TRTx											
	-TRTx			not reported separately for ESD patients						NOT MEASURED		
Brincker 1987		N	CR	PR	NC	PD	NE	Scale	Domain	F/U	+TRT n -TRT n	+TRT mn+sd -TRT mn+sd
	+TRTx	16	12	44	25	19	0					
	-TRTx	14	7	50	29	14	0			NOT MEASURED		

Question 4. Chemotherapy with versus without Thoracic Radiation Therapy, Extensive-Stage Disease
Table 4G: Adverse Events

Toxicity Type	Study	Severity or Grade	Results
Treatment-related mortality	Jeremic 1999	not applicable	F/U (yr) +TRTx n % -TRTx n % not reported
	Nou 1988	not applicable	F/U (yr) +TRTx n % -TRTx n % all until death 28 4 26 4 (p NS)
	Lebeau 1993	not applicable	F/U (yr) +TRTx n % -TRTx n %
	Rosenthal 1991	not applicable	F/U (yr) +TRTx n % -TRTx n %
	Brincker 1987	not applicable	F/U (yr) +TRTx n % -TRTx n %
Nausea	Jeremic 1999		F/U (yr) +TRTx n % -TRTx n %
	Nou 1988		F/U (yr) +TRTx n % -TRTx n %
	Lebeau 1993		F/U (yr) +TRTx n % -TRTx n %
	Rosenthal 1991		F/U (yr) +TRTx n % -TRTx n %
	Brincker 1987	"no significant differences between the two treatment groups"	F/U (yr) +TRTx n % -TRTx n %
Vomiting	Jeremic 1999	acute grades 3/4 nausea and vomiting	F/U (yr) +TRTx n % -TRTx n % not reported 55 9 54 34 (p = 0.0038)
	Nou 1988		F/U (yr) +TRTx n % -TRTx n %
	Lebeau 1993		F/U (yr) +TRTx n % -TRTx n %
	Rosenthal 1991		F/U (yr) +TRTx n % -TRTx n %
	Brincker 1987		F/U (yr) +TRTx n % -TRTx n %

Question 4. Chemotherapy with versus without Thoracic Radiation Therapy, Extensive-Stage Disease
Table 4G: Adverse Events (continued)

Toxicity Type	Study	Severity or Grade	Results
Anorexia	Jeremic 1999		F/U (yr) +TRTx n % -TRTx n %
	Nou 1988		F/U (yr) +TRTx n % -TRTx n %
	Lebeau 1993		F/U (yr) +TRTx n % -TRTx n %
	Rosenthal 1991		F/U (yr) +TRTx n % -TRTx n %
	Brincker 1987		F/U (yr) +TRTx n % -TRTx n %
Lethargy	Jeremic 1999		F/U (yr) +TRTx n % -TRTx n %
	Nou 1988		F/U (yr) +TRTx n % -TRTx n %
	Lebeau 1993		F/U (yr) +TRTx n % -TRTx n %
	Rosenthal 1991		F/U (yr) +TRTx n % -TRTx n %
	Brincker 1987		F/U (yr) +TRTx n % -TRTx n %
Neurosensory	Jeremic 1999		F/U (yr) +TRTx n % -TRTx n %
	Nou 1988		F/U (yr) +TRTx n % -TRTx n %
	Lebeau 1993		F/U (yr) +TRTx n % -TRTx n %
	Rosenthal 1991		F/U (yr) +TRTx n % -TRTx n %
	Brincker 1987	"no significant differences between the two treatment groups"	F/U (yr) +TRTx n % -TRTx n %

Question 4. Chemotherapy with versus without Thoracic Radiation Therapy, Extensive-Stage Disease
Table 4G: Adverse Events (continued)

Toxicity Type	Study	Severity or Grade	Results
Hearing loss	Jeremic 1999		F/U (yr) +TRTx n % -TRTx n %
	Nou 1988		F/U (yr) +TRTx n % -TRTx n %
	Lebeau 1993		F/U (yr) +TRTx n % -TRTx n %
	Rosenthal 1991		F/U (yr) +TRTx n % -TRTx n %
	Brincker 1987		F/U (yr) +TRTx n % -TRTx n %
Esophagitis	Jeremic 1999	acute grades 3/4 esophageal	F/U (yr) +TRTx n % -TRTx n % not 55 27 54 0 reported (p=0.0002)
	Nou 1988		F/U (yr) +TRTx n % -TRTx n %
	Lebeau 1993	10 cases of dysphagia reported (LSD+ESD patients), but not attributed to esophagitis	F/U (yr) +TRTx n % -TRTx n %
	Rosenthal 1991		F/U (yr) +TRTx n % -TRTx n %
	Brincker 1987	no significant difference between groups in stomatitis, not attributed to esophagitis	F/U (yr) +TRTx n % -TRTx n %
Bronchopulmonary	Jeremic 1999	acute grade 3 (no grade 4, either arm)	F/U (yr) +TRTx n % -TRTx n % not 55 5 54 0 reported (p=0.082)
	Nou 1988		F/U (yr) +TRTx n % -TRTx n %
	Lebeau 1993		F/U (yr) +TRTx n % -TRTx n %
	Rosenthal 1991		F/U (yr) +TRTx n % -TRTx n %
	Brincker 1987		F/U (yr) +TRTx n % -TRTx n %

Question 4. Chemotherapy with versus without Thoracic Radiation Therapy, Extensive-Stage Disease
Table 4G: Adverse Events (continued)

Toxicity Type	Study	Severity or Grade	Results
Pneumonitis	Jeremic 1999		F/U (yr) +TRTx n % -TRTx n %
	Nou 1988		F/U (yr) +TRTx n % -TRTx n %
	Lebeau 1993	3 cases radiation pneumonitis reported (one symptomatic), but not separated by SD versus ESD	F/U (yr) +TRTx n % -TRTx n %
	Rosenthal 1991		F/U (yr) +TRTx n % -TRTx n %
	Brincker 1987	no cases observed	F/U (yr) +TRTx n % -TRTx n %
Kidney	Jeremic 1999	acute grades 3 or 4	F/U (yr) +TRTx n % -TRTx n % not 55 0 54 22 reported (p = 0.001)
	Nou 1988		F/U (yr) +TRTx n % -TRTx n %
	Lebeau 1993		F/U (yr) +TRTx n % -TRTx n %
	Rosenthal 1991		F/U (yr) +TRTx n % -TRTx n %
	Brincker 1987		F/U (yr) +TRTx n % -TRTx n %
Anemia	Jeremic 1999	acute grades 3 or 4	F/U (yr) +TRTx n % -TRTx n % not 55 11 54 20 reported (p = 0.39)
	Nou 1988	hemoglobin nadir (median, range)	F/U (yr) +TRTx n med (rng) -TRTx n med (rng) until 28 84 g/L 26 84 g/L death (62-120) (51-117)
	Lebeau 1993		F/U (yr) +TRTx n % -TRTx n %
	Rosenthal 1991		F/U (yr) +TRTx n % -TRTx n %
	Brincker 1987	hemoglobin <6 mmol/l	F/U (yr) +TRTx n % -TRTx n % until 41 ~50 37 ~27 death (LSD+ESD) (LSD+ESD)

Question 4. Chemotherapy with versus without Thoracic Radiation Therapy, Extensive-Stage Disease
Table 4G: Adverse Events (continued)

Toxicity Type	Study	Severity or Grade	Results
Thrombocytopenia	Jeremic 1999	acute grades 3/4	F/U (yr) +TRTx n % -TRTx n % not 55 27 54 42 reported (p = 0.23)
	Nou 1988	thrombocyte count nadir (10^9/L) (median, range)	F/U (yr) +TRTx n med (rng) -TRTx n med (rng) until 28 25 26 27 death (<10-140) (<10-219)
	Lebeau 1993		F/U (yr) +TRTx n % -TRTx n %
	Rosenthal 1991		F/U (yr) +TRTx n % -TRTx n %
	Brincker 1987	platelets <75x10^3/μl	F/U (yr) +TRTx n % -TRTx n % until 41 ~63 37 ~10 death (LSD+ESD) (LSD+ESD)
Leukopenia or neutropenia	Jeremic 1999	acute grade 3/4 leukopenia	F/U (yr) +TRTx n % -TRTx n % not 55 44 54 61 reported (p = 0.18)
	Nou 1988	leukocyte count nadir (10^9/L) (median, range)	F/U (yr) +TRTx n med (rng) -TRTx n med (rng) until 28 0.5 26 0.5 death (<0.1-2.7) (<0.1-3.3)
	Lebeau 1993		F/U (yr) +TRTx n % -TRTx n %
	Rosenthal 1991		F/U (yr) +TRTx n % -TRTx n %
	Brincker 1987	leukocytes < 2.5x10^3/μl	F/U (yr) +TRTx n % -TRTx n % until 41 ~37 37 ~18 death (LSD+ESD) (LSD+ESD)

Question 4. Chemotherapy with versus without Thoracic Radiation Therapy, Extensive-Stage Disease
Table 4G: Adverse Events (continued)

Toxicity Type	Study	Severity or Grade	Results
Infection	Jeremic 1999	acute grades 3-5	F/U (yr) +TRTx n % -TRTx n % not 55 23 54 33 reported (p=0.64)
	Nou 1988	septicemia number (median, range)	F/U (yr) +TRTx n med (rng) -TRTx n med (rng) until 28 2 26 1 death (0-4) (0-4)
	Lebeau 1993		F/U (yr) +TRTx n % -TRTx n %
	Rosenthal 1991		F/U (yr) +TRTx n % -TRTx n %
	Brincker 1987	febrile episodes: no significant differences between arms	F/U (yr) +TRTx n % -TRTx n %
Other	Jeremic 1999	combined late grades 3/4 toxicities	F/U (yr) +TRTx n % -TRTx n % not 55 5 54 0 reported (p = 0.082)
	Nou 1988	"other serious side effects"	F/U (yr) +TRTx n % -TRTx n % until 28 29 26 8 death (p NS)
	Lebeau 1993		F/U (yr) +TRTx n % -TRTx n %
	Rosenthal 1991		F/U (yr) +TRTx n % -TRTx n %
	Brincker 1987	tolerated 75-100% of chemoTx doses in cycles after hemibody radiation completed	F/U (yr) +TRTx n % -TRTx n % until prog. 28 25 32 91 or death (LSD+ESD) (LSD+ESD)

Question 4. Chemotherapy with versus without Thoracic Radiation Therapy, Extensive-Stage Disease
Table 4H: Study Quality Ratings

Study	Initial Assembly of Comparable Groups	Low Loss to Followup, Maintenance of Comparable Groups	Measurements Reliable, Valid, Equal*	Interventions Comparable/ Clearly Defined	Appropriate Analysis of Results	Overall Rating
Jeremic 1999	partial (arms balanced but randomization method not described)	yes	yes	yes	yes	fair
Nou 1988	partial (arms balanced but randomization method not described)	yes	yes	yes	yes	fair
Lebeau 1993	partial (arms balanced for LSD+ESD patients, but data unavailable to compare ESD only groups)	yes	yes	partial (varied TRTx regimens; lack of details on PCI regimen and patient selection	partial (only reported overall survival separately for ESD patients)	poor (to address Q4)
Rosenthal 1991	uncertain (baseline data not reported separately for treatment groups)	uncertain (conflicting information on randomization to ±TRTx)	yes	yes	partial (only reported overall survival separately for ESD patients)	poor (to address Q4)
Brincker 1987	yes	no (excluded 13/43, died before day 100)	yes	yes	partial (toxicities not reported separately for ESD group)	poor

***** Those who rated response or progression were not described as blinded or masked to patients' allocated treatment in any of these reports.

Question 6: Positron Emission Tomography for Staging of Small-Cell Lung Cancer
Table 6A: Sample Selection

Study	Design	Inclusion	Exclusion	n, Enrolled	n, Withdrawn or Excluded	n, Evaluated
Blum 2004	partially prospective, partially retrospective	histologically/cytologically proven SCLC underwent PET imaging at this institution; consecutive patients; newly diagnosed in 15 who also underwent routine initial staging, restaging in 21; in all cases, PET scan based on review of all clinical data and was performed to guide clinical management; clinical information for 19 obtained from prospective PET SCLC database; clinical information for remaining patients was derived retrospectively		36		36
Bradley 2004	prospective	newly diagnosed confirmed limited stage SCLC, completed standard staging procedures, bilateral hilar involvement defined as limited stage, ipsilateral supraclavicular adenopathy eligible	evidence of disease beyond one hemithorax and mediastinum; diabetes-related fasting hyperglycemia	25	1 (refused to undergo PET)	24
Brink 2004	prospective	consecutive patients with histologically confirmed SCLC examined with FDG-PET during primary staging		120	6 (8 sites) (discrepant findings could not be clarified because patients did not attend follow-up)	114
Kamel 2003	prospective	consecutive patients with SCLC referred at this institution for whole-body FDG-PET 2/99-1/03; PET and conventional modalities used for initial staging in 24 patients and restaging after therapy in 20 patients (both in 2)	diabetes mellitus	45	3 (incomplete data)	42
Shen 2002	retrospective	histologically confirmed SCLC; KPS $\geq$ 60%; total serum bilirubin $\leq$ 2.0 mg/dL; serum creatinine $\leq$ 2.5 mg/dL; fasting blood sugar $\leq$ 150 mg/dL	prior CTx or RTx	25		25
Schumacher 2001	unclear	histologically proven SCLC, primary staging in 24, therapy follow-up in 4, both in 2; therapy was surgery, RTx and CTx (ACO, EPI-CO, VIP-E, VIC-E); all treatment stopped $\geq$1 mo before PET		30 (36 scans, 77 sites)		30

Question 6: Positron Emission Tomography for Staging of Small-Cell Lung Cancer
Table 6B: Patient Characteristics

Study	Age (yr)	Gender (%)	Stage		Race	Performance Status (%)	Comorbidities or Prognostic Factors (%)
			Limited %	Extensive %			
Blum 2004	med 64	M 66 F 33	78	22	NR	NR	NR
Bradley 2004	mn 60 rng 33-90	M 44 F 56	87.5	12.5	NR	NR	NR
Brink 2004	mn 60.8 sd 8.9	M 75 F 25	37	63	NR	NR	NR
Kamel 2003	mn 62 rng 45-83	M 64 F 36	62.5	37.5	NR	NR	NR
Pandit 2003	mn 63.8 sd 9.6	M 41 F 59	43	57	NR	NR	NR
Shen 2002	mn 56.4 sd 7.2 rng 45-68	M 72 F 28	40	60	NR	NR	NR
Schumacher 2001	mn 57 sd 13 rng 34-78	M 77 F 23	30	70	NR	NR	NR

Question 6: Positron Emission Tomography for Staging of Small-Cell Lung Cancer
Table 6C: Test Procedure and Interpretation

Study	PET Procedure	PET Interpretation	Conventional Staging Procedure	Conventonal Staging Interpretation
Blum 2004	≥ 4 hr fast; scanner – GE Quest 300-H; images with and without transmission attenuation correction; whole-body scans of neck, thorax, abdomen; images processed using iterative reconstruction of raw and attenuation-corrected data	physician reporting the PET scans had access to the results of the previous imaging and clinical information; PET scans were interpreted qualitatively; sites of increased uptake coded as uninvolved when due to intercurrent pathology or radiation pneumonitis; PET was not reinterpreted based on subsequent clinical course; PET of brain not performed	initial staging - high-quality CT of chest, upper abdomen, brain, usually bone scan; restaging after initial treatment - CT, bone scan, X-ray; technically inadequate outside imaging studies repeated internally	NR
Bradley 2004	4-hr fast, blood glucose determination (< 150 mg/dL), patient supine, 10-15 mCi FDG, series of overlapping 2 min transmission and 5 min emission scans at each bed position, 50 min after IV injection, from upper/mid neck to upper thigh, CTI/Siemans ECAT HR+ scanner, emission images reconstructed with ordered-subset estimation-maximization iterative algorithm with segmented attenuation correction, transmission images and non-attenuation-corrected images reconstructed by filtered back projection with a mathematical attenuation correction	FDG-PET images interpreted prospectively by subjective visual assessment (with ROC grading scheme) for presence of abnormal FDG accumulation, 2 experienced nuclear physicians first independently interpreted PET blinded to results of conventional imaging studies, then observers reread PET images in combination with conventional imaging studies, final PET interpretation based on consensus of 2 observers for blinded readings; also performed semiquantitative evaluation of average maximum standardized uptake value for primary tumor and up to 5 mediastinal metastatic disease sites	history, physical exam, chest X-ray, chest CT, upper abdominal CT, bone scan, contrast-enhanced CT/MRI of brain; all conventional staging procedures completed ≤ 4 wk of PET	NR
Brink 2004	12 hr fast, IV injection 5 MBq/kg FDG; elevated fasting plasma glucose (> 6.0 mmol/L) normalized with fast-acting insulin; whole-body scan 90 min after injection; scanner –CTI ECAT EXACT 922 tomograph with 16.2 cm field of view; spatial resolution 7.0 mm FWHM; brain scan 60 min after injection; transmission scan for attenuation correction 2m, emission scan 8 min at each bed position; data corrected for dead time, decay, photon attenuation, images reconstructed by iterative algorithm using ordered set expectation-maximisation and segmented attenuation correction.	images viewed on hard copy and computer workstation, read independently by 2 investigators blinded to other data; any hot spots interpreted as either benign or malignant (focal increased tracer uptake exceeding normal regional accumulation and lesion located at typical metastatic site); images then compared, consensus reached by discussion	whole-body PET performed after CT (mean 12 d, range 1-26 d); conventional staging by history, physical exam, bronchoscopy, thoracic/abdominal contrast-enhanced CT, cranial CT/MRI in 91, bone biopsy in 84 (refused in 36)	NR

Question 6: Positron Emission Tomography for Staging of Small-Cell Lung Cancer
Table 6C: Test Procedure and Interpretation (continued)

Study	PET Procedure	PET Interpretation	Conventional Staging Procedure	Conventonal Staging Interpretation
Kamel 2003	≥ 4 hr fast, IV injection of 300-400 MBq FDG, 40-50 rest for organ uptake, , urinary voiding before scan, 2-min transmission scans, static whole-body scan covered patient from pelvic floor to head, 2 scanners (Advance NXi PET scanner, DISCOVERY LS combined PET/CT in-line device); emission scans with 4-min acquisition time at each of 6-7 bed positions; image datasets reconstructed iteratively with segmented attenuation correction in 26 patients; PET/CT device image datasets reconstructed iteratively using CT data for attenuation correction in 16 patients	pre-PET staging and post-PET staging were always performed independently; PET interpreted with all available clinical information, including CT	history, physical exam, blood tests, bronchoscopy, contrast-enhanced CT of chest, upper abdomen, bone scan, CT/MRI of brain in 9	NR
Shen 2002	6 hr fast; fasting sugar levels obtained for all; 10 mCi (370 MBq) FDG IV injection; scan after 40-50 min; scanner – Siemens-CTI EXACT HR+ or GE advance PET system; 7-8 bed positions; transmission 3 min; emission 7 min; whole-body scan	agreement of at least 2 of 3 experienced nuclear medicine specialists blind to clinical stage	within 2 wk of PET: history, physical exam, blood chemistry, chest X-ray ± chest CT/MRI, brain CT/MRI, abdominal CT/MRI ± hepatic US, pelvic CT/MRI, bone scan, bone marrow biopsy	NR
Schumacher 2001	12 hr fast; IV injection 5 MBq FDG/kg; scans started after 90 min; scanner – Siemens ECAT EXACT 921/31 tomograph; 31 planes with 10.6 cm field of view; spatial resolution 6.0 mm FWHM; transmission scan 3 min; emission scan 9 min for each of 7-9 bed positions; from subinguingal region to skull base; images produced based on ordered subset expectation maximization iterative reconstruction algorithm including segmented attenuation correction; separate brain scans in 14	2 experienced blinded independent investigators; soft tissue/bone lesions defined as focally increased tracer uptake exceeding normal limits of regional FDG uptake in the area, if lesion located in typical metastatic site, or if standardized uptake value > 4; images reviewed on hard copy and computer workstation; if observers disagreed, consensus reached, used for analysis of results	within 2 wk before or after PET: CT/MRI of brain, thorax, abdomen carried out according to standard protocols, thin-section or contrast enhancement used if needed	NR

Question 6: Positron Emission Tomography for Staging of Small-Cell Lung Cancer
Table 6D: Reference Standard Procedure and Interpretation, Management Decisions

Study	Decision Rules for Receiving Reference Standard	Reference Standard Procedure	Reference Standard Interpretation	Management Decisions
Blum 2004	NR	NR	in case of discordance, TP defined as 1) site with biopsy+; or 2) site detected only by PET with tumor progression on structural imaging within 6 mo of PET without treatment; TN defined as 1) site with negative adequate biopsy; or 2) equivocal/negative site on conventional assessment with no progression for ≥ 6 mo without treatment	when available, PET data were used to assist in RTx planning (all FDG-avid lesions included in target volume)
Bradley 2004	protocol-defined approaches for further evaluation or biopsy: PET+ intrapulmonary parenchymal metastases outside RTx portal, do biopsy; thin-cut CT- or US-guided FNA where feasible; liver PET+, do biopsy/FNA cytology; adrenal PET+, do biopsy; bone PET+, evaluate by appropriate imaging studies (X-ray, CT, MRI, repeat bone scan) or biopsy or bone scan/MRI if multiple bone metastases suspected	NR	NR	left to the discretion of the referring physician, but confirmation of potential extensive-stage disease by biopsy was encouraged
Brink 2004	if discrepancies appeared between conventional staging and PET, selective additional examinations after review by 1-3 physicians; when discordant LN results between staging examinations did not influence disease stage, no validation sought	histology in ~20%; available data; follow-up	committee of physicians (2 clinicians, 2 nuclear specialists) achieved reference standard diagnosis by consensus; when histologic results were unavailable, consensus based on sum of available data, including follow-up, non-validated results excluded from data analysis	NR
Kamel 2003	when possible, biopsies or other imaging studies were performed to resolve discrepancies between modalities;	NR	NR	it was considered unethical not to use clear but unconfirmed PET findings for further management decisions, especially those with previously unknown extensive-stage disease; an experienced radiation oncologist compared pre-PET and post-PET tumor stages and changes in RTx decisions were determined

Question 6: Positron Emission Tomography for Staging of Small-Cell Lung Cancer
Table 6D: Reference Standard Procedure and Interpretation, Management Decisions (continued)

Study	Decision Rules for Receiving Reference Standard	Reference Standard Procedure	Reference Standard Interpretation	Management Decisions
Shen 2002	if final PET interpretation suggested previously unsuspected lesion, physical exam, biopsy, CT and/or additional nuclear imaging performed	final stage was verified by pathologic findings from thoracotomyy/mediastinoscopy. other imaging results, follow-up ≥ 1 yr	NR	NR
Schumacher 2001	PET findings were compared with the sum of the findings of other staging procedures	if discrepancies between PET and other staging procedures found, selective additional examinations performed or existing images re-evaluated; in some cases, clinical follow-up proved/disproved inconsistent findings; confirmation necessary within 4 wk	NR	NR

Question 6: Positron Emission Tomography for Staging of Small-Cell Lung Cancer
Table 6E: Diagnostic Accuracy Results

Study	Test	Focus	n	TP	FN	FP	TN	Prev	Sens	Sens 95% CIL	Sens 95% CIU	Spec	Spec 95% CIL	Spec 95% CIU	PPV	NPV	DA
Blum 2004	PET	any disease	36	36	0				100%	90.3%	100%						
Bradley 2004	PET	any disease	24	24	0	1	0		100%	85.8%	100%						
Brink 2004	PET	LNs	118	53	0	1	64	44.9%	100%	93.3%	100%	98.5%	91.7%	100%	98.1%	100%	99.2%
	Conv		118	37	16	4	61	44.9%	69.8%	55.7%	81.7%	93.8%	85.0%	98.3%	90.2%	79.2%	83.1%
	PET	dist, non-brain	70	45	1	2	22	65.7%	97.8%	88.5%	99.9%	91.7%	73.0%	99.0%	95.7%	95.7%	95.7%
	Conv		70	38	8	5	19	65.7%	82.6%	68.6%	92.2%	79.2%	57.8%	92.9%	88.4%	70.4%	81.4%
	PET	brain	91	6	7	2	76	14.3%	46.2%	19.2%	74.9%	97.4%	91.0%	99.7%	75.0%	91.6%	90.1%
	Conv		91	13	0	0	78	14.3%	100%	75.3%	100%	100%	95.4%	100%	100%	100%	100%
Kamel 2003																	
Shen 2002	PET	regl mets	18	20	0	2	0		100%	83.2%	100%						
		MD/HL LNs	9	9	0	2	0		100%	66.4%	100%						
		ips SC LNs	7	7	0	0	0		100%	59.0%	100%						
		ips lung	2	2	0	0	0		100%	15.8%	100%						
		distant	24	23	1	1	0		95.8%	78.9%	100%						
		contr SC LNs	5	5	0	0	0		100%	47.8%	100%						
		contr lung	3	3	0	1	0		100%	29.2%	100%						
		liver	3	3	0	0	0		100%	29.2%	100%						
		bone/marrow	6	6	0	0	0		100%	54.1%	100%						
		brain	2	1	1	0	0		50.0%	1.3%	99%						
		adrenal	2	2	0	0	0		100%	15.8%	100%						
		other extrathorac	3	3	0	0	0		100%	29.2%	100%						
Schumacher 2001																	

Question 6: Positron Emission Tomography for Staging of Small-Cell Lung Cancer
Table 6F: Staging Accuracy Results

Study	Test	Use	Correctly Upstaged #	Correctly Upstaged %	Incorrectly Upstaged #	Incorrectly Upstaged %	Correctly Downstaged #	Correctly Downstaged %	Incorrectly Downstaged #	Incorrectly Downstaged %	Identified Unsuspected Metastases Site	Identified Unsuspected Metastases #	Identified Unsuspected Metastases %	Ruled Out Suspected Metastases Site	Ruled Out Suspected Metastases #	Ruled Out Suspected Metastases %	Missed Metastases Site	Missed Metastases #	Missed Metastases %
Blum 2004	PET	staging	3	20															
Bradley 2004	PET	staging	1	4.2	1	4.2					lung regl LNs	1 6	4.2 25						
Brink 2004	PET	staging	10	8.3			3	2.5									brain	1	0.8
Kamel 2003	PET	staging	3	12.5	0	0	1	4.2	0	0	visceral/ soft tissue	1	4.2	adrenal	1	4.2	brain	2	8.3
		restaging	1	5	1	5	2	10	0	0	lung breast/ axilla	1 1	5 5	LN bone	2 1	10 5	LN	1	5
Shen 2002	PET	staging	1	4	0	0	1	4	0	0									
Schumacher 2001	PET	staging	5	19.2															
		restaging	1	16.7															

Question 6: Positron Emission Tomography for Staging of Small-Cell Lung Cancer
Table 6G: Patient Management and Other Results

Study	Test	Use	PET Changed Patient Management #	%	Changes	Other Findings
Blum 2004	PET	staging	4	26.7	forgone RTx for ED	in 11 of 14 discordant disease sites (79%) PET was found to be accurate; 9 of 25 follow-up patients achieved PET CR and had 13.7 mo median time to progression, compared with 9.7 mo for non-CR
			1	6.7	ED, received palliative CTx/RTx	
			2	13.3	RTx target volume changed	
		restaging	3	12	PCI omitted	
			3	12	PCI selected	
			2	8	forgone CTx, observation for NED	
Bradley 2004	PET	Staging	7	29.2	RTx target volume changed	PET correctly identified tumor in each primary or nodal SCLC mass that was suspected on CT; unblinded PET more accurate than blinded; PET found no brain metastases (all CT/MRI negative); blinded interobserver agreement 83%; unblinded interobserver agreement 96%
Brink 2004	PET		10	8.3	forgone RTx for ED	complete agreement between PET and other staging procedures in 75 patients; differences occurred in 45 patients at 65 sites (PET correct in 47/65, PET incorrect in 10/65, unconfirmed in 8/65); interobserver agreement kappa 0.94
			3	2.5	selected CTx/RTx	
			1	0.8	missed brain metastasis, affected treatment	
Kamel 2003	PET	either	12	29		incongruence between PET and anatomic imaging in 9 patients, but mismatch did not change final staging decision
		staging	9	37	forgone RTx for ED (3) altered radiation field (5) selected surgery (1)	
		restaging	3	15	CTx reinstituted (1) CTx discontinued (2)	
Shen 2002						41 of 42 (97.6%) metastases were identified by PET; there were 3 PET FPs and 1 FN
Schumacher 2001						PET and other staging tests agreed in 23 of 36 evaluations (6 for LD, 12 for ED, 5 for NED); disagreed in 13 patients (17 sites); 3 PET FPs (1 brain)

Question 6: Positron Emission Tomography for Staging of Small-Cell Lung Cancer
Table 6G: Study Quality Ratings

Study	Representative sample?	Clear Selection Criteria?	Reference standard correctly classifies target condition?	Period between test, reference standard short enough?	Whole sample or random selection received reference standard?
Blum 2004	Unclear	Unclear	Unclear	Unclear	Yes
Bradley 2004	Yes	Yes	Unclear	Unclear	Yes
Brink 2004	Unclear	Unclear	Unclear	Unclear	Yes
Kamel 2003	Unclear	Unclear	Unclear	Unclear	Yes
Shen 2002	Unclear	Unclaar	Unclear	Unclear	Yes
Schumacher 2001	Unclear	Unclear	Unclear	Unclear	Yes

Study	Patients received reference standard regardless of test results?	Reference standard independent of test?	Test execution sufficiently described?	Reference standard execution sufficiently described?
Blum 2004	Unclear	Unclear	Yes	No
Bradley 2004	Unclear	Yes	Yes	No
Brink 2004	No	Yes	Yes	No
Kamel 2003	Unclear	Unclear	Yes	No
Shen 2002	No	Unclear	No	No
Schumacher 2001	No	Unclear	Yes	No

Study	Test results interpreted blind to reference standard?	Reference standard results interpreted blind to test?	Clinical practice data available for test interpretation?	Uninterpretable/ indeterminate results reported?	Withdrawals explained?
Blum 2004	Unclear	Unclear	Yes	No	Yes
Bradley 2004	Unclear	Unclear	Yes/No	No	Yes
Brink 2004	Yes	Unclear	No	No	Yes
Kamel 2003	Unclear	Unclear	Yes	No	Yes
Shen 2002	Unclear	Unclear	No	No	Yes
Schumacher 2001	Unclear	Unclear	No	Yes	Yes

Question 8. Surgery versus No Surgery for Limited-Stage Disease
Table 8A: Sample Selection

Study	Inclusion	Exclusion	n, Randomized	n, Withdrawn	n, Evaluated for Primary Outcome
Lad et al. 1994 multicenter European/American trial (LCSG/ECOG/ EORTC) accrual 1983-89	confirmed diagnosis of pure SCLC histology; limited stage disease (one hemithorax with negative supraclavicular nodes and no pleural effusion); "fit for thoracotomy"; CR or PR after 5 cycles of CAV; resectable disease; normal brain CT scan	"true T1NOM0 small cell lesions: peripheral nodules"; supraclavicular nodal mets.; pleural, pericardial effusion; super. vena cava syndrome; esophageal invasion; <PR after 5 cycles of CAV; unresectable disease; unfit for thoracotomy	Total +Surg -Surg 146 70 76 [71 responders refused randomization post CAV]	Total +Surg -Surg 0 0 0	Total +Surg -Surg 146 70 76
Liao et al. 1995 one center RCT (Shanghai) accrual 1/90-12/91	stage II or III lung cancer (40 SCLC and 40 NSCLC, randomized separately, and outcomes reported separately); no other inclusion criteria reported	none reported	Total +Surg -Surg 40 20 20	Total +Surg -Surg 0 0 0	Total +Surg -Surg 40 20 20
Badzio et al. 2004; 2005 retrospective "pair-matched case-control" study single institution (Poland) accrual 1984-96	surgery if thoracotomy needed to establish diagnosis; stages I-IIIA; included if pre-op data sufficient for clinical staging; controls: suitable for surgery (one involved hemithorax, neg. ipsilateral supraclavicular nodes);	surgical patients: inadequate data for accurate clinical staging; controls: pleural effusion; "low performance status"; pair matched for: PS, clinical T and N stages, sex	Total +Surg -Surg 76 176 7 +Surg w inadequate pre-op. data for clinical staging 2 +Surg not matched to –Surg controls	Total +Surg -Surg 9 109 109 -Surg patients not matched to +Surg	Total +Surg -Surg 134 67 67 (23 in CR)
Shepherd et al. 1989 prospective multicenter study (Toronto); adjuvant surgery post chemo Tx; compared operated with not operated patients	confirmed SCLC by histology or cytology; central lesions; surgical candidates (defined as N1 or early N2 disease; or T3 N0)	peripheral nodule; extensive disease; medically unfit for surgery	Total +Surg -Surg 72 38 34	Total +Surg -Surg 15 15 ineligible for surgery post chemoTx for: poor response, 9 became unfit, 3 died in month1, 2 lost to follow-up, 1	Total +Surg -Surg 57 38 19 not operated since: randomized to only radiation (diff. protocol) n=10; refused operation, 9
Namikawa et al. 1994 retrospective analy-sis of one-center (Japan) series; treated 1960-86	all non-metastatic SCLC treated over study period	stage IV disease	Total +Surg -Surg 101 58 43 resected 43 explored 15	Total +Surg -Surg 0 0 0	Total +Surg -Surg 101 58 43
Hara et al. 1991a, 1991b; retrospect-tive analysis of one-center (Japan) series; 1972-89	stages I, II or IIIA histologically or cytologically proven localized SCLC; selected for surgery if technically resectable	stage > IIIA; non-resectable for: tumor extension into adjacent structures, medical contra-indications, refusal	Total +Surg -Surg 81 36 45	Total +Surg -Surg 0 0 0	Total +Surg -Surg 81 36 45

Question 8. Surgery versus No Surgery for Limited-Stage Disease
Table 8A: Sample Selection (continued)

Study	Inclusion	Exclusion	n, Randomized	n, Withdrawn	n, Evaluated for Primary Outcome
Friess et al. 1985 retrospective analysis of patients enrolled in SWOG 7628 trial, 1977-9	limited disease (1 hemithorax and ipselateral supraclavicular nodes); compared survival of those who underwent surgery before randomization to those not resected	extensive stage disease	Total +Surg -Surg 262 16 246	Total +Surg -Surg 1 1 0 one surgical patient had carcinoid, not SCLC	Total +Surg -Surg 261 15 246
Osterlind et al. 1985; retrospective analysis of patients from 6 trials at 2 Danish institutions, 3/73-9/81	histologically confirmed SCLC; no prior therapy but resection; no distant metastasis; operable based on bronchoscopy, mediastinoscopy and lung function tests	no pre-operative diagnosis (i.e., undergoing diagnostic thoracotomy); distant metastasis; mediastinoscopy not done	Total +Surg -Surg 79 33 46	Total +Surg -Surg 0 0 0	Total +Surg -Surg 79 33 46
Rostad et al. 2004 retrospective analysis, Cancer Registry of Norway; all cases 1993-9	all technically operable (T1 or T2, N0, M0) limited stage (Ia or Ib) SCLC cases in Norway	extensive disease; technically inoperable; medical contra-indication to surgery	Total +Surg -Surg 38 96	Total +Surg -Surg 18 (given adjuv. chemoTx)	Total +Surg -Surg 29 96
George et al. 1986 population-based registry analysis; all SCLC cases in Rochester, NY; 1975-81	limited disease (one hemithorax with or without ipsilateral hilar, supraclavicular or mediastinal lymph node involvement	extensive disease; pleural effusion; inadequate data in chart for staging or evaluation	Total +Surg -Surg 151	Total +Surg -Surg 52 (17, improper entry; 3, 2nd malignancy; 13, dead week 1; 1, refused Tx; 12, pathol. unavail.; 4, mixed histol.; 2, NSCLC	Total +Surg -Surg 101 13 88 (CTx only 43) (Rtx only 20) (CTx+RTx 25)

Question 8. Surgery versus No Surgery for Limited-Stage Disease
Table 8B: Patient Characteristics

Study	Age (yr)	Gender (%)	Race (%)	Performance Status (%)	Comorbidities or Prognostic Factors (%)
Lad et al. 1994 multicenter European/American trial (LCSG/ECOG/ EORTC) accrual 1983-89	+Surg -Surg mn md 59 rng 35-72 sd "groups evenly matched"	+Surg -Surg M 65 F 35 "groups evenly matched"	+Surg -Surg B W 92 O "groups evenly matched"	KPS +Surg -Surg ≥9 82 "groups equally balanced"	+Surg -Surg ≤10% weight loss 92 >5 cm^2 resid tumor 5 "groups equally balanced"
Liao et al. 1995 one center RCT (Shanghai) accrual 1/90-12/91	+Surg -Surg mn 50 54.4 md rng 33-74 31-66 sd	+Surg -Surg M 90 90 F 10 10	+Surg -Surg B not W reported O	+Surg -Surg NOT REPORTED	+Surg -Surg clinical stage: II 10 5 III 90 95
Badzio et al. 2004; 2005 retrospective "pair-matched case-control" study	+Surg -Surg mn 57 54 md rng 29-70 36-71 sd p=0.03	+Surg -Surg M 85 78 F 15 22 p=0.27	+Surg -Surg B not W reported O	WHO +Surg -Surg 0 60 58 1 36 33 2 4 9 p=0.57	+Surg -Surg % T1/T2 14/86 17/83 %N0/N1/N2 37/33/30 38/31/30 clinical stage: % 1/2/3 39/32/29 37/33/30 mean tumor size (cm) (range) 26 (1-96) 21 (1-64)
Shepherd et al. 1989; prospective multi-center study (Toronto); adjuvant surgery post chemo Tx; compared those given vs. not given surgery	+Surg -Surg mn md 60 59 rng 39-77 44-75 sd	+Surg -Surg M 68 53 F 32 47	+Surg -Surg B not W reported O	+Surg -Surg NOT REPORTED	+Surg -Surg (%) stage I 29 32 stage II 34 5 stage III 37 63
Namikawa et al. 1994 retrospective analysis of one- center (Japan) series; treated 1960-86	+Surg -Surg mn md NOT rng REPORTED sd	+Surg -Surg M NOT F REPORTED "proportion of women higher" in -Surg group	+Surg -Surg B not W reported O	+Surg -Surg NOT REPORTED	+Surg -Surg mean time from "onset" to initiation of treatment (months): resected: 2.4 3.1 explored: 2.9
Hara et al. 1991a, 1991b retrospective analysis of one- center (Japan) series; treated 1972-89	+Surg -Surg mn 64 63 md rng 44-76 45-83 sd	+Surg -Surg M 83 84 F 17 16	+Surg -Surg B not W reported O	ECOG +Surg -Surg 0 50 18 1 44 78 2 6 4	clinical stage +Surg -Surg I 33 4 II 31 13 IIIA 36 82

Question 8. Surgery versus No Surgery for Limited-Stage Disease
Table 8B: Patient Characteristics (continued)

Study	Age (yr)	Gender (%)	Race (%)	Performance Status (%)	Comorbidities or Prognostic Factors (%)
Friess et al. 1985; retrospective analysis of patients enrolled in SWOG 7628 trial, 1977-9	+Surg -Surg mn md NOT rng REPORTED sd	+Surg -Surg M NOT F REPORTED	+Surg -Surg B not W reported O	+Surg -Surg NOT REPORTED	age, sex, and initial PS of surgical subset was "no different" from the nonresected group
Osterlind et al. 1985; retrospective analysis of patients from 6 trials at 2 Danish institutions, 3/73-9/81	+Surg -Surg mn 55 60 md rng sd 8 6	+Surg -Surg M 82 72 F 18 28	+Surg -Surg B not W reported O	AJC[1] +Surg -Surg 0-1 83 91 2 17 6 3-4 0 3	+Surg -Surg symptom duration, months (med, rng): 2 (0-9) 3 (1-12) bone marrow or liver involvement: 9 11 LDH>ULN[2]: 50 22 AST>ULN[2]: 20 17
Rostad et al. 2004 retrospective analysis, Cancer Registry of Norway; all cases 1993-9	+Surg -Surg mn md "no age differ- rng ence" between sd groups	+Surg -Surg M NOT F REPORTED	+Surg -Surg B not W reported O	+Surg -Surg NOT REPORTED	+Surg -Surg
George et al. 1986; population-based registry analysis; all SCLC cases in Rochester, NY; 1975-81	all 101 31-40 2% 41-50 12% 51-60 29% 61-70 38% 71-80 14% >80 5%	all 101 M 65% F 35%	+Surg -Surg B W not O reported	+Surg -Surg not reported	22% enrolled on an ECOG trial protocol

[1] American Joint Committee for Cancer Staging, 1979

Question 8. Surgery versus No Surgery for Limited-Stage Disease
Table 8C: Treatments

Study	Chemotherapy regimen, per protocol	Surgical Procedures (+Surgery arm)	TRTx (if included)	PCI
Lad et al. 1994 multicenter European/American trial; accrual 1983-89	Agent / Dose / Schedule Cytoxan 1 g/m^2 day 1, q3wk, X5 doxorubicin 50 mg/m^2 day 1, q3wk, X5 vincristine 1.4 mg/m^2 day 1, q3wk, X5	thoracotomy and attempted resection: 54 complete, 4 partial resections; 12 unresectable (open & close)	Dose / Schedule 50 Gy 25 fractions, after surgery for + arm	30 Gy in 15 fracs; at same time as TRTx
Liao et al. 1995 one center RCT (Shanghai) accrual 1/90-12/91	Agent / Dose / Schedule ifosfamide 1.2 g/m^2 days 1-5 MESNA 400 mg days 1-5 doxorubicin 50 mg/m^2 day 1 vincristine 1 mg/m^2 day 1 (2-3 cycles initially, then surg or RTx, then 4 additional cycles; duration of cycles not reported)	procedures not described; surgery done after chemotherapy cycle 2 for most, cycle 3 for a few (#'s not reported); up to 4 more chemotherapy cycles post-operatively	Dose / Schedule TRTx used only in -surg arm, after 1st 2-3 cycles; dose and schedule not reported; up to 4 more chemotherapy cycles post TRTx	NOT REPORTED
Badzio et al. 2004; 2005 retrospective "pair-matched case-control" study	surgical patients given one of four regimens post-op: CAV, 4-8 cycles; CDE, 4-6 cycles; PE, 4-6 cycles; or MCCC/CAV/VI; control patients given CCMV or ACOM doses and schedules not reported	pneumonectomy, n=30; lobectomy, n=37	Dose / Schedule 30, 40 or 50 Gy n=39 from -surg arm only; in 10, 20 or 25 fractions, respectively	n=23 from, +surg arm only; doses and schedules not reported
Shepherd et al. 1989; prospective multi-center study (Toronto); adjuvant surgery post chemo Tx; compared those given vs. not given surgery	various regimens for variable number of cycles, including: CAV, 1-6 cycles, n=29 resected, 33 of 34 not resected; CAV+etoposide, 5 cycles, n=1 resected; PE, 3-6 cycles, n=2 resected, 1 of 34 not resected (chemotherapy regimens reported only for all 34 non-resected patients, eligible or ineligible)	of 38 patients who underwent thoracotomy, 8 required pneumonectomy, 25 had lobectomy, 5 not resected at thoracotomy (4 had unresectable disease; 1 had no identifiable residual tumor to resect); all had radical mediastinal lymph node dissection no thoracotomy for any –Surg patients	post-operative radiotherapy to tumor bed and mediastinum; total dose ranged from 25 Gy in 10 fracs. to 35 Gy in 20 fracs. -Surg patients "received the same radiotherapy at completion of chemotherapy"	20 Gy in five fracs, whole brain radioTx
Namikawa et al. 1994 retrospective single-center (Japan) series; treated 1960-86	NOT REPORTED	NOT REPORTED	NOT REPORTED	NOT REPORTED
Hara et al. 1991a 1991b retrospective analysis of one-center (Japan) series; treated 1972-89	various regimens for both +surg and –surg groups; VCMC 13 25 CAV 3 9 PE 4 3 CAV + PMP 4 1 CAV + CVMP 2 0 CAV + PE 8 5 others 2 2 (doses and schedules reported but not abstracted)	n=19, surgery→ adjuvant chemotherapy N=17, neoadj. chemoTx→surgery; complete pneumonectomy, 4 lobectomy, 27 bilobectomy 5 surgery "complete" 31 surgery "incomplete" 5	Dose / Schedule 46 Gy (avg) 30-70 Gy (range) 1.4-2.0 Gy daily in 25-36 fractions	NOT REPORTED

Question 8. Surgery versus No Surgery for Limited-Stage Disease
Table 8C: Treatments (continued)

Study	Chemotherapy regimen, per protocol	Surgical Procedures (+Surgery arm)	TRTx (if included)	PCI
Friess et al. 1985 retrospective analysis of patients enrolled in SWOG 7628 trial, 1977-9	all patients randomized to one of 4 treatment arms that "…included chemotherapy followed by radiation therapy to the primary site and whole brain prophylaxis." Surgical subset evenly and randomly distributed to 4 treatment arms (5, 3, 3, and 4)	12 lobectomy 3 pneumonectomy	2 courses 30 Gy with 15 Gy optional boost	NOT REPORTED
Osterlind et al. 1985; retrospective analysis of patients from 6 trials; 2 Danish institutions, 3/73-9/81	various regimens for both +surg and –surg groups; CCM 10 10 CCMV 19 17 CCMV+doxorubicin+ etoposide 4 19 (doses and schedules not reported)	11 (33%), complete resection 13 (39%), partial resection 9 (27%), neither pneumonectomy nor lobectomy (<partial resection)	+surg: n=11 (33%) -surg: n=15 (33%) no details re dose or schedule	+ surg: n=4 (12%) -surg: n=3 (7%) no details re dose, schedule
Rostad et al. 2004 retrospective analysis, Cancer Registry of Norway; all cases 1993-9	NOT REPORTED (for technically operable but not resected group; "The majority treated with combined chemotherapy or concurrent chemo-radiotherapy" using doxorubicin, cyclophosphamide, vincristine, or cisplatin based regimens)	lobectomy: 15 stage Ia, 5 stage Ib bilobectomy: 3 stage Ia, 1 stage Ib pneumonect.: 3 stage Ia, 4 stage Ib minor resect.: 5 stage Ia, 1 stage Ib 1 unknown, for stage or surgery	NO DETAILS REPORTED	NOT SPECIFIED
George et al. 1986; population-based registry analysis; all SCLC cases in Rochester, NY; 1975-81	CTx or CTx+RTx patients given CCM, CMVP, CC, or CAV doses and schedules not specified	not specified; of total n=13, 10 given adjuvant chemotherapy and 2 given adjuvant radiation therapy	NO DETAILS REPORTED	NOT SPECIFIED

Question 8. Surgery versus No Surgery for Limited-Stage Disease
Table 8D: Outcome Assessment

Study	Primary Outcomes	Secondary Outcomes	Response Criteria	Observer	F/U
Lad 1994 multicenter European/Ameri-can trial; accrual 1983-89	mortality (90% probability to detect HR = 2 at 2-sided p=0.05, assuming median OS = 30 mos in superior arm)	surgical success rate; sites of treatment failure; survival by TNM stage;	CR= no evidence of SCLC by pathology PR= NOT REPORTED SD= PD=	NOT SPECIFIED	Total +Surg -Surg mn md NOT REPORTED rng sd
Liao et al. 1995 one center RCT (Shanghai) accrual 1/90-12/91	overall survival; power analysis not reported	complete responses; rates of local relapse, distant metastasis	CR= PR= "WHO tumor treatment remission rate SD= standards" (not described or referenced) PD=	NOT SPECIFIED	Total +Surg -Surg mn md NOT REPORTED rng sd
Badzio et al. 2004; 2005 retrospective "pair-matched case-control" study	overall survival from time of diagnosis	time to local relapse or progression;	CR= PR= NOT REPORTED SD= PD=	NOT SPECIFIED	Total +Surg -Surg mn md 72 mos rng sd
Shepherd et al. 1989; prospec-tive multi-center study (Toronto); adjuvant surgery post chemo Tx; compared those given vs. not given surgery	overall survival from start of pre-op chemoTx to date of death or last follow-up	responses to pre-op chemoTx; survival by clinical and patho-logic (-Surg only) stage; sites of relapse	CR= PR= NOT REPORTED SD= PD=	NOT SPECIFIED	Total +Surg -Surg mn md NOT REPORTED rng but "…all patients… sd followed… for at least 1 year."
Namikawa et al. 1994 retrospective analysis of one-center (Japan) series; treated 1960-86	overall survival	none	CR= PR= NOT REPORTED SD= PD=		Total +Surg -Surg mn md NOT REPORTED rng sd
Hara et al. 1991a 1991b; retro-spective analysis of one-center (Japan) series; treated 1972-89	overall survival	response rates (pre-operative chemoTx and –Surg groups); sites of relapse; operative mortality	CR= no clinical evidence of disease PR= >50%↓, sum of shortest+longest dimensions of all measurable lesions for ≥4 wks SD= no objective progression or regression PD= definite progression of disease	NOT SPECIFIED	Total +Surg -Surg mn md NOT REPORTED rng sd

Question 8. Surgery versus No Surgery for Limited-Stage Disease
Table 8D: Outcome Assessment (continued)

Study	Primary Outcomes	Secondary Outcomes	Response Criteria	Observer	F/U
Friess et al. 1985 retrospective analysis of patients enrolled in SWOG 7628 trial, 1977-9	overall survival	none	NOT APPLICABLE	NOT APPLIC-ABLE	mn md rng sd Total +Surg -Surg NOT REPORTED
Osterlind et al. 1985; retrospec-tive analysis of patients from 6 trials; 2 Danish institutions, 3/73-9/81	overall survival	disease-free survival; relapse rate	CR= PR= NOT REPORTED SD= PD=	NOT SPECIFIED	mn md rng 3-9+ yr sd Total +Surg -Surg
Rostad et al. 2004 retrospective analysis, Cancer Registry of Norway; all cases 1993-9	overall survival	none	CR= PR= NOT REPORTED SD= PD=	NOT RELEVANT	mn md rng sd Total +Surg -Surg NOT REPORTED
George et al. 1986; population-based registry analysis; all SCLC cases in Rochester, NY; 1975-81	overall survival from time of diagnosis	response rates (non-surgical patients)	CR= PR= Used "…standard ECOG criteria determined SD= by the treating physician at the time" PD=	NOT SPECIFIED	mn md rng sd Total +Surg -Surg 48 mos

Question 8. Surgery versus No Surgery for Limited-Stage Disease
Table 8E: Survival Outcomes

Study	Overall Survival (%)								Time to Relapse or Progression (TTR/P)							
		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
Lad 1994 multicenter European/American trial; accrual 1983-89	+surg	70	15.4	~60	20	~20	~20	~20	+surg							
	-surg	76	18.6	~65	20	~20	~20	~20	-surg			NOT REPORTED				
				(log rank p=0.78)												
Liao et al. 1995 one center RCT (Shanghai) accrual 1/90-12/91		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
	+surg	20		79	52	24			+surg							
	-surg	20		63	18	18			-surg			NOT REPORTED				
				(log rank p=0.12; t-test for OS at 2 yr, p<0.05)												
Badzio et al. 2004, 2005; retrospective matched pair case-control		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
	+surg	67	22.3	70	43	~35	~30	27	+surg	67	20.9					
	-surg	67	11.2	45	17	~12	~4	4	-surg	67	7					
	in CR	23	22		36			26			(p < 0.001)					
			(p < 0.001; HR = 0.42; 95% CI: 0.28, 0.61)													
Shepherd et al. 1989; prospective multi-center study (Toronto); adjuvant surgery post chemo Tx; compared those given vs. not given surgery		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
	+surg	38	22.8	~63%	~47%	~36%	~36%	36%	+surg							
	-surg	19	11.8	~48%	~10%	~10%	~10%		-surg			NOT REPORTED				
			(p=0.049)													
Namikawa et al. 1994 retrospective analysis of one-center (Japan) series; treated 1960-86		N	Mn (mos)	1 yr	2 yr	3 yr	4 yr	5 yr		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
	+surg resect.	43	8.1						+surg							
	eplor.	15	5.1						-surg			NOT REPORTED				
				(statistical test result not stated)												
	-surg	43	5.2													
Hara et al. 1991a 1991b retrospective analysis of one-center (Japan) series; treated 1972-89		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
	+surg	36	33			56		38	+surg							
	-surg:								-surg			NOT REPORTED				
	CR	19	24.5			~32		21								
	PR	20	12.5					0								
	SD/PD	6	6.5					0								

Question 8. Surgery versus No Surgery for Limited-Stage Disease
Table 8E: Survival Outcomes (continued)

Study	Overall Survival (%)								Time to Relapse or Progression (TTR/P)							
Friess et al. 1985 retrospective analysis of patients enrolled in SWOG 7628 trial, 1977-9		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
	+surg	15	25		44				+surg							
	-surg	246	10.5		13.7				-surg			NOT REPORTED				
			(p=0.0037)		(p<0.05)											
	-surg, selected for "similar initial presentation" as +surg:															
		33	10 (range, 1-46+; p=0.03)													
Osterlind et al. 1985; retrospec-tive analysis of patients from 6 trials; 2 Danish institutions, 3/73-9/81		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr	DFS	N	Med (mos)	1.5 yr	2 yr	3 yr	4 yr	5 yr
	+surg	33		~37	~16	~14	~14		+surg	33		15	12			
	-surg	46		~50	~16	~10	~8		-surg	46		15	13			
	(p=0.35 by life table analysis)															
Rostad et al. 2004 retrospective analysis, Cancer Registry of Norway; all cases 1993-9		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
	+surg	29						44.9	+surg							
							95% CI:	23.9, 65.9	-surg			NOT REPORTED				
	-surg	96						11.3								
							95% CI:	4.2, 18.4								
George et al. 1986; population-based registry analysis; all SCLC cases in Rochester, NY; 1975-81		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr		N	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
	+surg	13	30.8	~70	~56	~46	~40	~40	+surg							
	-surg	88	12.4						-surg			NOT REPORTED				
	CTx	43	11.9	~43	~15	~10	~4	0								
	RTX	20	13.4	~58	~20	~20	~20	~18								
	both	25	14.1													
				(p=0.009 versus –surg)												

Question 8. Surgery versus No Surgery for Limited-Stage Disease
Table 8F: Tumor Response and Quality of Life

Study	Tumor Response (%)							Quality of Life						
Lad 1994 multicenter RCT; accrual 1983-89		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	+surg n	-surg n	+surg mn+sd	-surg mn+sd
	+surg	70	19											
	-surg	76	NOT REPORTED								NOT MEASURED			
Liao et al. 1995 one center RCT (Shanghai) 1/90-12/91		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	+surg n	-surg n	+surg mn+sd	-surg mn+sd
	+surg	20	70											
	-surg	20	80								NOT MEASURED			
Badzio et al. 2004, 2005; retrospect-tive "matched pair case-control" study		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	+surg n	-surg n	+surg mn+sd	-surg mn+sd
	+surg													
	-surg		NOT REPORTED								NOT MEASURED			
Shepherd et al. 1989; prospective multicenter trial (Toronto); adjuvant surgery post chemoTx; compared those given vs. not given surgery		N	CR	PR	SD	NC/PD	ED*	Scale	Domain	F/U	+surg n	-surg n	+surg mn+sd	-surg mn+sd
	+surg	38	45	50	---	5	0							
	-surg	34	29	32	---	32	6				NOT MEASURED			
	all	72	38	42	---	18	3							
	*ED = early death													
Namikawa et al. 1994 retrospective analysis, one-center (Japan) series; treated 1960-86		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	+surg n	-surg n	+surg mn+sd	-surg mn+sd
	+surg													
	-surg		NOT REPORTED								NOT MEASURED			
Hara et al. 1991a 1991b; retrospec-tive analysis of one-center (Japan) series; treated 1972-89		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	+surg n	-surg n	+surg mn+sd	-surg mn+sd
	+surg		NOT APPLICABLE											
	-surg	45	42.5	44		13.5					NOT MEASURED			

Question 8. Surgery versus No Surgery for Limited-Stage Disease
Table 8F: Tumor Response and Quality of Life (continued)

Study	Tumor Response (%)							Quality of Life						
Friess et al. 1985; retrospective analysis of patients enrolled in SWOG 7628 trial, 1977-9		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	+surg n	-surg n	+surg mn+sd	-surg mn+sd
	+surg													
	-surg		NOT REPORTED								NOT MEASURED			
Osterlind et al. 1985; retrospec-tive analysis of patients from 6 trials; 2 Danish institutions, 3/73-9/81		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	+surg n	-surg n	+surg mn+sd	-surg mn+sd
	+surg													
	-surg		NOT REPORTED								NOT MEASURED			
Rostad et al. 2004 retrospective analysis, Cancer Registry of Norway; all cases 1993-9		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	+surg n	-surg n	+surg mn+sd	-surg mn+sd
	+surg													
	-surg		NOT REPORTED								NOT MEASURED			
George et al. 1986; population-based registry analysis; all SCLC cases, Rochester, NY; 1975-81		N	CR	PR	SD/NR	PD	NE	Scale	Domain	F/U	+surg n	-surg n	+surg mn+sd	-surg mn+sd
	+surg	13	92	0	0	8	0							
	-surg	88	32											
	CTx	43	12	25	16	47	0				NOT MEASURED			
	RTx	20	55	10	15	20	0							
	both	25	48	40	4	8	0							

Question 8. Surgery versus No Surgery for Limited-Stage Disease
Table 8G: Adverse Events

Toxicity Type	Study	Severity or Grade	Results
Treatment-related (operative) mortality	Lad et al. 1994	not applicable	F/U (yr) not reported; +surg n 70; % 2.9; -surg n 76; % not reported
	Liao et al. 1994	not applicable	F/U (yr) not reported; +surg n 20; % 0; -surg n 20; % 0
	Badzio et al. 2004, 2005	not applicable	F/U (yr); +surg n; %; -surg n; % NOT REPORTED
	Shepherd et al. 1989	not applicable	F/U (yr) >1; +surg n 38; % 0; -surg n eligible 19; [2 of 72 (3%) died after 1st course of chemoTx]
	Namikawa et al. 1994	not applicable	F/U (yr); +surg n; %; -surg n; % NOT REPORTED
	Hara et al. 1991a, 1991b	not applicable	F/U (yr) not reported; +surg n 36; % 0; -surg n 45; % not reported
	Friess et al. 1985	not applicable	F/U (yr); +surg n; %; -surg n; % NOT REPORTED
	Osterlind et al. 1985	not applicable	F/U (yr) 3-9+; +surg n; %; -surg n; % NOT REPORTED
	Rostad et al. 2004	not applicable	F/U (yr); +surg n; %; -surg n; % NOT REPORTED
	George et al. 1986	not applicable	F/U (yr) 3.7 (mn); +surg n 13; % 0; -surg n 88; % 1 (given CTx+RTx)

Shepherd et al. (1989) is the only study that reported postoperative complications other than mortality. Among 38 resected, they observed:

1 severe bronchospasm (2.6%)
1 prolonged atelectasis (2.6%)
1 pulmonary edema (2.6%)
2 transient arrhythmias (5.3%)
1 assisted ventilation for 6 weeks (2.6%)

Question 8. Surgery versus No Surgery for Limited-Stage Disease
Table 8H: Study Quality Ratings

Study	Initial Assembly of Comparable Groups	Low Loss to Followup, Maintenance of Comparable Groups	Measurements Reliable, Valid, Equal	Interventions Comparable/ Clearly Defined	Appropriate Analysis of Results	Overall Rating
Lad et al. 1994 multicenter RCT European/American	uncertain (report states groups "evenly matched" but baseline data pooled across arms)	yes (all randomized patients included in analysis)	yes	yes	uncertain peri-operative mortality only reported adverse event	fair
Liao et al. 1995 one center RCT (Shanghai)	uncertain insufficient data on baseline character-istics (no data on performance status)	no 15-20% per arm lost to follow-up	yes	uncertain extent of surgery, TRTx regimen not reported	uncertain operative complications not reported	poor
Badzio et al. 2004 retrospective "pair-matched case-control" one-center study	uncertain not randomized; "pair-matched case-control" study; groups differed significantly in age	yes (all matched pairs followed and analyzed)	yes	uncertain regimens, doses varied and not specified	no no data on adverse events	poor
Shepherd et al. 1989; prospective multi-ctr study (Toronto); adjuvant surgery post chemo Tx; compared those given vs. not given surgery	uncertain not randomized; more females, stage III patients in -Surg group; more males, stage II patients in +Surg group	yes all followed and analyzed	yes	uncertain regimens, doses varied and inadequately specified	yes most complete reporting on operative complications	fair
Namikawa et al. 1994 retrospective analy-sis, one-center series	no not randomized; inadequate data comparing base-line characteristics	yes all followed and analyzed	yes	uncertain regimens, doses varied and not specified	no statistical test results not reported, no data on adverse events	poor
Hara et al. 1991 retrospective analysis of one-center (Japan) series; treated 1960-86	no not randomized; large differences between groups for stage, PS	yes all followed and analyzed	yes	uncertain regimens, doses, varied (although well reported)	yes	poor
Friess et al. 1985 retrospective analy-sis of patients enrolled in SWOG 7628 trial, 1977-9	uncertain (report states groups "evenly matched" but baseline data not reported)	yes all followed and analyzed	yes	yes	uncertain surgical group denominator unavailable for mortality	fair

Question 8. Surgery versus No Surgery for Limited-Stage Disease
Table 8H: Study Quality Ratings (continued)

Study	Initial Assembly of Comparable Groups	Low Loss to Followup, Maintenance of Comparable Groups	Measurements Reliable, Valid, Equal	Interventions Comparable/ Clearly Defined	Appropriate Analysis of Results	Overall Rating
Osterlind et al. 1985; retrospective analysis of patients from 6 trials; 2 Danish institutions, 3/73-9/81	yes while not randomized, groups appear similar	yes all followed and analyzed	yes	partial chemoTx, TRTx and PCI doses and schedules not reported	partial only reported OS and DFS	fair
Rostad et al. 2004 population-based registry analysis	no not randomized; no data comparing base-line characteristics	yes all in database followed and analyzed	yes	uncertain regimens, doses varied and not specified	no no data on adverse events	poor
George et al. 1986 population-based registry analysis	no not randomized; no data comparing base-line characteristics	yes all in database followed and analyzed	yes	uncertain regimens, doses varied and not specified	no no data on adverse events	poor

Question 9. Treatment of Recurrent/Progressive Disease
Table 9A: Sample Selection, Randomized Trials

Study	Inclusion	Exclusion	n, Randomized	n, Withdrawn or Excluded	n, Evaluated for Primary Outcome
O'Brien 2005	relapsed SCLC ineligible for further IV CTx; PS 0-2		141		141
Sculier 2002 1/94 – 4/01 European Lung Cancer Working Party	Proven SCLC; prior CTx did not include platinum or etoposide; evaluable/ measureable lesion; KPS $\geq$ 60; adequate hematologic, hepatic, renal function;	Active or non-cured malignancy; age > 75; active infectious disease, psychological disorders, MI < 3 mo, CHF/arrhythmia,	72	7	65
von Pawel 2001 31 centers in Europe, South Africa and Australia	Limited or extensive SCLC had recurred $\geq$ 3 mo after CR/PR to 1st-line CTx; enrollment stratified by stage, response duration, presence liver metastases; $\geq$ 2 cm measurable disease; LE $\geq$ 2 mo; adequate bone marrow, hepatic, renal function; $\geq$ 4 wks since surgery, 24 hrs since RTx;	Previous/current malignancies; brain metastases allowable if signs/symptoms attributable to them or on corticosteroids; severe or uncontrolled medical problems	106		106
von Pawel 1999 International multicenter trial	Documented progressive, limited or extensive SCLC; PD $\geq$ 60 d after 1st-line CTx; $\geq$ 1 bidimensionally measurable lesion; ECOG PS 0-2; adequate bone marrow, hepatic, renal function; $\geq$ 4 wks since surgery, 24 hrs since RTx;	Previous/current malignancies; brain metastases if symptomatic or on corticosteroids; pre-existing cardiac disease (CHF/arrhythmias/MI < 3 mo); CAV contraindicated; exceeded lifetime doses of doxorubicin or epirubicin; prior topotecan; > 1 prior CTx regimen	211		211
Postmus 1993 6/86 – 5/90 Multiple European centers	Proven SCLC; age $\leq$ 75; ECOG PS 0-3; adequate hematoogic, hepatic, renal function; documented progression $\leq$ 3 mo of last CTx; previously treated with combination CTx on EORTC 08862 protocol;	CNS metastases	68		68
Trillet-Lenoir 1992 8/87 – 4/91 8 centers in France	Documented relapsing SCLC to 1st-line CTx; adequate hematologic, hepatic function	Age > 65; KPS < 60%; severe renal, cardiac disease	37	5	32
O'Bryan 1990 SWOG	SCLC; failed or relapsed after 1st-line CTx; measurable tumor; recovered from prior therapy; KPS 3 or better; LE $\geq$ 6 wks; good risk = tolerated prior CTx, no prior RTx, age $\leq$ 65	Prior treatment with this study's combination of drugs (but use of cisplatin or vincristine allowable);	103 (+26 nonrandomized patients)		103

Question 9. Treatment of Recurrent/Progressive Disease
Table 9A: Sample Selection, Randomized Trials (continued)

Study	Inclusion	Exclusion	n, Randomized	n, Withdrawn or Excluded	n, Evaluated for Primary Outcome
Spiro 1989 02/82 – 09/85 Multiple centers in the United Kingdom	2-stage randomized trial: stage 1 – 1st-line chemotherapy (4 or 8 cycles of CVE), stage 2 – 2nd-line chemotherapy/ supportive care; histologically, cytologically proven SCLC; < 75;	Vascular, renal, neurological disease which would preclude chemotherapy	610	440	170
Wolff 1986 US center	Proven SCLC; prior CTx not including etoposide; recurrent and measurable disease; age ≤ 65; LE > 2 mo; KPS > 60%; normal peripheral blood cell counts;	Evidence of serious organ dysfunction not attributable to tumor	79	2	77

Question 9. Treatment of Recurrent/Progressive Disease
Table 9B: Patient Characteristics, Randomized Trials

Study	Age (yr)	Gender (%)	Previous Treatment Regimens (%)	Performance Status (%)	Comorbidities or Prognostic Factors (%)
O'Brien 2005	po T / BSC mn md 60 / 59 rng sd	All M 73 F 27		PS / po T / BSC 0/1 73 / 67	po T / BSC ED 68 / 61 med TTP (d) 84 / 90
Sculier 2002	PE / CbPE mn md 58 / 59 rng 41-73 / 39-70 sd	PE / CbPE M 84 / 76 F 16 / 24	PE / CbPE EVI 84 / 79 VAC, other 16 / 21 RTx 6 / 18 Surgery 3 / 0	KPS / PE / CbPE 60-70 45 / 32 80-100 55 / 68	PE / CbPE > 5% ↓ wt 16 / 29 OR 1st CTx 74 / 68
von Pawel 2001	po T / iv T mn 59.9 / 58.2 md rng 38-79 / 35-74 sd	po T / iv T M 75.0 / 79.6 F 25.0 / 20.4		PS / po T / iv T 0 19.2 / 33.3 1 65.4 / 38.9 2 15.4 / 27.8	po T / iv T limited 26.9 / 25.9 extensive 71.2 / 72.2 liver mets 30.8 / 31.5
von Pawel 1999			iv T / CAV Platinum 51.4 / 44.2 CAV 18.7 / 15.4 PE+CAV 12.1 / 16.3 RTx 61.7 / 55.8 Immunotherapy 0.0 / 1.9 Surgery 14.0 / 27.9	ECOG / iv T / CAV 0 16.8 / 19.2 1 59.8 / 61.5 2 23.4 / 19.2	iv T / CAV Prior brain RTx 25.2 / 23.1 Med TTP-wks 24.4 / 22.9 Liver mets 40.2 / 40.4 Brain mets 11.2 / 24.0 Limited 16.8 / 15.4 Extensive 83.2 / 84.6
Postmus 1993	IMP / VP / CDE avg 57 / 58 / 55 rng 38-69 / 39-73 / 43-67 sd	MP / VP / CDE M 71 / 86 / 88 F 29 / 14 / 12	IMP / VP / CDE 1 1st-line cycle 0 / 9 / 0 2 cycles 14 / 32 / 8 3 cycles 10 / 14 / 0 4 cycles 5 / 14 / 16 5 cycles 71 / 32 / 52 > 5 cycles 0 / 0 / 24	ECOG / IMP / VP / CDE 0 24 / 18 / 20 1 43 / 45 / 40 2 24 / 32 / 20 3 10 / 5 / 20	1st-2nd-line / IMP / VP / CDE 0-4 wks 38 / 64 / 44 5-8 29 / 32 / 28 9-13 33 / 5 / 28 Stage Limited 29 / 45 / 40 Extensive 71 / 55 / 60
Trillet-Lenoir 1992	PE1 / PE2 mn 56.73 / 52.47 md rng sd 8.7 / 5.95	PE1 / PE2 M 100 / 88 F 0 / 12		KPS / PE1 / PE2 mn 79.17 / 74.71 sd 13.82 / 10.06	PE1 / PE2 mn LDH 431.4 / 565.7 sd, LDH 108.0 / 423.7 1st-line ORR 100 / 76
O'Bryan 1990	BTOC / PE mn md 58 / 61 rng 41-75 / 38-76 sd	BTOC / PE M 80 / 64 F 20 / 36	BTOC / PE CAV 49 / 52 Etoposide 24 / 19 Other 27 / 29	KPS / BTOC / PE 0-1 53 / 39 2-3 47 / 61	BTOC / PE Limited 16 / 21 Extensive 84 / 79 Good risk 24 / 64 Poor risk 76 / 36

Question 9. Treatment of Recurrent/Progressive Disease
Table 9B: Patient Characteristics, Randomized Trials (continued)

Study	Age (yr)	Gender (%)	Previous Treatment Regimens (%)	Performance Status (%)	Comorbidities or Prognostic Factors (%)
Spiro 1989	MA PE mn md rng sd	MA BSC M F	MA BSC	MA BSC	MA BSC
Wolff 1986	100 200 300 < 50 19 11 15 50-60 38 56 46 > 60 42 33 31	100 200 300 M 58 93 81 F 42 7 19	100 200 300 1 CTx reg 88 78 73 2 CTx regs 12 19 12 3 CTx regs 0 4 15 RTx 54 52 73 Surgery 23 22 38	KPS 100 200 300 60 0 15 0 70 46 33 46 80 27 41 31 90 19 7 12 100 8 4 12	Site 100 200 300 Contra lung 19 15 4 Liver 19 26 19 Brain 15 11 19 Marrow 15 15 12 Bone 15 30 23 Subcut 4 7 4 Med LNs 31 22 23 SC LNs 27 30 0

Question 9. Treatment of Recurrent/Progressive Disease
Table 9C: Treatments, Randomized Trials

Study	Treatment Regimen				Outcomes	Response Criteria	Observer	Follow-up
O'Brien 2005	Group po T BSC	Agent topotecan best supportive care	Dose 2.3 mg/ m^2	Schedule d1-5, q 21 d	Overall survival (1^O), symptom control, tumor response, adverse events	WHO criteria		
Sculier 2002	Group PE CbPE 	Agent cisplatin etoposide carboplatin cisplatin etoposide	Dose 20 mg/m^2 100 mg/m^2 200 mg/m^2 20 mg/m^2 100 mg/m^2	Schedule d1-3, q 21 d, ≥ 3 cycles d1-3, q 21 d, ≥ 3 cycles d1, q 21 d, ≥ 3 cycles d2-3, q 21 d, ≥ 3 cycles d1-3, q 21 d, ≥ 3 cycles	Tumor response (1^O), response duration, survival, adverse outcomes	CR= all clinically detectable disease gone, ≥ 4 wks PR= ↓ by ≥50%, all measureable lesions, ≥ 4 wks SD= ↓ in lesion size by <50% or ↑ by <25%, no PD ≥ 3 mo PD= ↑ by ≥25%, cross sectional area, ≥1 lesion/new lesion		mn md 46 mo rng 2-90 mo sd
von Pawel 2001	Group po T iv T	Agent topotecan topotecan	Dose 2.3 mg/m^2 1.5 mg/m^2	Schedule po, d1-5, q 21 d, ≥ 4 cycles iv, d1-5, q 21 d, ≥ 4 cycles	Tumor response (1^O), time to progression, survival, symptoms, adverse events	WHO criteria	Blinded	mn md rng sd
Von Pawel 1999	Group iv T CAV 	Agent topotecan cytoxan doxorubin vincristine	Dose 1.5 mg/m^2 1 g/m^2 45 mg/m^2 2 mg	Schedule iv, d1-5, q 21 d, 1-15 cycles d1, q 21 d, 1-7 cycles d1, q 21 d, 1-7 cycles d1, q 21 d, 1-7 cycles	Tumor response (1^O), time to progression, survival, symptoms, adverse events	WHO criteria	Blinded	mn md rng sd

Question 9. Treatment of Recurrent/Progressive Disease
Table 9C: Treatments, Randomized Trials (continued)

Study	Treatment Regimen				Outcomes	Response Criteria	Observer	Follow-up
Postmus 1993	Group	Agent	Dose	Schedule	Tumor response (1^O), survival, adverse events	WHO criteria		mn md rng sd
	IMP	ifosfamide	5 g/ m^2	d1, q 28 d, max 5 cycles				
		mesna	4.35 g/ m^2	d1, q 28 d, max 5 cycles				
		carboplatin	400 mg/ m^2	d1, q 28 d, max 5 cycles				
	VP	vincristine	2 mg	d1, 8, q 28 d, max 5 cycles				
		carboplatin	400 mg/ m^2	d1, q 28 d, max 5 cycles				
	CDE	cytoxan	1 g/ m^2	d1, q 28 d, max 5 cycles				
		doxorubicin	45 mg/ m^2	d1, q 28 d, max 5 cycles				
		etoposide	100 mg/ m^2	d1, 3, 5, q 28 d, max 5 cycles				
	IMP, VP, CDE were 1^{st}-line regimens, progression on IMP/VP treated with 2^{nd}-line CDE, progression on CDE treated with 2^{nd}-line VIMP							
Trillet-Lenoir 1992	Group	Agent	Dose	Schedule	Tumor response (1^O), survival, adverse events			mn md rng sd
	PE1	cisplatin	20 mg/m^2	d1-5, q 28 d				
		etoposide	60 mg/m^2	d1-5, q 28 d				
	PE2	cisplatin	40 mg/m^2	d1-5, q 28 d				
		etoposide	100 mg/m^2	d1-5, q 28 d				
O'Bryan 1990	Group	Agent	Dose	Schedule	Tumor response (1^O), survival, adverse events	CR= all clinically detectable disease gone, $\geq$ 4 wks PR= ↓ by $\geq$50%, all measureable lesions, $\geq$ 4 wks		mn md rng sd
	BTOC	vincristine	2 mg	d1, 21, 42				
		thiotepa	20 mg/m^2	d1, 21, 42				
		cytoxan	.375/.5 g/ m^2	d1, 21, 42				
		carmustine	100 mg/m^2	d1, 21, 42				
	PE	cisplatin	50 mg/m^2	d2				
			75 mg/m^2	d2				
		etoposide	100 mg/m^2	d1, 3, 4				
			125 mg/m^2	d1, 3, 4				
Spiro 1989	Group	Agent	Dose	Schedule	Survival (1^O), progress-sion-free survival, tumor ressponse	CR= all clinically detectable disease gone, PR= ↓ by $\geq$50%, all measureable lesions, $\geq$ 3 wks SD= ↓ in lesion size by <50%		mn md rng sd
	MA	methotrexate	50 mg/ m^2	q 21 d, $\leq$ 9 cycles				
		doxorubicin	50 mg/ m^2	q 21 d, $\leq$ 9 cycles				
	BSC	best supportive care						

Question 9. Treatment of Recurrent/Progressive Disease
Table 9C: Treatments, Randomized Trials (continued)

Study	Treatment Regimen				Outcomes	Response Criteria	Observer	Follow-up
Wolff 1986	Group	Agent	Dose	Schedule	Tumor response (1^{O}), survival, adverse events	SECSG criteria		mn md rng sd
	E100	etoposide	100 mg/m^2	d1-3				
	E200	etoposide	200 mg/m^2	d1-3				
	E300	etoposide	300 mg/m^2	d1-3				

Question 9. Treatment of Recurrent/Progressive Disease
Table 9D Survival Outcomes

Study	Overall Survival (%)							Progression-Free Survival (%)						
O'Brien 2005		N	Med	1 yr	2 yr	3 yr	4 yr 5 yr		N	Med	1 yr	2 yr	3 yr	4 yr 5 yr
	po T	71	26 wks	49 (6 mo)				po T	71	84 d				
	BSC	70	14 wks	26				BSC	70	90 d				
	HR=0.64 (95% CI: 0.45, 0.90, p=0.0104)													
Sculier 2002		N	Med	1 yr	2 yr	3 yr	4 yr 5 yr		N	Med	1 yr	2 yr	3 yr	4 yr 5 yr
	PE	31	18.9 wks	18										
	CbPE	34	33.0 wks	19										
	Log-rank, p=0.11													
von Pawel 2001		N	Med	1 yr	2 yr	3 yr	4 yr 5 yr		N	Med	1 yr	2 yr	3 yr	4 yr 5 yr
	po T	52	32.3 wks	~25				po T	52	14.9 wks	~5			
	iv T	54	25.1 wks	~8				iv T	54	13.1 wks				
	adjusted RR=0.90 (95% CI 0.55, 1.47, NS)							adjusted RR=0.98 (95% CI 0.63, 1.54, NS)						
von Pawel 1999		N	Med	1 yr	2 yr	3 yr	4 yr 5 yr		N	Med	1 yr	2 yr	3 yr	4 yr 5 yr
	iv T	107	25.0 wks	14.2				iv T	107	13.3 wks				
	CAV	104	24.7 wks	14.4				CAV	104	12.3 wks				
	Log-rank, p=0.772, adjusted RR=1.17 (p=0.322)							p=0.552						
Postmus 1993		N	Med	1 yr	2 yr	3 yr	4 yr 5 yr		N	Med	1 yr	2 yr	3 yr	4 yr 5 yr
	VIMP	43	19 wks											
	CDE	25	22 wks											
Trillet-Lenoir 1992		N	Med	1 yr	2 yr	3 yr	4 yr 5 yr		N	Med	1 yr	2 yr	3 yr	4 yr 5 yr
	PE1	15	13 wks											
	PE2	17	16.5 wks											
O'Bryan 1990		N	Med	1 yr	2 yr	3 yr	4 yr 5 yr		N	Med	1 yr	2 yr	3 yr	4 yr 5 yr
	BTOC	45	13 wks											
	PE	58	16 wks											
	(RR 1.3, 95%CI 0.9, 2.0)													
	BTOCgood	11	10 wks											
	PEgood	16	35 wks											
	(RR 3.3, 95%CI 1.2, 9.1)													
	BTOCpoor	34	14 wks											
	PEpoor	68	12 wks											
	(RR1.1, 95%CI 0.7, 1.8)													
Spiro 1989		N	Med	1 yr	2 yr	3 yr	4 yr 5 yr		N	Med	1 yr	2 yr	3 yr	4 yr 5 yr
	MA													
	BSC													
Wolff 1986		N	Med	1 yr	2 yr	3 yr	4 yr 5 yr		N	Med	1 yr	2 yr	3 yr	4 yr 5 yr
	E100	26	12.6 wks	~4										
	E200	27	20.0 wks	~12										
	E300	26	22.5 wks	~24										
	Log-rank, Gehan-Wilcoxon, p=NS)													

Question 9. Treatment of Recurrent/Progressive Disease
Table 9E*:* Tumor Response and Quality of Life, Randomized Trials

Study	Tumor Response (%)							Quality of Life						
O'Brien 2005		N	CR	PR	SD	PD	NE		Scale	Domain	F/U	n	mn±sd	
	po T	71	7		44				QoL EQ-5D: significantly faster deterioration in BSC arm					
	BSC	70												
Sculier 2002		N	CR	PR	SD	PD	NE		Scale	Domain	F/U	n	mn±sd	
	PE	31	0	29										
	CbPE	34	9	38										
	Median response duration: PE 5.2 mo, CbPE 7.8 mo													
von Pawel		N	CR	PR	SD	PD	NE					po Topotecan		iv Topotecan	
2001	po T	52	1.9	21.2	19.2	30.8	26.9	Scale	Domain	F/U		n	% improved	n	% improved
	iv T	54	3.7	11.1	29.6	42.6	13.0	Symptoms	chest pain	post-CTx		19	42.1	22	31.8
	Difference in ORR = 8.3% (95% CI -6.6%, 23.1%, NS)								dyspnea			29	13.8	33	27.3
	Median response duration: po T 18.1 wks, iv T 13.9 wks								cough			31	16.1	36	22.2
									hemoptysis			3	33.3	10	40.0
									anorexia			27	18.5	29	31.0
									insomnia			25	32.0	27	26.6
									hoarseness			14	35.7	24	37.5
									fatigue			33	21.2	36	16.7
									impaired ADLs			31	25.8	36	22.2
von Pawel		N	CR	PR	SD	PD	NE					iv Topotecan		CAV	
1999	iv T	107	0.0	24.3	19.6	45.8	10.3	Scale	Domain	F/U		n	% improved	n	% improved
	CAV	104	1.0	17.3	11.5	52.9	17.3	Symptoms	chest pain	post-CTx		44	25.0	41	17.1
	Difference in ORR, p=0.285								dyspnea*			68	27.9	61	6.6
	Median response duration iv T 14.4, CAV 15.3 (p=0.300)							*p<0.05	cough			69	24.6	61	14.8
									hemoptysis			15	26.7	12	33.3
									anorexia*			56	32.1	57	15.8
									insomnia			57	33.3	53	18.9
									hoarseness*			40	32.5	38	13.2
									fatigue*			70	22.9	65	9.2
									impaired ADLs*			67	26.9	63	11.1
Postmus 1993		N	CR	PR	SD	PD	NE		Scale	Domain	F/U	n	mn±sd		
	VIMP	25	4	56	8	24	8								
	CDE	43	14	37	19	23	7								
	Median response duration VIMP 16 wks (4-30), CDE 19 wks (12-34)														
Trillet-Lenoir		N	CR	PR	SD	PD	NE		Scale	Domain	F/U	n	mn±sd		
1992	PE1	15	6.6	20	13.3	60									
	PE2	17	11.8	23.5	11.8	52.9									
O'Bryan 1990		N	CR	PR	SD	PD	NE		Scale	Domain	F/U	n	mn±sd		
	BTOC	45	0	13											
	PE	58	2	10	(p=0.91)										
	BTOCgood	11	27												
	PEgood	16	27												
	BTOCpoor	34	9												
	PEpoor	68	9												

Question 9. Treatment of Recurrent/Progressive Disease
Table 9E*:* Tumor Response and Quality of Life, Randomized Trials

Study	Tumor Response (%)							Quality of Life				
Spiro 1989		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	n	mn±sd
	MA	170	4	19	45	32	1					
Wolff 1986		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	n	mn±sd
	E100	26		4								
	E200	27		7								
	E300	26		4								

Question 9. Treatment of Recurrent/Progressive Disease
Table 9F: Adverse Events, Randomized Trials

Toxicity Type	Study	Description	Group	n	Gr 3 %	Gr 4 %	p value[1]
Treatment-related mortality	O'Bryan 1990	Drug-related deaths	BTOC	45	4		0.28
			PE	84	1		
Alopecia	Sculier 2002		PE	28	21 (3/4)		0.15
			CbPE	31	39		
	von Pawel 2001		po T	52	1.9	0.0	0.06
			iv T	54	13.0	0.0	
	von Pawel 1999		iv T	107	0.0 (3/4)		1.0
			CAV	104	0.0		
Fatigue	von Pawel 2001		po T	52	5.8	0.0	0.36
			iv T	54	1.9	0.0	
	von Pawel 1999		iv T	107	4.7 (3/4)		0.28
			CAV	104	8.7		
Diarrhea	von Pawel 2001		po T	52	7.7	0.0	0.054
			iv T	54	0.0	0.0	
	von Pawel 1999		iv T	107	0.9 (3/4)		1.0
			CAV	104	0.0		
Nausea	O'Brien 2005		po T	71	1		1.0
			BSC	70	0		
	von Pawel 1999		iv T	107	39.3 (3/4)		0.89
			CAV	104	40.4		
Vomiting	O'Brien 2005		po T	71	3		0.50
			BSC	70	0		
	Sculier 2002	Nausea/vomiting	PE	30	7 (3/4)		0.23
				32	0		
	von Pawel 2001		po T	52	11.5	0.0	0.16
			iv T	54	3.7	0.0	
	von Pawel 1999		iv T	107	2.9 (3/4)		1.0
			CAV	104	1.9		
	Wolf 1986	Nausea/vomiting/bloody diarrhea/ stomatitis	E100	26	5	0	0.44
			E200	27	4	0	
			E300	26	10	0	
Anorexia	von Pawel 1999		iv T	107	0.9 (3/4)		1.0
			CAV	104	0.0		
Diarrhea	O'Brien 2005		po T	71	6		0.12
			BSC	70	0		
Lethargy	O'Brien 2005	Fatigue	po T	71	4		1.0
			BSC	70	4		
Neurosensory	O'Brien 2005	Pain	po T	71	3		0.44
			BSC	70	6		
Neuromotor							
Hearing loss							

[1] Comparison of grade 3 and above versus others Fisher's exact test.

Question 9. Treatment of Recurrent/Progressive Disease
Table 9F: Adverse Events, Randomized Trials (continued)

Toxicity Type	Study	Description	Group	n	Gr 3 %	Gr 4 %	p value[2]
Esophagitis							
Bronchopulmonary	O'Brien 2005	Dyspnea	po T	71	3		0.32
			BSC	70	9		
	von Pawel 2001	Dyspnea	po T	52	9.6	0	1.0
			iv T	54	9.3	0 (5:1.9)	
			po T	52	1.9	0 (5: 3.8)	0.36
		Pulmonary embolism	iv T	54	0	0 (5: 1.9)	
Pneumonitis	von Pawel 2001	Pneumonia	po T	52	5.8	1.9	0.054
			iv T	54	0.0	0.0	
Hepatic							
Kidney							
Hemorrhage							
Anemia	O'Brien 2005		po T	71	25 (3/4)		
	von Pawel 2001		po T	52	27.5	3.9	1.0
			iv T	54	26.4	3.8	
	von Pawel 1999		iv T	104	39.4	2.9	0.001
			CAV	101	17.8	2.0	
Thrombocytopenia	O'Brien 2005		po T	71		7	
	Sculier 2002		PE	30	17 (3/4)		0.07
			CbPE	32	38		
	von Pawel 2001		po T	52	25.5	27.5	0.85
			iv T	54	24.5	24.5	
	von Pawel 1999		iv T	104	28.8	28.8	<0.001
			CAV	101	9.9	5.0	
	Postmus 1993		VIMP	25	8	45	<0.001
			CDE	43	6	3	
	Trillet-Lenoir 1992		PE1	15	0	7	0.041
			PE2	17	18	24	
	Wolff 1986	Neutropenia	E100	26	0	15	<0.001
			E200	27	0	13	
			E300	26	24	33	
Leukopenia or neutropenia	O'Brien 2005	Neutropenia	po T	71		33	
	Sculier 2002	Leukopenia	PE	30	60 (3/4)		0.76
			CbPE	32	56		
	von Pawel 2001	Leukopenia	po T	52	27.5	17.6	0.006
			iv T	54	45.3	28.3	
		Neutropenia	po T	52	21.6	35.3	<0.001
			iv T	54	25.9	67.3	

[2] Comparison of grade 3 and above versus others Fisher's exact test.

Question 9. Treatment of Recurrent/Progressive Disease
Table 9F: Adverse Events, Randomized Trials (continued)

Toxicity Type	Study	Description	Group	n	Gr 3 %	Gr 4 %	p value
Leukopenia or neutropenia	von Pawel 1999	Leukopenia	iv T	104	54.8	31.7	0.34
			CAV	101	37.6	43.6	
		Neutropenia	iv T	104	18.3	70.2	0.83
			CAV	99	15.2	71.7	
	Postmus 1993	Leukopenia	VIMP	25	26	40	1.0
			CDE	43	38	25	
	Trillet-Lenoir 1992	Leukopenia	PE1	15	33	13	0.021
			PE2	17	12	76	
	Wolff 1986		E100	26	5	0	<0.001
			E200	27	25	54	
			E300	26	0	86	
Infection	O'Brien 2005	Febrile neutropenia	po T	71		3	
		Neutropenic infections	po T	71		1	
		Sepsis	po T	71		4	
	Sculier 2002		PE	30	3 (3/4)		0.96
			CbPE	33	3		
	von Pawel 2001	Fever	po T	52	3.8	1.9 (5:1.9)	0.20
			iv T	54	1.9	0.0	
Other							

Question 9. Treatment of Recurrent/Progressive Disease
Table 9G: Study Quality Ratings, Randomized Trials

Study	Initial Assembly of Comparable Groups	Low Loss to Followup, Maintenance of Comparable Groups	Measurements Reliable, Valid, Equal	Interventions Comparable/ Clearly Defined	Appropriate Analysis of Results	Overall Rating
O'Brien 2005						? Available only in abstract
Sculier 2002	Partial (arms balanced but randomization method not described)	Yes	Partial (overall response rate was primary outcome)	Yes	Yes	Fair
von Pawel 2001	Partial (arms balanced but randomization method not described)	Yes	Yes	Yes	Yes	Fair
von Pawel 1999	Partial (randomization method adequate, but age and gender distributions not specified)	Yes	Yes	Yes	Yes	Fair
Postmus 1993	Partial (arms balanced but randomization method not described)	Yes	Partial (overall response rate was primary outcome)	Yes	Yes	Fair
Trillet-Lenoir 1992	Partial (arms balanced but randomization method not described)	Yes	?	No	Yes	Poor
O'Bryan 1990	Partial (arms balanced but randomization method not described)	Yes	Partial (overall response rate was primary outcome)	No	Yes	Poor
Spiro 1989	Partial (arms balanced but randomization method not described)	?	Yes	Yes	No	Poor
Wolff 1986	No	Yes	Partial (overall response rate was primary outcome)	No	No	Poor

Question 9. Treatment of Recurrent/Relapsed Disease
Table 9H: Sample Selection, Phase II Studies

Study	Inclusion	Exclusion	n, Enrolled	n, Withdrawn	n, Evaluated
Ando 2004 2/98 – 5/01 Multiple centers in Japan	Diagnosis of SCLC; refractory (off CTx < 2 mo, n=16) or relapsed (off CTx > 2 mo, n=9) after initial etoposide regimen; measurable disease; ECOG PS ≥2; adequate bone marrow, hepatic, rental function; age 15-75	brain metastases; severe medical problems that would interfere with compliance	25		25
Agelaki 2004 11/99 – 09/02 Multiple centers in Greece	Confirmed SCLC, refractory or relapsing, bidimensionally measurable disease, limited or extensive and had relapsed after ≥ 1 CTx regimen, WHO PS 0-2, LE ≥ 3 mo, ≥ 4 wks since CTX, RTx to < 25 % of marrow-containing bones ≥ 4 wks after; adequate hematologic, renal, hepatic function; brain metastases allowed if previous RTx with clinical, radiologic improvement; age 18-75	Infections, malnutrition, concurrent active malignancy	31	5 NE	26
Goto 2004 10/98-03/01 Multiple centers in Japan	Histologically/cytologically confirmed SCLC; responded to 1st-line therapy, relapsed ≥ 8 wks; age ≤ 75; ECOG PS 0-2; measurable disease; adequate hematologic, hepatic, renal function	Massive pleural effusion; prior RTx to area larger than 1/3 bone marrow volume; active infection; contraindications to use or irinotecan	40		40
Ardizzoni 2003 1/97 – 4/99 Multiple European centers	Confirmed SCLC, relapsed, ≥ bidimensionally measurable lesion outside areas of prior RTx, WHO PS 0-2; PD after 1st-line CTX (except camptothecin analogues; cisplatin allowable if responsive, CTx ≥ 6 mo before;1st-line CTx regimen given twice allowable; all CTx/Rtx stopped ≥ 4wks with recovery from side effects; asymptomatic brain metastases allowable; brain RTx allowable after current treatment; symptomatic brain metastases allowable if prior treatment adequate; adequate hematologic, renal, hepatic function; age 18-75;	Pre-existing uncontrolled cardiac disease; documented MI < 3 mo; ≥ grade 2 sensory/motor neuropathy; active infection; past or current history of neoplasms	116	6 ineligible	110
Hainsworth 2003 3/98 – 2/99 6 US centers	Proven SCLC; PD after 1 CTx regimen; ≤ 2 course prior RTx; < 25% of marrow-bearing bone in RTx fields; brain metastases allowable if minimal neurologic impairment with whole brain RTx; ECOG PS 0-2; adequate hematologic, hepatic, renal function		30		30
Hoang et al. 2003 4/98 – 10/01 Wiconsin Oncology Group	Previously treated SCLC patients; sensitive (recurrence > 3 mo after 1st-line CTx) or refractory (PD or recurrence ≤ 3 mo); limited or extensive; measurable/evaluable; 1 prior CTx regimen; ECOG PS 0-2; LE ≥ 3 mo; age ≥ 18; adequate hematologic, hepatic, renal function; ≥ 4 wks since CTx/surgery; ≥ 24 hr since RTx; clinically stable brain metastase allowable		27	3	24
Masters 2003 12/97 – 9/98 Multiple US centers	Proven SCLC; sensitive (relapse ≥ 90 d after CTx) or refractory (relapse < 90 d after CTx); limited or extensive; PD after initial CTx; prior RTx allowable, measurable disease outside field or clear PD within field; ECOG PS 0-2; adequate renal, hepatic, bone marrow function	Ongoing toxicity > grade 1; prior gemcitabine treatment	46	4 2 ineligible, 2 rapid CNS progression	42

Question 9. Treatment of Recurrent/Relapsed Disease
Table 9H: Sample Selection, Phase II Studies (continued)

Study	Inclusion	Exclusion	n, Enrolled	n, Withdrawn	n, Evaluated
Kosmas 2001 Multiple centers in Greece	Confirmed SCLC; relapsed after CbE CTx ± TRTx; not curable by other 2nd-line CTx or RTx; WHO PS 0-2; LE ≥ 3 mo; adequate hematopoietic, hepatic, renal function	previous CTx; active CAD; unstable diabetes mellitus; NCI ≥ grade 2 peripheral neuropathy; prior RTx to > 30% of bone marrow	33		33
Kakolyris 2001 11/97 – 8/99 Multiple centers in Greece	Confirmed SCLC; refractory; had failed 1 prior 1st-line CTx; WHO PS 0-2; LE ≥ 3 mo; adequate hematologic, hepatic, renal function; brain metastases allowable if RTx given, lesions stable, clinically improved; Age < 75	Other medical problems severe enough to affect compliance; ≥ 20% ↓ body weight; active infection; massive liver metastases; second primary tumor	32	3 NE	29
van der Lee 2001 2/97 – 11/98 Multiple centers in the Netherlands	Proven SCLC; relapsed ≤ 3 mo of last CTx; limited or extensive; prior RTx allowable if not all measurable lesions in field; age ≥ 18; ECOG PS 0-3; adequate hematologic, hepatic, renal function	Uncontrolled infection; prior gemcitabine; symptomatic brain metastases; other malignancy < 3 yr before	41	3 NE	38
Sessa 2000 3/95 – 8/97 16 European centers	Confirmed SCLC; progressive recurrent after 1st-line CTx; ≥ 1 bidimensionally measurable lesion; WHO PS 0-2; 1 prior CTx regimen that did not include camptothecin analogues; adequate hematologic, hepatic and renal function	Signs of brain or leptomeningeal disease; history CHF; active heart disease requiring anti-arrhythmics	67	5 NE	62
Sonpavde 2000 8/96 – 1/98 Hoosier Oncology Group	Recurrent, measurable SCLC; KPS > 50%; adequate hematologic, hepatic, cardiac, renal function; 1 prior combination CTx regimen		46		46
Groen 1999 2/96 – 9/97 3 centers in the Netherlands	Proven SCLC; relapsed < 3 mo after last CTx; age 18-75; ECOG PS 0-3; bidimensionally measurable disease; adequate hematologic, hepatic, renal function; concurrent RTx allowable if not all measurable sites in field	Significant cardiac disease; uncontrolled infection; concurrent CTx	35	1 NE	34
Ardizzoni 1997 7/92 – 9/94 22 European centers	Confirmed SCLC; PD after 1 1st-line CTx that did not include a camptothecin analog; ≥ 1 bidimensionally measurable lesion outside RTx field; age ≤ 75; WHO PS 0-2; LE > 3 mo; ≥ 3 wks since systemic treatment, recovered from side effects; brain mets with neurologic symptoms allowable if controlled by RTx/steroids; adequate hematologic, hepatic, renal function		101	8	93

Question 9. Treatment of Recurrent/Relapsed Disease
Table 9H: Sample Selection, Phase II Studies (continued)

Study	Inclusion	Exclusion	n, Enrolled	n, Withdrawn	n, Evaluated
Gridelli 1997 Multiple centers in Italy 8/94-2/96	Proven pretreated SCLC; ECOG PS 0-2; age ≤ 75; normal platelet, renal, hepatic function;	Significant heart disease	30		30
Einhorn 1995 2/90 – 8/93 Hoosier Oncology Group	Refractory SCLC; no previous ifosfamide		46	5	41
Faylona 1995 2/90 – 8/93 Hoosier Oncology Group	Previously treated progressive or recurrent SCLC; KPS ≥ 50; adequate bone marrow, renal function; 1 prior CTx regimen	Prior ifosfamide or etoposide; history of CHF; patients who progressed within 4 wks on EP	46	4	42
Sculier 1995 9/91 – 12/93 12 European centers	Proven SCLC; prior non-platinum CTx and failed 1st-line; had evaluable/measurable lesion; KPS ≥ 60; age < 75	Other prior malignancy; active infectious disease, CNS disease, psychiatric disorders, recent MI, ≥ WHO grade II peripheral polyneuropathy; CTx/ RTx < 4 wks before	41		41
Smyth 1994 Multiple European centers	Verified SCLC; evidence of PD; locally advanced or metastatic extensive disease; ≥ 1 lesion measurable bidimensionally; WHO PS 0-2; age 18-75; adequate hematologic, hepatic, renal function; no more than 1 prior CTx regimen; if prior RTx, assessed site outside field	No more than one prior CTx	34	6	28
Albain 1993 SWOG-8605 Multiple US centers	Diagnosis of SCLC; measurable or evaluable disease; progressed during initial therapy or relapsed after an interval of response; limited or extensive; ≥ 3 wks since prior CTx; must have failed ≥ 1 CTx regimen; after interim analysis prior CTx limited to regimen with cyclophosphamide or EP; limited stage patients must have failed RTx with measurable/evaluable disease outside field; brain metastases allowable if patients could receive brain RTx; initial SWOG PS 0-4, then limited to 0-2		69	2	67
Jassem 1993 6/90 – 5/91 8 European centers	Confirmed SCLC; progressive recurrent not amenable for curative surgery/RTx; response to 1st-line CTx; ≥ 3 mo since prior CTx; measurable/evaluable disease outside irradiated area; brain/lepto-meningeal disease allowable if controlled by RTx	Previous/current other malignancies; poor medical risks because of non-malignant systemic disease, active uncontrolled infection, peripheral neuropathy	26	1	25

Question 9. Treatment of Recurrent/Relapsed Disease
Table 9H: Sample Selection, Phase II Studies (continued)

Study	Inclusion	Exclusion	n, Enrolled	n, Withdrawn	n, Evaluated
Einhorn 1990 5/88 – 9/88 Hoosier Oncology Group	Consecutive patients diagnosed with SCLC; measurable/evaluable progressive disease; ≥ 1 prior combination CTx regimen; KPS ≥ 50; adequate hematologic, hepatic, renal function; CTx finished ≥ 3 wks		26		26
Graziano 1990 6/83-5/84 Multiple US centers	Documented measurable SCLC, failed to respond to or relapsed after initial response to 1 prior CTx regimen; prior mono etoposide or cisplatin allowable; CALGB PS 0-2; ≥ 4 wks since surgery, RTx, CTx; adequate hematologic, hepatic, renal function	previous/concomitant malignancy; serious medical/ psychiatric illness	43	8	35
JCOGLC 1990 1/86 – 1/88 Multiple centers in Japan	Proven SCLC/NSCLC; nonresected; evaluable/measurable; LE ≥ 3 mo; adequate hematologic, hepatic, renal function; age ≥ 15; > 4 wks since any prior CTx/RTx; 1st-line and 2nd+-line		31		31
Sculier 1990 Multiple European centers	Failed (relapse/no response) to a 1st-line treatment with etoposide+vindesine±cisplatin; evaluable/measurable disease;KPS ≥ 50; adequate hematologic, hepatic, renal function; ≤ 75	history of prior malignancy; active infectious disease; recent myocardial infarction; congestive heart failure; cardiac arrhythmia	49	4	45
Issell 1985 Multiple US centers	Refractory SCLC; failure to responde to previous combination CTx with ≥ 3 Rx; measurable disease	Prior etoposide; evidence of liver or renal failure	116	21	95

Question 9. Treatment of Recurrent/Relapsed Disease
Table 9I: Patient Characteristics, Phase II Studies

Study	Age	Gender (%)	Stage (%)	Time Since Last CTx (%)	Initial Re-ponse (%)	Previous Treatment Regimens (%)	Race (%)	Performance Status (%)	Other Factors (%)
Ando. 2004	mn 65.3 md rng sd 9.7	M 96 F 4	LD 36 ED 64	< 2 mo 64 > 2 mo 36	CR 0 PR 60 SD 32 PD 8 NE	PE 16 CbP 84 TRTx 20 Surgery 4		ECOG 0-1 88 2 12	Refractory 64 Relapsed 36
Agelaki 2004	mn md 60 rng 38-78 sd	M 94 F 6	LD 6 ED 94			#1 CTx 48 #2 CTx 39 #3 CTx 10 PE 100 Topotecan 48 CVE 3 Docataxel/ Gemcitibine 6			Refractory 48 Chemosensitive 52
Goto 2004	mn md 40 rng 41-74 sd	M 72.5 F 27.5	LD 12.5 ED 87.5			PE 28 CbE 28 PE-VAE 15 PI 5 Other CTx 10 TRTx 20		ECOG 0 22.5 1 75 2 2.5	
Ardizzoni 2003	Sensitive md 60 rng (38-73) Refractory md 55 rng (35-75)	Sensitive M 79 F 21 Refractory M 17 F 83	Sensitive LD 27 ED 74 Refractory LD 33 ED 67	Sensitive md 165 d Refractory md 30 d		Sen Ref TRTx 69 31 med#CTx 3 3 Cisplatin 22 5 Carbopl 24 36 Etopos 90 83		WHO Sen Ref 0 18 12 1 71 64 2 12 24	Sensitive 62 Refractory 38
Hainsworth 2003	mn md 62 rng 34-78 sd	M 57 F 43			CR 23 PR 57 SD 20 PD NE	Plat/E 57 Plat/E/pacl 40 Plat/E/pacl/ topotecan 3			Relapsed 43 Refractory 57
Hoang 2003	mn md 61 rng 45-74 sd	M 63 F 37	LD 11 ED 89			CTx 100 RTx 56		ECOG 0-1 93 2 7	Sensitive 56 Refractory 44
Masters 2003	mn 60.6 md 60.1 rng 41-83 sd	M 59.5 F 40.5			CR 33 PR 38 SD 14 PD 14 NE	TRTx 57 Mono CTx 7 Comb 86 Both 7 Surgery 19	B 5 W 95 H A O	ECOG 0 24 1 55 2 21	Relapsed 43 Refractory 57 ≥ 5% ↓ wt 24

Question 9. Treatment of Recurrent/Relapsed Disease
Table 9I: Patient Characteristics, Phase II Studies (continued)

Study	Age	Gender (%)	Stage (%)	Time Since Last CTx (%)	Initial Re-ponse (%)	Previous Treatment Regimens (%)	Race (%)	Performance Status (%)	Other Factors (%)
Kosmas 2001	mn 62 md rng 55-70 sd	M 91 F 9	LD 45 ED 55	≤ 3 mo 61 > 3 mo 39	CR 18 PR 58 SD 12 PD 12 NE	CTx 100 TRTx 42		WHO md 1 rng 0-2	Metastatic sites LNs 39 Liver 27 Bone 15 Brain 18 Lung nodules 24 Adrenals 27 Other 6
Kakolyris 2001	mn md 60.5 rng 38-77 sd	M 84 F 16	LD 0 ED 100			EP 84 CAB 16 RTx 47 Surgery 6		WHO 0 28 1 63 2 9	Metastatic sites 1 metastasis 28 2 metastases 50 3 metastases 22 lung 91 liver 22 LNs 75 Bone 16 Adrenal 13 CNS 22 Skin 3
van der Lee 2001	< 60 58 ≥ 60 42	M 76 F 24	LD 34 ED 66			#1 CTx 24 #2 CTx 47 #3 CTx 29 1st CDE 89 1st ECE 3 1st oral E 8			
Sessa 2000	Sensitive md 60 rng 39-76 Refractory md 61 rng 36-79	Sensitive M 65 F 35 Refractory M 69 F 31		Sensitive md 7.9 mo rng 3.2-19.6 Refractory md 2.1 rng 0.2-7.5		CTx + RTx 44		WHO Sen Ref 0 19 28 1 62 55 2 19 17	
Sonpavde 2000	mn md 63 rng 43-77 sd	M 54 F 46	LD 63 ED 37	≤ 3 mo 30 > 3 mo 70	CR 39 PR 46 SD 2 PD 13 NE	Platinum-E ± VIP 100 RTx 59		KPS med 80 rng 50-90	Sites Lung 91 Liver 43 Adrenal 17 Bone 13 Cervical LN 9 Brain 4

Question 9. Treatment of Recurrent/Relapsed Disease
Table 9I: Patient Characteristics, Phase II Studies (continued)

Study	Age	Gender (%)	Stage (%)	Time Since Last CTx (%)	Initial Re-ponse (%)	Previous Treatment Regimens (%)	Race (%)	Performance Status (%)	Other Factors (%)
Groen 1999	mn md 59 rng 40-73 sd	M 69 F 31	LD 44 ED 56	med 6 wks 0-11	CR 15 PR 65 SD 18 PD 3 NE	#1 CTx 53 #2 CTx 44 #3 CTx 3 CTx 100 RTx 21 1st CDE 97		ECOG 0 21 1 56 2 18 3 6	
Ardizzoni 1997	mn md 58 rng sd	M 69 F 31	LD 62 ED 38	≤ 6 mo 82 > 6 mo 18		≤ 3 CTx Rx 58 > 3 CTx Rx 42 RTx 37 ImmunoTx 6 Surgery 12		WHO 0 25 1 57 2 18	Sensitive 49 Refractory 51
Gridelli 1997	mn md 61 rng 44-74 sd	M 93 F 7	LD 10 ED 90			Prior etopos 73		ECOG 0 7 1 47 2 47	Sensitive 60 Refractory 40
Einhorn 1995	mn md 61 rng 45-76 sd	M 78 F 22	LD 22 ED 78	< 6 mo 44 ≥ 6 mo 56		Cisplatin 85 RTx 49		KKPS 80-100 63 70 29 50-60 7	
Faylona 1995	mn md 60 rng 45-76 sd	M 79 F 22	LD 21 ED 79	< 6 mo 43 ≥ 6 mo 57		Cisplatin 86 RTx 50			
Sculier 1995	mn md 59 rng 40-74 sd	M 90 F 10	LD 25 ED 75		CR 3 PR 78 SD PD 20 NE	IVE 85 IVA 10 EVI 5		KPS med 80 rng 60-100	> 5% ↓ wt 13
Smyth 1994	mn md 61 rng 36-72 sd	M 82 F 18				CTx 79 RTx 24 Surgery 24		WHO 0 24 1 65 2 12	
Albain 1993	mn md 59 rng 30-76 sd	M 79 F 21	LD 9 ED 91			1 CTx reg 88 ≥ 2 CTx reg 12 2-4 CTx Rx 46 > 4 CTX Rx 54 RTx 50		SWOG 0-1 54 2-4 46	1 site 5 >1 sites 95 relapse after response 27 PD on treatment 66

Question 9. Treatment of Recurrent/Relapsed Disease
Table 9I: Patient Characteristics, Phase II Studies (continued)

Study	Age	Gender (%)	Stage (%)	Time Since Last CTx (%)	Initial Re-ponse (%)	Previous Treatment Regimens (%)	Race (%)	Performance Status (%)	Other Factors (%)
Jassem 1993	mn md 59 rng 41-73 sd	M 76 F 24			CR 44 PR 56 SD PD NE	RTx 60		WHO med 1 rng 0-2	
Einhorn 1990		M 58 F 42	LD 50 ED 50			EP 96 CAV 54		KPS med 70 rng 50-100	
Graziano 1990	mn md 60 rng 35-69 sd	M 66 F 34		md 2 mo rng 1-27		md# CTx Rx 4 rng 2-7 md# CTx reg 2 rng 1-10 RTX 74%		CALGB 0 11 1 46 2 40	Time since diagnosis < 1 yr 71 ≥ 1 yr 29
JCOGLC 1990									
Sculier 1990	mn md 59 rng 36-74 sd	M 93 F 7	LD 33 ED 67		CR/ PR 47	PEV 36 EV 64		KPS md 70 rng 50-90	
Issell 1985	mn md 60 rng 27-85 sd	M 74 F 26	LD 17 ED 83			ADR –CCNU 61 CCNU –ADR 21 ADR+CCNU 18		ECOG 0-1 49 2-4 51	1st relapse 80 2nd relapse 17 3rd relapse 3

Question 9. Treatment of Recurrent/Relapsed Disease
Table 9J: Treatments, Phase II Studies

Study	Treatment Regimen			Outcomes	Response Criteria	Observer	Follow-up
Ando. 2004	Agent Irinotecan Cisplatin	Dose 60 mg/m^2 30 mg/m^2	Schedule d1, 8, 15, q 4 wks, ≥ 2 cycles if no PD d1, 8, 15, q 4 wks, ≥ 2 cycles if no PD	Tumor response, survival, adverse events	WHO criteria		
Agelaki 2004	Agent Gemcitabine Irinotecan	Dose 1g/ m^2 300 mg/ m^2	Schedule d1, 8, q 21 d to progress-ion/max cycles d8, q 21 d to progress-ion/max cycles	Tumor response, survival, adverse events	WHO criteria		
Goto 2004	Agent Cisplatin Etoposide Irinotecan	Dose 25 mg/m^2 60 mg/m^2 90 mg/m^2	Schedule d1, q 7 d, 9 cycles d1-3, q 21 d, 5 cycles d1, q 14 d, 4 cylces	Tumor response, survival, progression-free survival, adverse events	WHO criteria		
Ardizzoni 2003	Agent Topotecan Cisplatin	Dose .75 mg/ m^2 60 mg/m^2	Schedule d1-5, q 21 d, max 6 cycles d1, q 21 d, max 6 cycles	Tumor response, adverse events, overall survival, time to progression	WHO criteria		
Hainsworth 2003	Agent Vinorelbine Gemcitabine	Dose 20 mg/m^2 1 g/m^2	Schedule d1, 8, 15, q 28 d, max 6 cycles d1, 8, 15, q 28 d, max 6 cycles	Tumor response, response duration, survival, adverse events	CR= all clinically detectable disease gone, ≥ 4 wks PR= ↓ by ≥50%, all measureable lesions, ≥ 4 wks SD= ↓ in lesion size by <50% or ↑ by <25%, no PD ≥ 3 mo PD= ↑ by ≥25%, cross sectional area, ≥1 lesion, or any new lesion		
Hoang 2003	Agent Gemcitabine	Dose 1.25 g/m^2	Schedule d1, 8, q 21 d	Tumor response, time to progression, survival, adverse events	ECOG criteria		
Masters 2003	Agent Gemcitabine	Dose 1 g/m^2	Schedule d1, 8, 15, q 28 d	Tumor response, duration of remission, survival, adverse events	Standard criteria		

Question 9. Treatment of Recurrent/Relapsed Disease
Table 9J: Treatments, Phase II Studies (continued)

Study	Treatment Regimen			Outcomes	Response Criteria	Observer	Follow-up
Kosmas 2001	Agent Paclitaxel Ifosfamide Cisplatin	Dose 175 mg/m^2 5 g/m^2 100 mg/m^2	Schedule d1, planned 6 cycles d1-2, planned 6 cycles d1-2, planned 6 cycles	Tumor response, time to progression, survival, adverse events	CR= no clinical, radiol evidence of tumor, ≥ 4 wks PR= ↓ by ≥50%, all measureable lesions, ≥ 4 wks SD= ↓ in lesion size by <50% or ↑ by ≤25% PD= ↑ by ≥25%, cross sectional area, ≥1 lesion, or any new lesion		
Kakolyris 2001	Agent Paclitaxel Carboplatin	Dose 200 mg/m^2 AUC=6	Schedule d1, q 4 wks, to 6 cycles or response + 3 cycles d2, q 4 wks, to 6 cycles or response + 3 cycles	Tumor response, time to progression, survival, adverse events	WHO criteria		mn md 8 mo rng 1-17.5 sd
van der Lee 2001	Agent Gemcitabine	Dose 1 g/m^2	Schedule d1, 8, 15, q 28 d, max 5 Cycles	Tumor response, survival, adverse events	WHO criteria		
Sessa 2000	Agent GI147211 (camptothecin-derivative)	Dose 1.2 mg/m^2	Schedule d1-5, q 21 d, ≥ 2 cycles	Tumor response, response duration, adverse events	WHO criteria		
Sonpavde 2000	Agent Doxorubicin Paclitaxel	Dose 40 mg/m^2 175 mg/m^2	Schedule q 21 d q 21 d	Tumor response, survival, time to progression, adverse events			
Groen 1999	Agent Paclitaxel Carboplatin	Dose 175 mg/m^2 AUC=7	Schedule q 21 d, max 5 cycles q 21 d, max 5 cycles	Tumor response, response duration, time to progression, survival, adverse events	CR= complete resolution of all signs of known disease, ≥ 4 wks PR= ↓ by ≥50%, all measureable lesions, ≥ 4 wks SD= ↓ in lesion size by <50% or ↑ by <25% PD= ↑ by ≥25%, cross sectional area, ≥1 lesion, or any new lesion		
Ardizzoni 1997	Agent Topotecan	Dose 1.5 mg/ m^2	Schedule d1-5, q 21 d, max 6 mo after max response	Tumor response, time to progression, survival, adverse events			

Question 9. Treatment of Recurrent/Relapsed Disease
Table 9J: Treatments, Phase II Studies (continued)

Study	Treatment Regimen			Outcomes	Response Criteria	Observer	Follow-up
Gridelli 1997	Agent VM-26 Lonidamine	Dose 100 mg/m^2 600 mg	Schedule d1-3, q 21 d, max 6 cycles po, d1-5, q 21 d, max 6 Cycles	Tumor response, progression-free survival, survival, adverse events	WHO criteria		
Einhorn 1995	Agent Ifosfamide Etoposide Cisplatin	Dose 1.2 g/m^2 37.5 mg/m^2 20 mg/m^2	Schedule d1-4, q 28 d, max 4 cycles d1-4, q 28 d, max 4 cycles d1-4, q 28 d, max 4 cycles	Tumor response, adverse events			
Faylona 1995	Agent Ifosfamide Etoposide Cisplatin	Dose 1.2 g/m^2 37.5 mg/m^2 20 mg/m^2	Schedule d1-4, q 28 d, max 4 cycles po, d1-21/d1-14, q 28 d, max 4 cycles d1-4, q 28 d, max 4 cycles	Tumor response, progression-free survival, survival, adverse events	CR= all clinically detectable disease gone, ≥ 4 wks PR= ↓ by ≥50%, all measureable lesions, ≥ 4 wks SD= ↓ in lesion size by <50% or ↑ by <25%, no PD ≥ 3 mo PD= ↑ by ≥25%, cross sectional area, ≥1 lesion, or any new lesion		
Sculier 1995	Agent Carboplatin Cisplatin	Dose 100 mg/m^2 25 mg/m^2	Schedule d1, q 7 d, max 24 cycles d1, q 7 d, max 24 cycles	Tumor response, survival, adverse events	CR= all clinically detectable disease gone, ≥ 4 wks PR= ↓ by ≥50%, all measureable lesions, ≥ 4 wks SD= ↓ in lesion size by <50% or ↑ by <25%, no PD ≥ 3 mo PD= ↑ by ≥25%, cross sectional area, ≥1 lesion, or any new lesion		
Smyth 1994	Agent Docataxel	Dose 100 mg/m^2	Schedule d1, q 21 d, max 7 cycles	Tumor response, respons duration, adverse events	WHO criteria		
Albain 1993	Agent Cytoxan Cytarabine Vincristine	Dose 500 mg/ m^2 250 mg/m^2 2 mg	Schedule d1, q 21 d, max 4 cycles d1, q 21 d, max 4 cycles d14, q 21 d, max 4 cycles	Tumor response, survival, adverse events	SWOG criteria		
Jassem 1993	Agent Vinorelbine	Dose 30 mg/m^2	Schedule d1, q 7 d, max 13 cycles	Tumor response, adverse events	WHO criteria		

Question 9. Treatment of Recurrent/Relapsed Disease
Table 9J: Treatments, Phase II Studies (continued)

Study	Treatment Regimen			Outcomes	Response Criteria	Observer	Follow-up
Einhorn 1990	Agent Etoposide	Dose 50 mg/m^2	Schedule po, daily	Tumor response, response duration, survival, adverse events	CR= no clinical, radiol evidence of tumor, ≥1 mo PR= ↓ by ≥50%, all measureable lesions, ≥1 mo SD= ↓ in lesion size by <50% or ↑ by <25% PD= ↑ by ≥25%, cross sectional area, ≥1 lesion, or any new lesion		
Graziano 1990	Agent Etoposide Cisplatin	Dose 80 mg/m^2 20 mg/m^2	Schedule d1-5, q 21 d, ≥ 2 cycles d1-5, q 21 d, ≥ 2 cycles	Tumor response, survival, adverse events	CR= no clinical, radiol evidence of tumor, ≥ 4 wks PR= ↓ by ≥50%, all measureable lesions, ≥ 4 wks SD= ↓ in lesion size by <50% or ↑ by <25% PD= ↑ by ≥25%, cross sectional area, ≥1 lesion, or any new lesion		
JCOGLC 1990	Agent Carboplatin	Dose 300 mg/m^2	Schedule d1, q 28 d	Tumor response	CR= no clinical, radiol evidence of tumor, ≥1 mo PR= ↓ by ≥50%, all measureable lesions, ≥1 mo SD= ↓ in lesion size by <50% or ↑ by <25% PD= ↑ by ≥25%, cross sectional area, ≥1 lesion, or any new lesion		
Sculier 1990	Agent Cytoxan Vincristine Doxorubicin	Dose 1 g/m^2 1.4 mg/m^2 45 mg/m^2	Schedule d1, q 21-28 d, 10 cycles d1, q 21-28 d, 10 cycles d1, q 21-28 d, 10 cycles	Tumor response	CR= no clinical, radiol evidence of tumor, ≥ 4 wks PR= ↓ by ≥50%, all measureable lesions, ≥ 4 wks SD= ↓ in lesion size by <50% or ↑ by <25% PD= ↑ by ≥25%, cross sectional area, ≥1 lesion, or any new lesion		
Issell 1985	Agent Etoposide	Dose 80 mg/m^2 160 mg/m^2	Schedule d1-5, q 21-28 d po, d2-5, q 21-28 d (last 16 patients)	Tumor response, adverse events			

Question 9. Treatment of Recurrent/Relapsed Disease
Table 9K Survival Outcomes, Phase II Studies

Study	Overall Survival (%)								Progression-Free Survival (%)							
Ando 2004		N	Med	1 yr	2 yr	3 yr	4 yr	5 yr		N	Med	1 yr	2 yr	3 yr	4 yr	5 yr
		25	7.9 mo	44	20											
Agelaki 2004		N	Med	1 yr	2 yr	3 yr	4 yr	5 yr		N	Med	1 yr	2 yr	3 yr	4 yr	5 yr
	Total	31	6 mo	17												
	Refractory	15	5.37 mo													
	Relapsed	16	5.97 mo													
Goto 2004		N	Med	1 yr	2 yr	3 yr	4 yr	5 yr		N	Med	1 yr	2 yr	3 yr	4 yr	5 yr
		40	11.8	49	~15	~5				40	5.0	~10	~3			
Ardizzoni 2003		N	Med	1 yr	2 yr	3 yr	4 yr	5 yr	TTP	N	Med	1 yr	2 yr	3 yr	4 yr	5 yr
	Sensitive	68	6.4 mo	19.7					Sensitive	68	4.7 mo					
	Refractory	42	6.1 mo	15.2					Refractory	42	3.0 mo					
Hainsworth 2003		N	Med	1 yr	2 yr	3 yr	4 yr	5 yr		N	Med	1 yr	2 yr	3 yr	4 yr	5 yr
		30	5 mo	~15												
Hoang 2003		N	Med	1 yr	2 yr	3 yr	4 yr	5 yr		N	Med	1 yr	2 yr	3 yr	4 yr	5 yr
	Sensitive	15	8.8 mo	33.3					Sensitive	15	6 mo					
	Refractory	12	4.2	16.7					Refractory	12	5.6					
	Total	27	6.4	25.4					Total	27	6					
Masters 2003		N	Med	1 yr	2 yr	3 yr	4 yr	5 yr		N	Med	1 yr	2 yr	3 yr	4 yr	5 yr
	Relapsed	24	7.3													
	Refractory	18	6.9													
	Total	42	7.1	~28												
Kosmas 2001		N	Med	1 yr	2 yr	3 yr	4 yr	5 yr	TTP	N	Med	1 yr	2 yr	3 yr	4 yr	5 yr
		33	28 wks	12						33	20 wks					
Kakolyris 2001		N	Med	1 yr	2 yr	3 yr	4 yr	5 yr	TTP	N	Med	1 yr	2 yr	3 yr	4 yr	5 yr
		32	7 mo	15						32	5.5 mo					
van der Lee 2001		N	Med	6 mo	2 yr	3 yr	4 yr	5 yr		N	Med	1 yr	2 yr	3 yr	4 yr	5 yr
		41	17 wks	30												
Sonpavde 2000		N	Med	1 yr	2 yr	3 yr	4 yr	5 yr	TTP	N	Med	1 yr	2 yr	3 yr	4 yr	5 yr
		46	25 wks							46	14 wks					
Groen 2000		N	Med	1 yr	2 yr	3 yr	4 yr	5 yr	TTP	N	Med	1 yr	2 yr	3 yr	4 yr	5 yr
		34	31 wks	9						34	21 wks					
Ardizzoni 1997		N	Med	1 yr	2 yr	3 yr	4 yr	5 yr	TTP	N	Med	1 yr	2 yr	3 yr	4 yr	5 yr
	Sensitive	46	6.9 mo	~28					Overall	93	2.8 mo					
	Refractory	47	4.7 mo	~9												
Gridelli 1997		N	Med	1 yr	2 yr	3 yr	4 yr	5 yr	PFS	N	Med	1 yr	2 yr	3 yr	4 yr	5 yr
		30	4 mo	10%						30	2 mo					
Einhorn 1995		N	Med	1 yr	2 yr	3 yr	4 yr	5 yr		N	Med	1 yr	2 yr	3 yr	4 yr	5 yr
		41	29 wks													
Faylona 1995		N	Med	1 yr	2 yr	3 yr	4 yr	5 yr		N	Med	1 yr	2 yr	3 yr	4 yr	5 yr
		42	29 wks	~22						42	20 wks	~5				
Sculier 1995		N	Med	1 yr	2 yr	3 yr	4 yr	5 yr		N	Med	1 yr	2 yr	3 yr	4 yr	5 yr
		40	16.6 wks	~10												
Albain 1993		N	Med	6 mo	2 yr	3 yr	4 yr	5 yr		N	Med	1 yr	2 yr	3 yr	4 yr	5 yr
		67	2.5 mo	16												

Question 9. Treatment of Recurrent/Relapsed Disease
Table 9K Survival Outcomes, Phase II Studies (continued)

Study	Overall Survival (%)							Progression-Free Survival (%)						
Einhorn 1990	N 26	Med 18 wks	1 yr	2 yr	3 yr	4 yr	5 yr	N	Med	1 yr	2 yr	3 yr	4 yr	5 yr
Graziano 1990	N 35	Med 6.0 mo	1 yr 14	2 yr	3 yr	4 yr	5 yr	N	Med	1 yr	2 yr	3 yr	4 yr	5 yr
Sculier 1990	N	Med	1 yr	2 yr	3 yr	4 yr	5 yr	N	Med	1 yr	2 yr	3 yr	4 yr	5 yr
Issell 1985	N 95	Med 12 wks	1 yr	2 yr	3 yr	4 yr	5 yr	N	Med	1 yr	2 yr	3 yr	4 yr	5 yr

Question 9. Treatment of Recurrent/Relapsed Disease
Table 9L Tumor Response and Quality of Life, Phase II Studies

Study	Tumor Response (%)							Quality of Life				
Ando 2004		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	n	mn±sd
	Refractory	16	0	81	13	6						
	Relapsed	9	0	78	22	0						
	Total	25		80	16	4						
Agelaki 2004		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	n	mn±sd
	Total	31	0	10	22	68						
	Refractory	15		13								
	Relapsed	15		6								
Goto 2004		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	n	mn±sd
		40	13	65	10	10	3					
Ardizzonl 2003		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	n	mn±sd
	Sensitive	68	1.5	27.9	36.8	5.9	14.7					
	Refractory	42	0	23.8	26.2	38.1	9.5					
Hainsworth 2003		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	n	mn±sd
		28	0	10	36	54						
Hoang 2003		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	n	mn±sd
		27	0	0	11	78						
Masters 2003		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	n	mn±sd
	Relapsed	24	0	16.7	0	75.0	8.3					
	Refractory	18	0	5.6	5.6	88.9	0					
	Total	42	0	11.9	2.4	81.0	4.8					
Kosmas 2001		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	n	mn±sd
		33	24.2	48.5	15	12						
Kakolyris 2001		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	n	mn±sd
		32	3	22	22	53						
	median response duration 3 mo (1-9)											
van der Lee 2001		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	n	mn±sd
		38	0	13	21	66						
Sessa 2000		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	n	mn±sd
		66	0	16.6	32							
	median response duration 160 d (129-189) PR											
	median response duration 146.5 d (77-321) SD											
Sonpavde 2000		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	n	mn±sd
		46	7	35	13							
Groen 1999		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	n	mn±sd
		34	6	68	24	3						
Ardizzoni 1997		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	n	mn±sd
	Sensitive	46	13	24	31	29	2					
	Refractory	47	2	4	40	43	0					
	Total	93	8	14	36	36	1					
	Median response duration 7.6 mo (5.1-12.2)											
Gridelli 1997		N	CR	PR	SD	PD	NE	Scale	Domain	F/U	n	mn±sd
		30	3.3	10	10	70						

Question 9. Treatment of Recurrent/Relapsed Disease
Table 9L Tumor Response and Quality of Life, Phase II Studies (continued)

Study	Tumor Response (%)						Quality of Life				
Einhorn 1995	N	CR	PR	SD	PD	NE	Scale	Domain	F/U	n	mn±sd
	41	15	39								
Faylona 1995	N	CR	PR	SD	PD	NE	Scale	Domain	F/U	n	mn±sd
	42	14	40								
Sculier 1995	N	CR	PR	SD	PD	NE	Scale	Domain	F/U	n	mn±sd
	38	13	21	55							
Smyth 1994	N	CR	PR	SD	PD	NE	Scale	Domain	F/U	n	mn±sd
	34	0	21	21	35	18					
	median response duration 4.7 mo (3.5-12.6)										
Albain 1993	N	CR	PR	SD	PD	NE	Scale	Domain	F/U	n	mn±sd
	67	0	4	15							
Jassem 1993	N	CR	PR	SD	PD	NE	Scale	Domain	F/U	n	mn±sd
	25	0	16	28	48						
Einhorn 1990	N	CR	PR	SD	PD	NE	Scale	Domain	F/U	n	mn±sd
	26	4	19	23							
	median response duration 9 wks (6-20)										
Graziano 1990	N	CR	PR	SD	PD	NE	Scale	Domain	F/U	n	mn±sd
	35	3	17	43	17						
JCOGLC 1990	N	CR	PR	SD	PD	NE	Scale	Domain	F/U	n	mn±sd
	31	38.7									
Sculier 1990	N	CR	PR	SD	PD	NE	Scale	Domain	F/U	n	mn±sd
	45	0	13	31	56						
Issell 1985	N	CR	PR	SD	PD	NE	Scale	Domain	F/U	n	mn±sd
	95	1	11								

Question 9. Treatment of Recurrent/Relapsed Disease
Table 9M: Adverse Events, Phase II Studies

Toxicity Type	Study	Group/Description	n	Gr 3 %	Gr 4 %
Treatment-related mortality	Agelaki 2004		31	0	
	Ardizzoni 2003	Sensitive, early death, toxicity	68	7.4	
		Refractory, early death, toxicity	42	0	
	Hainsworth 2003		30	0	
	Groen 1999		35	0	
	Gridelli 1997		30	0	
	Faylona 1995		42	14	
	Albain 1993		67	6	
	Sculier 1990		45	2	
	Issell 1985		95	1	
Alopecia	Ando 2004		25	0	
	Goto 2004		40	0	
	Ardizzoni 2003	Sensitive	68	19	0
		Refractory	42	10	0
	Hainsworth 2003		30	0 (3/4)	
	Masters, 2003		44	0	0
	Kosmas 2001		33	100	0
	Sessa 2000		241 cycles	0	0
	Ardizzoni 1997		403 cycles	0.7	0
	Gridelli 1997		30	10	0
	Smyth 1994		27	0	0
	Jassem 1993		25	28	4
Fatigue	Agelaki 2004		31	13	
	Hainsworth 2003		30	17 (3/4)	
	Masters, 2003		44	2	0
	Kosmas 2001		33	0	0
	Kakolyris 2001		32	19	0
	Groen 1999		35	0	0
	Ardizzoni 1997	Fatigue/malaise	403 cycles	2.7	0.7
	Smyth 1994	Asthenia/malaise/fatigue	22	27	5
Diarrhea	Ando 2004		25	8	0
	Agelakii 2004		31	10(3/4)	
	Goto 2004		40	8	
	Ardizzoni 2003	Sensitive	68	1	1
		Refractory	42	2	0
	Kosmas 2001		33	0	0
	Kakolyris 2001		32	0	0
	Sonpavde 2000		46	2	
	Groen 1999		35	0	3
	Ardizzoni 1997		403 cycles	0.2	0
	Faylona 1995		42	2	
	Smyth 1994		14	7	0

Question 9. Treatment of Recurrent/Relapsed Disease
Table 9M: Adverse Events, Phase II Studies (continued)

Toxicity Type	Study	Group/Description	n	Gr 3 %	Gr 4 %
Nausea	Ardizzoni 2003	Sensitive	68	3	0
		Refractory	42	2	0
	Masters, 2003		44	2	0
	van der Lee 2001		38	0	0
	Sessa 2000		241 cycles	2.4	0.4
	Groen 1999		35	0	0
	Ardizzoni 1997		403 cycles	0.7	0
	Smyth 1994		16	13	0
	Jassem 1993		25	0	0
Vomiting	Ando 2004	Nausea and vomiting	25	0	0
	Goto 2004	Nausea and vomiting	40	8	
	Ardizzoni 2003	Sensitive	68	0	0
		Refractory	32	10	0
	Hainsworth 2003	Nausea and vomiting	30	3 (3/4)	
	Masters, 2003		44	0	2
	Kosmas 2001	Nausea and vomiting	33	18	0
	Kakolyris 2001	Nausea and vomiting	32	0	0
	Sessa 2000		241 cycles	1.2	0
	Groen 1999		35	0	0
	Ardizzoni 1997		403 cycles	0.2	0
	Gridelli 1997	Nausea and vomiting	30	0	0
	Faylona 1995	Nausea and vomiting	42	2	
	Sculier 1995	Nausea and vomiting	38	3	3
	Smyth 1994		11	0	0
	Jassem 1993	Nausea and vomiting	25	0	0
Anorexia	Ardizzoni 2003	Sensitive	68	4	1
		Refractory	32	2	0
	Masters, 2003		44	2	0
Lethargy	Ardizzoni 2003	Sensitive	68	15	0
		Refractory	32	7	0
Neurosensory	Ardizzoni 2003	Sensitive	68	1	0
		Refractory	32	0	0
	Masters 2003		44	0	0
	Kakolyris 2001	Neurotoxicity	32	0	0
	Sonpavde 2000	Neurotoxicity	46	11	
	Groen 1999	Paresthesia	35	3	0
	Faylona 1995	Neurologic	42	12	
	Sculier 1995	Neurological	35	3	0
	Smyth 1994		14	7	7
	Jassem 1993	Neurotoxicity	25	4	0
Neuromotor	Ardizzoni 2003	Sensitive	68	1	0
		Refractory	32	0	2
	Masters 2003		44	14	0

Question 9. Treatment of Recurrent/Relapsed Disease
Table 9M: Adverse Events, Phase II Studies (continued)

Toxicity Type	Study	Group/Description	n	Gr 3 %	Gr 4 %
Hearing loss					
Esophagitis	Faylona 1995		42	2	2
Bronchopulmonary	Ando 2004		25	0	
	Ardizzoni 2003	Shortness of breath, sensitive Refractory	68 42	10 7	0 2
	Masters, 2003		44	9	0
	Kosmas 2001		33	0	0
	van der Lee 2001	Dyspnea	38	0	0
	Faylona 1995		42	2	
Pneumonitis	Hoang 2003		27		4 (5)
Hepatic	Ando 2004		25	0	0
	Goto 2004		40	3	
	Groen 1999	AST/ALT elevation	35	0	0
	Ardizzoni 1997		403 cycles	1.0	0
	Gridelli 1997		30	6.6	0
Kidney	Ando 2004		25	0	0
	Goto 2004		40	0	
	Kosmas 2001		33	0	0
	Einhorn 1995		41	2	2
	Faylona 1995		42	2	2
	Sculier 1995		35	0	0
Hemorrhage	Ardizzoni 2003	Sensitive Refractory	68 42	21 (1-3) 26 (1-3)	
	Masters, 2003		44	9	0
	Sculier 1995		35	0	0
Anemia	Ando 2004		25	4	0
	Goto 2004		40	45	
	Hainsworth 2003		30	0	6
	Masters, 2003		44	5	2
	Kosmas 2001		33	18	0
	Kakolyris 2001		32	0	3
	van der Lee 2001		38	0	0
	Sessa 2000		241 cycles	3	0.4
	Groen 1999		132 cycles	17	0
	Ardizzoni 1997		403 cycles	8.9	2.9
	Gridelli 1997		30	0	0
	Faylona 1995		42	29	2
	Smyth 1994		22	5	0
	Jassem 1993		25	4	0

Question 9. Treatment of Recurrent/Relapsed Disease
Table 9M: Adverse Events, Phase II Studies (continued)

Toxicity Type	Study	Group/Description	n	Gr 3 %	Gr 4 %
Thrombocytopenia	Ando 2004		25	12	0
	Goto 2004		40	33	
	Hainsworth 2003		30	37	3
	Hoang 2003		27	30	0
	Masters, 2003		44	18	9
	Kosmas 2001		33	36	9
	Kakolyris 2001		32	9	0
	van der Lee 2001		38	29	0
	Sessa 2000		241 cycles	15	7
	Groen 1999		132 cycles	21	10
	Ardizzoni 1997		403 cycles	17.6	11.9
	Gridelli 1997		30	0	6.6
	Einhorn 1995		41		48
	Faylona 1995		42	24	48
	Sculier 1995		38	31	13
	Smyth 1994		5	0	0
	Jassem 1993		25	0	0
Leukopenia or neutropenia	Ando 2004	Neutropenia	25	12	12
	Agelaki 2004	Neutropenia	31	29	(3 or 4)
		Febrile neutropenia		6	
	Goto 2004	Leukopenia	40	55	
		Neutropenia		73	
	Ardizzoni 2003	Sensitive, Leukopenia	68	33.8	47.1
		Neutropenia,		14.7	61.8
		≥ 1 episode febrile neutropenia		19	
		Refractory, Leukopenia	42	43.9	31.7
		Neutropenia		26.8	48.8
		≥ 1 episode febrile neutropenia		15	
	Hainsworth 2003	Leukopenia	30	20	6
		Granulocytopenia	30	33	10
	Hoang 2003	Neutropenia	27	15	15
		Febrile Neutropenia	27	4	0
	Masters, 2003	Leukopenia	44	16	2
		Granulocytopenia	44	20	7
	Kosmas 2001	Leukopenia	33	27	46
		Neutropenia	33	18	73
		Febrile neurtropenia	33	18	
	Kakolyris 2001	Neutropenia	32	22	16
	van der Lee 2001	Leukopenia	38	18	0
	Sessa 2000	Neutropenia	241 cycles	16.5	9
	Sonpavde 2000	Granulocytopenia	46	17	63
	Groen 1999	Leukopenia	132 cycles	27	6

Question 9. Treatment of Recurrent/Relapsed Disease
Table 9M: Adverse Events, Phase II Studies (continued)

Toxicity Type	Study	Group/Description	n	Gr 3 %	Gr 4 %
Leukopenia or neutropenia	Ardizzoni 1997	Leukopenia Neutropenia	403 cycles	58.5 28.0	9.9 46.9
	Gridelli 1997	Leukopenia	30	13.3	13.3
	Einhorn 1995	Granulocytopenia	41		71
	Faylona 1995	Granulocytopenia	42	33	71
	Sculier 1995	Leukopenia	38	8	5
	Smyth 1994	Leukopenia Neutropenia	32 31	41 23	28 71
	Jassem 1993	Leukopenia Neutropenia	25 25	28 16	4 16
	Sculier 1990	Leukopenia	45	27	3
Infection	Goto 2004		40	3	
	Goto 2004	Fever	40	0	
	Masters, 2003	Fever	44	0	0
	van der Lee 2001	Fever	38	0	0
	Sessa 2000		241 cycles	1.2	0.4
	Ardizzoni 1997		403 cycles	1.0	0.5
	Faylona 1995		42		29 10(5)
	Sculier 1995		35	0	0
	Smyth 1994		13	15	15
	Jassem 1993		25	0	0
Other	Goto 2004	Hyponatremia	40	5	
	Goto 2004	Mucositis	40	0	
	Goto 2004	Arrhythmia	40	5	
	Goto 2004	Eruption	40	3	
	Goto 2004	Allergy	40	0	

Acronyms/Abbreviations Used in Tables

-	without
#	number
#	number
Δ	change
?	unknown, unclear
+	with
<p	less than a partial resection
1°	primary
18-FDG	18-fluorodeoxyglucose
95% CIL	lower limit 95% confidence interval
95% CIU	upper limit 95% confidence interval
A	Asian
A	doxorubicin (Adriamycin®)
abstr	abstract
ACCP	American College of Chest Physicians
AHRQ	Agency for Healthcare Research and Quality
ALT	alanine transaminase
Alt	alternating
AP	anterioposterior
ASCO	American Society of Clinical Oncology
AST	aspartate transaminases
ASTRO	American Society for Therapeutic Radiology and Oncology
B	bilobectomy
B	Black
BSC	best supportive care
c	complete
C	cyclophosphamide
CALGB	Cancer and Leukemia Group B
Cb	carboplatin
CCNU	lomustine
CD	cyclophosphamide- and/or doxorubicin-based chemotherapy
chemoTx	chemotherapy
CI	confidence interval
CNS	central nervous system
Conc	concurrent
cont'd	continued
contr	contralateral
Conv	conventional
CPHM	Cox proportional hazard model
CR	complete response
CT	computed tomography
Ctrl	control
CTx	chemotherapy
d	day
DA	diagnostic accuracy
dist	distant
Dx	diagnosis
E Alt	early alternating
E	etoposide
E	etoposide
ea	each
ECOG	Eastern Cooperative Oncology Group
endosc	endoscopic
EORTC LCCG	European Organization for the Research and

	Treatment of Cancer Lung Cancer Cooperative Group
EPC	Evidence-based Practice Center
EQ-5D	EuroQOL 5-dimension health-related quality of life instrument
ES	extensive stage
ESD	extensive-stage disease
F	female
F	fractions
F/d	fractions per day
F/U	follow-up
FDA	Food and Drug Administration
FE	fixed effects
FEV1	forced expiratory volume in 1 second
FN	false negative
FNA	fine-needle aspiration
FP	false positive
Frac(s)	fraction(s)
FWHM	full width, half maximum
GQ	good quality
Gy	Gray
H	Hispanic
HL	hilar
HR	hazard ratio
hr	hour
Hyper	hyperfractionated
ips	ipsilateral
IV	intravenous
K-M	Kaplan-Meier
KPS	Karnofsky Performance Status
L Alt	late alternating
L	lobectomy
L	lomustine
L95	upper limit 95% confidence interval
LCSG	Lung Cancer Study Group
LDH	lactic dehydrogenase
LINAC	linear accelerator
LN	lymph node
LRFS	local recurrence-free survival
LRFS	local recurrence-free survival
LS	limited stage
LSD	limited-stage disease
M	male
M	methotrexate
MBq	megabecquerel
mCi	milliCurie
md	median
MD	mediastinal
mets	metastases
MeV	megaelectron volt
mg	milligram
M-H	Mantel-Haenszel
MI	myocardial infarction
mn	mean
mo(s).	month(s)
MR	meta regression
MRI	magnetic resonance imaging
MS	mediastinal
N	no

n	number
N	pooled number
NCI	National Cancer Institute
NE	not evaluable
NED	no evidence of disease
neg	negative
NNEC	non-neuroendocrine carcinoma
NNT	number needed to treat
nonrandom.	nonrandomized
NOS	not otherwise specified
NR	not reported
NS	nonsignificant
NSCLC	non-small-cell lung cancer
O	other
OR	odds ratio
ORR	overall response rate
OS	overall survival
P	cisplatin
p	partial
P	pneumonectomy
PA	posterioanterior
PCI	prophylactic cranial radiation
PD	progressive disease
PE	platinum/etoposide chemotherapy
PET	positron emission tomography
PFS	progression-free survival
PI	primary investigator
po	oral
P-OR	Peto odds ratio
pos	positive
PR	partial response
PS	performance status
Pt	platinum
pub	publication
PWIFR	percent/proportion with in-field recurrence
Q	heterogeneity statistic
QoL	quality of life
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
R/I	ruled in
R/O	ruled out
radiol	radiologic
RadioTx	radiotherapy
RCT	randomized, controlled trial
RD	risk difference
RE	random effects
reg	regimen
regl	regional
retrospect	retrospective
RFS	recurrence-free survival
rng	range
RNS	radionuclide scan
ROC	receiver operating characteristic
RR	relative risk
RR	risk ratio
SC	supraclavicular
SC/LC	small-cell/large-cell subtype
SCLC	small cell lung cancer
SD	stable disease
SE	standard error

Sens	sensitivity
Seq	sequential
Spec	specificity
STARD	Standards for Reporting of Diagnostic Accuracy
sup-clav	supraclavicular
supraclav	supraclavicular
surg	surgery
SWOG	Southwest Oncology Group
T	thoracotomy only (open and close)
TN	true negative
TNM	Tumor, Node, Metastasis (staging system)
TP	true positive
TRTx	thoracic radiotherapy
TTF	time to failure
Tx	treatment; therapy
U.S.	United States
U95	upper limit 95% confidence interval
ULN	upper limit of normal
US	ultrasound
V	vincristine
VC	vital capacity
Ve	vindesine
W	White
WBC	white blood cell
WHO	World Health Organization
wk(s)	week(s)
Wt	weight
XRT	radiotherapy
Y	yes
yr	year

Abbreviations of Combination Chemotherapy Regimens

ACO	doxorubicin, cyclophosphamide, and vincristine
ACOM	doxorubicin, lomustine, methotrexate, vincristine
BTOC	vincristine, thiotepa, cyclophosphamide, carmustine
CAE	cyclophosphamide, doxorubicin, etoposide
CAV	cyclophosphamide, doxorubicin, vincristine
CbE	carboplatin, etoposide
CbPE	carboplatin, cisplatin, etoposide
CC	cyclophosphamide, lomustine
CCM	cyclophosphamide, lomustine, methotrexate
CCMV	cyclophosphamide, lomustine, methotrexate, vincristine
CDE	cyclophosphamide, doxorubicin, etoposide
CE-CAP	cyclophosphamide, doxorubicin, cisplatin
COME	cyclophosphamide, vincristine, methotrexate, etoposide
COMF	cyclophosphamide, vincristine, methotrexate, fluorouracil
CVMP	cyclophosphamide, vincristine, methotrexate, cisplatin
EP	etoposide, platinum compound
iv T	intravenous topotecan
LCAE	lomustine, cyclophosphamide, doxorubicin, etoposide
M-CAV	methotrexate, cyclophosphamide, doxorubicin, vincristine
MCCC/VI	methotrexate, cyclophosphamide, lomustine, ifosfamide, etoposide
PE	cisplatin, etoposide
PEVe	platinum, epirubicin, etoposide
PMP	cisplatin, methotrexate, procarbazine
po T	oral topotecan
VCMV	vincristine, cyclophosphamide, mitomycin, chromomycin
VIC-E/VICE	vincristine, ifosfamide, carboplatin, etoposide
VIMP	vincristine, ifosfamide, mesna, carboplatin
VIP-E	etoposide, ifosfamide, cisplatin, and epirubicin

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Appendix D. Listing of Excluded Studies

Exclusion Codes

UNR study unrelated to treatment/staging of SCLC (citation review)

FNA foreign language, no abstract
INV investigational therapy
NPD no primary data
NRA narrative review article
NRD non-relevant disease
NSP not correct study population
NRQ non-relevant study question
NSD not correct study design
SCS single center phase II single arm study

FEW too few subjects
<50 for single-arm studies, XRT, PCI (Qs 1-4)
<25 for diagnostic accuracy studies (Q5); single-arm studies, mixed SCLC/NSCLC, surgery, 2nd+-line therapy (Qs 6-8)
(no lower limit for RCTs)

Controlled trial of twelve versus six courses of chemotherapy in the treatment of small-cell lung cancer. Report to the Medical Research Council by its Lung Cancer Working Party. Br J Cancer. 1989 Apr;59(4):584-90.
Notes: NRQ

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Notes: NRQ

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Notes: NRA

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Notes: NPD NRQ

Agelaki S, Veslemes M, Syrigos K, et al. A multicenter phase II study of the combination of gemcitabine and docetaxel in previously treated patients with small cell lung cancer. Lung Cancer 2004; 43(3):329-33.
Notes: FEW

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Notes: NRQ

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Notes: NRQ; may inform Q7

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Notes: NSD

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Notes: NRQ

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Notes: FEW, NSD

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Notes: INV

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Notes: NRQ

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Notes: NSD

Armstrong JG. Long-term outcome of small cell lung cancer. Cancer Treat Rev 1990; 17(1):1-13.
Notes: NRA

Armstrong JG, Rosenstein MM, Kris MG, et al. Twice daily thoracic irradiation for limited small cell lung cancer. Int J Radiat Oncol Biol Phys 1991; 21(5):1269-74.
Notes: NSD

Armstrong JG, Rosenstein MM, Scher HI, et al. Limited small cell lung cancer: prognostic significance of a complete response to the induction phase of chemotherapy followed by thoracic irradiation. Radiology 1991; 178(3):875-8.
Notes: NRQ

Arriagada R. Re: Prophylactic cranial irradiation for patients with small-cell lung cancer. J Natl Cancer Inst 1995; 87(10):766; author reply 767.
Notes: NPD

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Notes: NPD

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Notes: NSD

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Notes: NRQ

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Notes: NSD

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Notes: NRQ

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Notes: NPD

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Notes: NRQ

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Notes: NRQ

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Notes: NSD

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Notes: NPD; but maybe cite in write-up for Q1

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Notes: NPD

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Notes: NSP NRD (NSCLC)

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Notes: INV

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Notes: NRA

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Notes: NRQ

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Notes: FEW

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Notes: NPD

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Notes: SCS

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Notes: NSD

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Notes: NRQ

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Notes: NRQ

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Notes: NRA

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Notes: NPD

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Notes: NRA

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Notes: NRA

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Notes: NRQ; large cell neuroendocrine

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Notes: SCS

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Notes: NRQ

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Notes: NRQ

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Notes: FEW

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Notes: NSP

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Notes: SCS

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Notes: NRQ NSD

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Notes: NRQ

Appendix E. Technical Expert Panel (TEP) and Reviewers

Technical Expert Panel (TEP)

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