Evidence-based Series 7-13-2 EDUCATION AND INFORMATION 2013

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Prophylactic Cranial Irradiation in Small Cell Lung Cancer

Kotalik J, Yu E, Markman BR, Evans WK, and members of the Lung Cancer Disease Site Group

Report Date: November 2003

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See Section 3: Document Summary and Review Tool for details.

The reviewed EBS report, which is available on the CCO Web site (http://www.cancercare.on.ca), consists of the following three sections:

Section 1: Clinical Practice Guideline
Section 2: Systematic Review
Section 3: Document Summary and Review Tool

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### Guideline Report History

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A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Prophylactic Cranial Irradiation in Small Cell Lung Cancer: A Clinical Practice Guideline

Kotalik J, Yu E, Markman BR, Evans WK, and members of the Lung Cancer Disease Site Group

The 2003 guideline recommendations require an UPDATE

This means that the DSG/GDG will rewrite the guideline at the earliest opportunity. Until then the recommendations remain of some use in clinical decision making. Please see Section 3: Document Summary and Review Tool for a summary of updated evidence published between 2003 and 2012.

Report Date: November 2003

Guideline Questions
1. What is the role of prophylactic cranial irradiation in patients with small cell lung cancer who have achieved complete response/remission?
2. What dose and fractionation schedules of prophylactic cranial irradiation are optimal?
3. Does the use of prophylactic cranial irradiation in patients with small cell lung cancer in complete remission affect quality of life?

Target Population
These recommendations apply to adult patients with limited- or extensive-stage small cell lung cancer who have achieved complete remission in response to induction therapy (chemotherapy or chemoradiotherapy).

Recommendations
• For patients who have achieved complete response after induction therapy, prophylactic cranial irradiation is recommended. There is insufficient evidence to make a definitive recommendation with respect to dose. There is some indication that 30 to 36 Gy in 2 to 3 Gy per fraction or a biologically equivalent dose may produce a better outcome than a lower dose or less aggressive fractionation regimen.

Qualifying Statements
• The schedule commonly used in Canada is 25 Gy in 10 fractions over two weeks. Data from further research, including a trial currently ongoing that compares 25 Gy in 10
fractions with 36 Gy in 18 fractions, will be required to determine optimal dose of prophylactic cranial irradiation.

- There is insufficient evidence to make recommendations concerning the optimal timing of prophylactic cranial irradiation in relation to the administration of chemotherapy. Lung Cancer Disease Site Group members generally felt that it should be given as soon as possible after completion of chemotherapy.

Methods

Entries to MEDLINE (1985 through October 2003), CANCERLIT (1985 through October 2002), EMBASE (1980 through 2003, week 34), and the Cochrane Library (2003, Issue 4) databases were systematically searched for evidence relevant to this practice guideline report.

Evidence was selected and reviewed by two members of the Practice Guidelines Initiative’s Lung Cancer Disease Site Group and methodologists. This practice guideline report has been reviewed and approved by the Lung Cancer Disease Site Group, which comprises medical and radiation oncologists, pathologists, surgeons, a medical sociologist, and patient representatives.

External review by Ontario practitioners was obtained through a mailed survey. Final approval of the practice guideline report was obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Key Evidence Update

- There is strong evidence to recommend prophylactic cranial irradiation for patients who have achieved complete remission following chemotherapy or chemoradiotherapy. Data from randomized controlled trials demonstrate that prophylactic cranial irradiation decreases the frequency of brain metastases and increases disease-free survival in these patients. Two meta-analyses conducted on an overlapping set of studies report increased overall survival, and one reports increased disease-free survival with prophylactic cranial irradiation.

- There is evidence from randomized controlled trials with data for up to two years of follow-up that prophylactic cranial irradiation does not produce significant late neurotoxicity. There is evidence from one randomized controlled trial that prophylactic cranial irradiation does not have a detrimental effect on quality of life in the first 12 months following the completion of therapy. There is insufficient evidence to comment on the long-term effects of prophylactic cranial irradiation on quality of life.

Related Guidelines

Practice Guidelines Initiative Practice Guideline Report:

- #7-13-1: The role of combination chemotherapy in the initial management of limited-stage small-cell lung cancer.
- #7-13-3: The role of thoracic radiotherapy as an adjunct to standard chemotherapy in limited-stage small cell lung cancer.
**Funding**
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Evidence-Based Series 7-13-2: Section 2

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Prophylactic Cranial Irradiation in Small Cell Lung Cancer: A Systematic Review

Kotalik J, Yu E, Markman BR, Evans WK, and members of the Lung Cancer Disease Site Group

The 2003 guideline recommendations require an UPDATE

This means that the DSG/GDG will rewrite the guideline at the earliest opportunity. Until then the recommendations remain of some use in clinical decision making. Please see Section 3: Document Summary and Review Tool for a summary of updated evidence published between 2003 and 2012.

Report Date: November 2003

I. QUESTIONS
1. What is the role of prophylactic cranial irradiation (PCI) in patients with small cell lung cancer (SCLC) who have achieved complete response/remission?
2. What dose and fractionation schedules of PCI are optimal?
3. Does the use of PCI in patients with SCLC in complete remission affect quality of life?

II. CHOICE OF TOPIC AND RATIONALE
Brain metastases are a common cause of treatment failure, particularly in patients with SCLC who have achieved a complete response with chemotherapy or chemoradiotherapy (1,2). Although PCI is known to be effective in reducing the rate of metastases, its role in the management of patients with SCLC has been controversial. There has been uncertainty about whether there is any survival benefit with PCI and whether the risks of late-occurring neurologic toxic effects outweigh any treatment benefit.

III. METHODS
Guideline Development
This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario’s Program in Evidence-based Care, using the methods of the Practice Guidelines Development Cycle (1u). Evidence was selected and reviewed by two members of the PGI’s Lung Cancer Disease Site Group (Lung DSG) and methodologists. Members of the Lung DSG disclosed potential conflict of interest information.
The practice guideline report is a convenient and up-to-date source of the best available evidence on the use of PCI in SCLC, developed through systematic reviews, evidence synthesis, and input from practitioners in Ontario. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the DSG are offered. The report is intended to promote evidence-based practice. The Practice Guidelines Initiative is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners was obtained through a mailed survey consisting of items that address the quality of the original draft practice guideline report and recommendations and whether the recommendations should serve as a practice guideline. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee (PGCC).

The PGI has a formal standardized process to ensure the currency of each guideline report. This consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

**Literature Search Strategy** MEDLINE (1985 through December 1999), CANCERLIT (1985 through October 1999), and the Cochrane Library (1999, Issue 4) databases were systematically searched. “Carcinoma, small cell” (Medical subject heading (MeSH)) was combined with “cranial irradiation” (MeSH) and each of the following phrases used as text words: “prophylactic cranial irradiation”, “whole brain irradiation”, “elective brain irradiation”, “prophylactic brain irradiation”, “prophylactic whole brain irradiation”, “whole brain radiation”. These terms were then combined with the search terms for the following study designs: practice guidelines, systematic reviews, meta-analyses, reviews, randomized controlled trials, and controlled clinical trials. In addition, the Physician Data Query (PDQ) clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) was searched for reports of new or ongoing trials. Relevant articles and abstracts were selected and reviewed by three reviewers and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles.

**Update**

The original literature search has been updated using MEDLINE (through October 2003), CANCERLIT (through October 2002), EMBASE (1980 through 2003, week 34), the Cochrane Library (2003, Issue 4), and the conference proceedings of the 1997-2003 annual meetings of the American Society of Clinical Oncology. The PDQ clinical trials database was also searched for reports of new or ongoing trials.

**Inclusion Criteria**

Articles were selected for inclusion in this overview of the evidence if they were the following:
1. Meta-analyses or individual randomized controlled trials that compared the administration of PCI with no administration of PCI to patients with SCLC who had achieved complete response to induction therapy (chemotherapy or chemoradiotherapy).
2. Abstracts of meta-analyses or trials were also considered.

**Exclusion criteria**

1. Phase I and II studies were not considered for inclusion in this report because of the availability of randomized controlled trials.
2. Papers published in a language other than English were not considered.
Synthesizing the Evidence

It was decided not to pool the results of the individual randomized controlled trials because of the availability of an up-to-date, published meta-analysis that included the most recent randomized trials comparing PCI with no PCI in patients with SCLC who had achieved complete response to induction chemotherapy or chemoradiotherapy.

IV. RESULTS

Literature Search Results

The following were eligible for inclusion in the systematic review of the evidence: six randomized controlled trials described in eight reports (3-10); one fully published individual-patient-data meta-analysis (11), which synthesized the data from the six published randomized controlled trials and one additional unpublished study.

Update

One additional relevant meta-analysis was identified from literature search updates (2u).

Outcomes

Randomized Controlled Trials

Table 1 summarizes six randomized controlled trials of PCI compared with observation in patients with SCLC who had achieved complete remission in response to chemotherapy or chemoradiotherapy; data from the trials are presented in Table 2.

Table 1. Published randomized controlled trials comparing patients in complete remission of SCLC who received PCI to those who did not: study descriptions.

<table>
<thead>
<tr>
<th>First Author, Year (Reference)</th>
<th>Accrual Period</th>
<th>Median Follow-up (yrs)</th>
<th>Total N Patients</th>
<th>Initial Treatment</th>
<th>PCI Dose (dose/fx)</th>
<th>PCI N Patients</th>
<th>% with Limited Disease</th>
<th>No PCI N Patients</th>
<th>% with Limited Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aisner 1982 (3) Aisner 1983 (4)</td>
<td>1977-80</td>
<td>Data from interim analysis</td>
<td>29</td>
<td>CT</td>
<td>30 Gy/10 fx (3 Gy)</td>
<td>15</td>
<td>NR</td>
<td>14</td>
<td>NR</td>
</tr>
<tr>
<td>Ohonoshi 1993 (5)</td>
<td>1981-86</td>
<td>8.5</td>
<td>46</td>
<td>CT with/without RT</td>
<td>40 Gy/20 fx (2 Gy)</td>
<td>23</td>
<td>61%</td>
<td>23</td>
<td>70%</td>
</tr>
<tr>
<td>Wagner 1996 (6) ECOG 3589/ RTOG 92-01 (abstract) Arriagada 1995 (7) PCI 85</td>
<td>1991-94</td>
<td>1.5</td>
<td>31</td>
<td>CT with/without RT</td>
<td>25 Gy/10 fx (2.5 Gy)</td>
<td>16</td>
<td>87%</td>
<td>15</td>
<td>73%</td>
</tr>
<tr>
<td>Laplanche 1998 (8) PCI 88</td>
<td>1985-93</td>
<td>5.2</td>
<td>300</td>
<td>CT with/without RT or surgery CT + RT</td>
<td>24 Gy/8 fx (3 Gy) over 12 days, 4 fx/wk *</td>
<td>145</td>
<td>84%</td>
<td>149</td>
<td>79%</td>
</tr>
<tr>
<td>Gregor 1997 (9) UKCCR/ EORTC</td>
<td>1988-94</td>
<td>5</td>
<td>211</td>
<td>CT with/without RT</td>
<td>†</td>
<td>194</td>
<td>100%</td>
<td>120</td>
<td>100%</td>
</tr>
</tbody>
</table>
*  Recommended protocol was 24 Gy/8 fx (3 Gy) over 12 days, 4 fx/wk. However, participating centres were free to use their local protocol, as long as the total dose was 24 to 30 Gy delivered in less than 3 weeks with fractions ≤ 3Gy.

†  During the first period of the trial (1987-91), there were three arms: no PCI vs. PCI 24 Gy/12 fx vs. PCI 36 Gy/18 fx. Trial was redesigned in 1991 with 2 arms: PCI vs. no PCI, with PCI regimen chosen by local radiotherapist from a list of recommended regimens: 20 Gy/5 fx or 24 Gy/8fx or 30 Gy/10fx or 36 Gy/18fx.

Table 2. Published randomized controlled trials comparing patients in complete remission of SCLC who received PCI to those who did not: study outcomes.

<table>
<thead>
<tr>
<th>First Author, Year, (Reference)</th>
<th>Disease-free Survival</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Patients with Brain Metastases (%)</td>
<td>Comparisons of Disease-free Survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aisner 1982 (3)</td>
<td>PCI</td>
<td>At interim analysis: 0 (0%)</td>
</tr>
<tr>
<td>Aroney 1983 (4)</td>
<td>no PCI</td>
<td>5 (36%)</td>
</tr>
<tr>
<td>Ohonoshi 1993 (5)</td>
<td>PCI</td>
<td>Over entire clinical course, median follow-up, 8.5 yrs: 5 (22%)</td>
</tr>
<tr>
<td></td>
<td>no PCI</td>
<td>12 (52%)</td>
</tr>
<tr>
<td>Wagner 1996 (6)</td>
<td>ECOG 3589/ RTOG 92-01 (abstract)</td>
<td>Median follow-up, 1.5 yrs: 3 (19%)</td>
</tr>
<tr>
<td></td>
<td>PCI</td>
<td>8 (53%)</td>
</tr>
<tr>
<td></td>
<td>no PCI</td>
<td>No statistical comparisons reported</td>
</tr>
<tr>
<td>Arriagada 1995 (7) PCI 85</td>
<td>PCI</td>
<td>2-yr NR (40%) (95% CI, 30% to 50%)</td>
</tr>
<tr>
<td></td>
<td>no PCI</td>
<td>9 (67%) (95% CI, 58% to 75%)</td>
</tr>
<tr>
<td>Laplanche 1998 (8) PCI 88</td>
<td>PCI</td>
<td>4-yr NR (44%) (95% CI, 32% to 57%)</td>
</tr>
<tr>
<td></td>
<td>no PCI</td>
<td>11 (51%) (95% CI, 38% to 63%)</td>
</tr>
<tr>
<td>RR brain mets, 0.71 (95% CI, 0.45 to 1.12); p=0.14 logrank</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gregor 1997 (9) UKCCR/ EORTC</td>
<td>PCI†</td>
<td>2-yr/ 3-yr NR (30%)/ NR (38%)</td>
</tr>
<tr>
<td></td>
<td>no PCI</td>
<td>9.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR, 0.86 (95% CI, 0.66 to 1.12); p=0.25 logrank</td>
</tr>
</tbody>
</table>

Notes: CT - chemotherapy, ECOG - Eastern Cooperative Oncology Group, EORTC - European Organization for Research and Treatment of Cancer, fx - fraction(s), Gy - Gray, NR - not reported, PCI - prophylactic cranial irradiation, RT - radiotherapy, RTOG - Radiation Therapy Oncology Group, SCLC - small cell lung cancer, UKCCR - United Kingdom Coordinating Committee for Cancer Research, wk - weeks, yrs - years.

*  Recommended protocol was 24 Gy/8 fx (3 Gy) over 12 days, 4 fx/wk. However, participating centres were free to use their local protocol, as long as the total dose was 24 to 30 Gy delivered in less than 3 weeks with fractions ≤ 3Gy.

†  During the first period of the trial (1987-91), there were three arms: no PCI vs. PCI 24 Gy/12 fx vs. PCI 36 Gy/18 fx. Trial was redesigned in 1991 with 2 arms: PCI vs. no PCI, with PCI regimen chosen by local radiotherapist from a list of recommended regimens: 20 Gy/5 fx or 24 Gy/8fx or 30 Gy/10fx or 36 Gy/18fx.
Aisner et al (3) and Aroney et al (4) reported a small randomized trial that was part of one of three sequential protocols (numbers 7510, 7705, and 8020) carried out at the University of Maryland Cancer Center. Of 40 patients with extensive- and limited-stage SCLC eligible for randomization, 11 patients refused randomization, 15 patients were assigned to PCI, and 14 patients were randomized to observation. At interim analysis, there were significantly fewer patients with brain metastases in the PCI group compared with control. Observation of the patients who had refused randomization and had not received PCI indicated that four of those 11 patients had developed intracranial metastases. Because of the observed benefit of PCI seen at interim analysis, randomization to PCI or control was stopped, and all subsequent patients who achieved complete response to induction therapy were given PCI. Data on long-term neurologic toxicity were not provided.

Ohonoshi et al (5) randomized 46 of 50 eligible patients to PCI or observation. At 8.5 years median follow-up for both groups, there were significantly fewer brain metastases and significantly longer disease-free survival in the PCI group compared with observation. The difference in overall survival between the two groups was not significant. Late neurotoxicity was reported to be infrequent.

Wagner et al (6), in the final report of an incomplete ECOG/RTOG trial (E3589/R92-01) published in abstract form, reported no significant differences in median survival or disease-free survival between PCI and control. The trial was prematurely closed due to slow accrual of patients.

Arriagada et al carried out two of the larger trials evaluating PCI in patients with SCLC who had achieved complete remission. In the first trial (PCI 85), 300 patients were randomized to PCI or control (7). There were significant differences between the groups, favouring PCI, for the overall two-year rate of brain metastases and the two-year rate of brain metastases as an isolated first site of relapse. There were no significant differences between the two groups with respect to two-year overall survival rates, neuropsychological function, or abnormalities observed in computed tomography brain scan.

In the subsequent trial carried out by the same research group (PCI 88) (8), 211 patients were randomized to PCI or observation. There were no significant differences observed between the groups for the four-year cumulative rate of brain metastases, disease-free survival, or overall survival at a median follow-up of five years. This trial was closed prematurely because the publication of the results of PCI 85 (which occurred while this trial was ongoing) convinced the investigators that PCI should be administered to all patients.

Arriagada et al (10) pooled individual patient data from PCI 85 and PCI 88 to obtain results based on 505 patients. There were significant differences in favour of PCI for two-year rates of overall brain metastases and two-year rates of isolated brain metastases but no difference for two-year overall survival rates. Data on late neurological complications were not provided.

Gregor et al (9) reported data from a UKCCCR/EORTC trial carried out from 1987 to 1995 in which 314 SCLC patients were randomized to PCI or observation. The initial protocol randomized patients to one of three arms: PCI 36 (36 Gy over 18 fractions), PCI 24 (24 Gy in 12 fractions) or observation. To increase accrual, the protocol was modified to one of two
groups: clinician’s choice of PCI regimen or observation. In the revised design, the most commonly used PCI regimens were 30 Gy in 10 fractions and 8 Gy in a single dose. PCI data were pooled over both protocols. Results indicated a statistically significant reduction in the percentage of patients with brain metastases and in brain metastasis-free survival for the PCI patients relative to controls. Furthermore, PCI patients demonstrated a survival advantage, although this difference was not statistically significant. There was no evidence of significant cognitive impairment attributable to PCI in psychometric data collected during the first year post-randomization.

All of the above-described randomized controlled trials involved patients who received PCI after completion of induction chemotherapy or chemoradiotherapy that had resulted in complete response. The optimum timing of PCI in relation to the administration of chemotherapy was not evaluated.

**Meta-analysis**

Aupérin et al (11) conducted a meta-analysis on individual patient data from seven trials (six trials reported above and one unpublished trial carried out by a group of Danish researchers in collaboration with the National Cancer Institute). The meta-analysis included data from 987 patients with SCLC in complete remission randomized to receive PCI or no PCI in trials conducted from 1977 to 1995. The primary endpoint was overall survival. PCI doses ranged from 8 to 40 Gy, given in one to 20 fractions, corresponding to 2 to 3 Gy per fraction. The relative risk (RR) of death for PCI compared with control was 0.84 (95% confidence interval [CI], 0.73 to 0.97; p=0.01), corresponding to a relative reduction in mortality of 16% (standard deviation, 6%) in favour of PCI and to a 5.4% absolute increase in the three-year survival rate (from 15.3% for control to 20.7% for PCI). PCI decreased the cumulative incidence of brain metastases. The RR of brain metastases was 0.46 (95% CI, 0.38 to 0.57; p<0.001), corresponding to a 54% (standard deviation, 7%) reduction in the risk of brain metastases and to an absolute decrease of 25.3% in the cumulative incidence of brain metastases at three years (from 58.6% for control to 33.3% for PCI). PCI significantly improved disease-free survival (RR, 0.75; 95% CI, 0.65 to 0.86; p<0.001). When trials were categorized into four dose groups (8 Gy, 24-25 Gy, 30 Gy, 36-40 Gy) and analyzed using indirect comparisons, there was a significant trend towards an increased effect of PCI on brain metastases with increasing total PCI dose (p=0.02). Survival data did not differ significantly according to total PCI dose (p=0.89). Data on toxicity were not provided.

**Update**

In 2001, Meert et al conducted a meta-analysis on data extracted from twelve fully-published trial reports of PCI versus no PCI in the treatment of SCLC (2u). The meta-analysis included a subset of five trials involving 894 patients who had achieved a complete response to induction chemotherapy. All five trials were also included in the earlier individual patient data meta-analysis by Aupérin et al (11), and similar results were obtained. A benefit in favour of PCI was detected for survival (hazard ratio for four studies reporting survival data, 0.82; 95% CI, 0.71-0.96) and incidence of brain metastases (hazard ratio for all five studies, 0.49; 95% CI, 0.39-0.62) (2u). The 2001 systematic review and meta-analysis also intended to evaluate the use of pre-treatment brain imaging and the neuropsychological toxicity of PCI. However, the authors reported that these data were not well described in the studies, and subgroup analyses exploring the association between the use of pre-treatment brain imaging and survival or incidence of brain metastases were not conducted separately for the trials of PCI in complete responders. Only two studies reported pre- and post-treatment neuropsychological assessments, and both are discussed in this guideline (7,9).
Dose-response Relationship for PCI

In addition to the data from indirect comparisons in the meta-analysis noted above, there is evidence from one randomized controlled trial of a possible dose-response relationship in patients with SCLC who have achieved complete remission in response to induction therapy.

Gregor et al (9) reported an initial three-armed randomized trial of no PCI versus PCI 24 (24 Gy in 2 Gy fractions) versus PCI 36 (36 Gy in 2 Gy fractions). Results indicated little difference in controlling brain metastases between PCI 24 and no PCI (hazard ratio, 0.71; 95% confidence interval, 0.36 to 1.43; p-value not reported). There was a significant difference between PCI 36 and no PCI (hazard ratio, 0.16; 95% confidence interval, 0.07 to 0.36; p=0.0007). The authors suggested that there may be a dose-response relationship for PCI and that higher doses (above 24 Gy in 2 Gy fraction range) were more effective in reducing the risk of brain metastases. Doses above 36 Gy in 2 Gy fractions were not investigated. With the dose range of 36 Gy over 18 fractions or its biologically equivalent dose, no significant neurotoxicity attributable to PCI was observed (9). Five other randomized controlled trials (4-8) with PCI doses ranging from 24 Gy in 3 Gy fractions to 40 Gy in 2 Gy fractions showed benefits in brain metastasis-free survival.

Quality of Life and Cognitive Functioning

There have been two randomized controlled trials that have examined cognitive functioning as outcomes for PCI therapy, one of which also examined quality of life. The first prospective trial that assessed the possible neurotoxicity of PCI was carried out by Arriagada et al (7). Three hundred patients with SCLC in complete remission were randomized to PCI or observation. A neurologic examination that included the assessment of cranial nerves, sensory function, tendon reflexes, cerebellar function, walking, mood, and higher functions was carried out by neurologists at the time of random assignment and repeated at 6, 18, 30, and 48 months. There were no statistically significant differences between PCI and observation in the relative risks of the two-year cumulative incidence of neuropsychological changes. Computed tomography scans of the brain were repeated at the same intervals, and the two-year rates of abnormalities (27% and 21% for PCI and control, respectively) were not significantly different (RR, 1.48; p=0.60 logrank).

The second prospective study that examined quality of life as well as cognitive functioning was reported by Gregor et al (9). Of the 314 patients in the study, 136 patients (84 PCI, 52 control) were included in the evaluation of quality of life and cognitive functioning. Psychometric assessment included auditory mental tracking, perceptual organization, visual memory, memory span, and verbal learning. The National Adult Reading Test was administered at the time of randomization, and the Paced Auditory Serial Addition Task, Rey Osterrieth Complex Figure Test, and the Auditory Verbal Learning Test were administered at randomization, six months, and 12 months. At each assessment, quality of life (physical and psychological symptoms and activities of daily living), anxiety, and depression were assessed using the Rotterdam Symptom Checklist and the Hospital Anxiety and Depression Scale.

The proportion of patients in the Gregor study showing cognitive impairment at baseline was substantial but similar in the two groups. New impairment was observed at six months and 12 months, but there was no evidence of sustained deterioration with time and no notable difference between PCI and control (no statistical comparisons provided). With respect to quality of life, the symptoms showing the greatest deterioration from baseline to six months were tiredness, lack of energy, irritability, decreased sexual interest, shortness of breath, and cough. Progression of these symptoms was greater in the control group. On the Rotterdam Symptom Checklist, 93% of patients reported normal or near-normal activities of
daily living at baseline, six months, and 12 months. There was no difference on the Hospital Anxiety and Depression Scale between PCI and control. No significance values were provided.

V. INTERPRETATIVE SUMMARY

All six published randomized controlled trials provided data on disease-free survival. Four of the trials (3, 5, 7, 9) demonstrated significant benefits in disease-free survival with PCI in patients with SCLC who had achieved complete responses after chemotherapy with or without radiotherapy. None of the five published randomized controlled trials that provided data on overall survival (5-9) demonstrated a statistically significant benefit in overall survival with PCI for patients with SCLC in complete remission.

One individual patient data meta-analysis (11) demonstrated a survival benefit for patients in complete remission treated with PCI. The relative risk of death for PCI compared with control was 0.84 (95% CI, 0.73 to 0.97; p=0.01), corresponding to a RR in the risk of death of 16% in favour of PCI and an absolute improvement in survival of 5.4% at three years. PCI was shown to increase disease-free survival (p<0.001) and to decrease the cumulative incidence of brain metastases (p<0.001).

Data from six randomized controlled trials (4-9) indicated that administration of PCI at doses ranging from 24 Gy in 3 Gy fractions to 40 Gy in 2 Gy fractions decreased the frequency of brain metastases. Doses below 24 Gy in 2 Gy fractions were not effective in reducing the risk of brain metastases. Radiation doses of 30 Gy to 36 Gy in 2 to 3 Gy fractions or biologically equivalent doses were associated with no differences in quality of life between PCI and no PCI patients at 12 month follow-up in the one randomized controlled trial that incorporated the formal assessment of quality of life parameters (9).

Only two randomized controlled trials evaluated possible neurotoxicity from PCI (7, 9), and one of these trials (9) assessed changes in quality of life. Psychometric assessment for up to 12 months in one study (9) and neurocognitive evaluation for up to 48 months (with two-year cumulative incidence data) in the other study (7) did not detect any differences between PCI and no PCI groups. Taken together, these findings suggest that any possible early neurotoxicity associated with PCI is not clinically significant.

Update

A meta-analysis published in 2001 confirmed the survival benefit demonstrated for PCI in patients with SCLC in complete remission, with a hazard ratio of 0.82 (95% CI, 0.71-0.96) (2u). This meta-analysis was conducted on a subset of the studies reported in the earlier meta-analysis by Auperin et al (11); therefore, this finding is not surprising. The 2001 meta-analysis reported that most studies did not include or clearly report the use of pre-treatment brain imaging, but it is unclear if this type of assessment would have an impact on the survival advantage detected for PCI.

VI. ONGOING TRIALS

Gregor (12) reported that the EORTC and UK Medical Research Council (MRC) were planning two parallel randomized trials of PCI for patients with SCLC. These are listed below.

<table>
<thead>
<tr>
<th>Protocol IDs</th>
<th>Protocol title and description</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC-RA-22993,</td>
<td>Phase III randomized study of prophylactic cranial irradiation in patients with previously treated extensive-stage small cell lung cancer. Patients who are responsive to initial chemotherapy are randomized to receive PCI or no further therapy. Outcomes of interest: incidence of brain metastases, survival, quality of life, and toxicity. Projected accrual: 287 patients within 3 years. Status: active. Summary last</td>
</tr>
</tbody>
</table>
Phase III randomized study of high-dose versus standard-dose prophylactic cranial radiotherapy in patients with limited-stage small cell lung cancer in complete remission. Standard-dose PCI is defined as 10 fractions over 12 days, and high-dose PCI is defined as 18 fractions over 24 days or 24 fractions over 16 days. Outcomes of interest: incidence of brain metastases, survival, quality of life, late sequelae. Projected accrual: 700 patients. Status: active. Summary last modified: April 2001.

RTOG-0212

Phase II/III randomized study of prophylactic cranial irradiation in patients with limited stage small cell lung cancer. Patients with a complete response to chemotherapy, with or without thoracic radiotherapy, are randomized to 1 of 3 treatment arms: daily PCI, 5 days/week for 2 weeks; daily PCI, 5 days/week for 2.6 weeks; or twice daily PCI, 5 days/week for 3.4 weeks. Outcomes of interest: incidence of brain metastases, survival, chronic neurotoxicity, and quality of life. Projected accrual: 264 patients within 3.5 years. Status: active. Summary last modified: March 2003.

VII. DISEASE SITE GROUP CONSENSUS PROCESS

Based on strong evidence that patients with SCLC who achieve a complete remission after induction therapy (chemotherapy or chemoradiotherapy) have a substantial decrease in the frequency of brain metastases and improved disease-free survival, and on an individual-patient-data meta-analysis demonstrating an improvement in overall survival, the Lung DSG felt confident to recommend the use of PCI in this situation.

Meta-analyses provide an estimate of the overall magnitude of a treatment effect for a body of available evidence. However, meta-analyses should be carefully assessed before relying on them as the basis for a treatment recommendation, in the absence of a large, definitive trial. Because of concern about the robustness of the meta-analysis, the modest value of $p=0.01^2$ and the absence of randomized trial data supporting PCI-improved overall survival, the authors of this practice guideline report and the members of the Lung DSG advise caution in the interpretation of these data. However, there is strong evidence from four published randomized controlled trials that PCI decreases the frequency of brain metastases and increases the disease-free survival rate in patients with SCLC who achieve complete responses after induction chemotherapy or chemoradiation therapy.

Members of the Lung DSG discussed whether those patients with extensive disease who achieve complete remission should receive PCI, particularly as their overall survival is shorter than the survival of patients with limited disease and there are virtually no long-term survivors. The Lung DSG concluded that, as the randomized trials included patients with extensive disease who had achieved complete response and there was an overall benefit in terms of disease-free survival, patients with extensive disease should not be denied the potential benefit of a reduced risk of central nervous system metastases. This

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2 Dr. G. DeBoer, a biostatistician from the Toronto-Sunnybrook Regional Cancer Centre, was invited to the June 26, 1998 Lung DSG meeting to provide an overview of meta-analysis and an expert opinion on the discrepancy between the results of two meta-analyses cited in a practice guideline under development by the Lung DSG. In his presentation on meta-analysis, he defined a range of “modest” p-values as 0.01 to 0.1.
recommendation also takes into account the fact that the staging of lung cancer may not be accurate and that the presence of extensive disease may not have been proven by biopsy. Although Lung DSG members acknowledged that central nervous system metastases can be treated when they occur, the psychological and physical consequences of brain metastases are grave, the neurological sequelae of the metastases often resolve incompletely after treatment, and survival is generally short once central nervous system metastases occur. For these reasons, the Lung DSG concluded that it was reasonable to offer PCI to those patients with extensive disease who achieve a complete response, in an effort to extend disease-free survival and maintain a good quality of life for the patient for as long as possible.

The widespread adoption of PCI following the achievement of a complete response to treatment in SCLC has been inhibited by concerns about acute and late neurological sequelae. These concerns arose from early small reports of acute neurological deterioration of cognitive and other neurological functions when radiotherapy was given in large fractions, high total dose, and in combination with chemotherapy drugs, particularly nitrosoureas. Concerns about these potential neurological consequences and American concerns about medical-legal actions strongly influenced care providers against using PCI. Recent trials of PCI have carefully assessed the cognitive functioning of patients before, during, and after treatment. It is noteworthy that cognitive functioning, at least as measured by psychometric instruments, is commonly impaired prior to the administration of PCI and has shown no deterioration during PCI relative to those who do not receive PCI. Therefore, most investigators have concluded that serious acute neurotoxicity is not a major concern when the doses of radiotherapy recommended in this report are used. Although not commented on in the studies reviewed, Lung DSG members felt that short-term somnolence following PCI was a common side effect.

Most studies have not followed patients for more than several years. However, Lung DSG members have observed individual patients who have survived five or more years who have developed dementia. Whether this is directly related to PCI or to other factors is unknown, but it remains a concern and follow-up studies of long-term survivors are needed to inform this issue.

There is insufficient evidence available to comment on the optimal timing of PCI in relation to the administration of chemotherapy. The Lung DSG felt that PCI should not be concurrent with chemotherapy because of the potential interaction of the drugs and radiation on the brain vasculature or neural tissue, which might increase the risk of late neurotoxicity. Members of the Lung DSG felt that PCI should be given as soon as possible after completion of chemotherapy in complete responders.

In an attempt to obtain additional information about possible dose-response relationships, the Lung DSG considered a review of PCI versus no PCI for patients with SCLC that did not meet the inclusion criteria for this systematic review. Suwinski et al (13) published a review based on a total of 40 trials of PCI versus no PCI, including 11 randomized and 12 nonrandomized trials, most of which involved patients with SCLC who had not achieved complete response to induction therapy. Two of the six randomized controlled trials cited above were included in the Suwinski analysis. The authors reported that a dose range of 30 to 35 Gy in 2 to 3 Gy fractions reduced the incidence of brain metastases within the remaining lifetime of the patients by 80%. They also suggested that PCI be administered early (within 60 days of starting induction therapy), which would mean that many patients would receive cranial irradiation concurrently with chemotherapy and would not have achieved complete remission. The toxicity resulting from concurrent administration of PCI and chemotherapy was not discussed.
Members of the Lung DSG expressed concern that too low a dose of radiation is probably ineffective. The radiation dose recommendation is 30 to 36 Gy in 2 to 3 Gy fractions or the biological equivalent.

Update
As a result of feedback received during the peer review process prior to the publication of this guideline, the Lung DSG amended the description of Suwinski et al (13) from ‘meta-analysis’ to ‘review’ and revised the last paragraph of this section as follows:

Members of the Lung DSG expressed concern that too low a dose of radiation is probably ineffective. The Lung DSG concluded that there is some indication that 30 to 36 Gy in 2 to 3 Gy per fraction or a biologically equivalent dose may produce a better outcome than a lower dose or less aggressive fractionation regimen.

VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT
This section describes the external review activities undertaken for the original guideline report.

Draft Recommendations
Based on the evidence described in the original report above, the Lung DSG drafted the following recommendations:

Target Population
These recommendations apply to patients with limited or extensive stage small cell lung cancer who have achieved complete remission in response to induction therapy (chemotherapy or chemoradiotherapy).

Draft Recommendations
 There is strong evidence to recommend prophylactic cranial irradiation (PCI) for patients who have achieved complete remission following chemotherapy or chemoradiotherapy. Randomized controlled trial data demonstrate that PCI decreases the frequency of brain metastases and increases disease-free survival in these patients. One fully published meta-analysis reports increased overall survival and disease-free survival.
 For patients who have achieved complete response after induction therapy, PCI is recommended in a dose of 30 to 36 Gy in 2 to 3 Gy per fraction or biologically equivalent dose.
 There is insufficient evidence to make recommendations concerning the optimal timing of PCI in relation to administration of chemotherapy, although it is generally felt that it should be given shortly after completion of chemotherapy.
 There is evidence from randomized controlled trials with data for up to two years of follow-up that PCI does not produce significant late neurotoxicity. There is evidence from one randomized controlled trial that PCI does not have a detrimental effect on quality of life in the first 12 months following the completion of therapy. There is insufficient evidence to comment on the long-term effects of PCI on quality of life.

Practitioner Feedback
Based on the evidence contained in the original report and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods
Practitioner feedback was obtained through a mailed survey of 88 practitioners in Ontario (38 medical oncologists, 22 radiation oncologists, and 28 surgeons). The survey
consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Lung DSG reviewed the results of the survey.

**Results**

Key results of the practitioner feedback survey are summarized in Table 3. Sixty-one surveys (70.9%) were returned. Forty-five respondents (73.8%) indicated that the practice-guideline-in-progress report was relevant to their clinical practice and 46 practitioners completed the survey.

**Summary of Comments from Practitioners and Lung DSG Actions**

Seventeen respondents (37.0%) provided written comments. Although the feedback from practitioners was highly supportive of the evidence-based draft recommendations, there were concerns about the dose of PCI that should be used and whether patients with extensive disease should be treated even when they achieve a complete remission. Both issues had been discussed during the development of the guidelines, but because of the concerns expressed by some respondents to the survey of practitioners, the Lung DSG discussed these issues again.

It was recognized that 25 Gy in 10 fractions over two weeks was a very common dose and fractionation regimen for PCI in Canada, in part, because it had been the standard regimen in several National Cancer Institute of Canada clinical trials. The guideline recommends 30 Gy in 15 fractions over three weeks or a biologically equivalent dose. The radiation oncologists on the Lung DSG felt that 25 Gy in two weeks and 30 Gy in three weeks are biologically equivalent doses.

The data concerning the use of PCI in patients with extensive disease are not as robust as for limited disease; however, the randomized trial data demonstrating a (non-significant) survival advantage for PCI included patients with extensive disease who had achieved a complete response to chemotherapy. Therefore, Lung DSG members felt that there was no reason to revise the recommendation.

**Modifications**

None.

Table 3. Practitioner responses to eight items on the practitioner feedback survey.

<table>
<thead>
<tr>
<th>Item</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Item</strong></td>
<td><strong>Strongly agree or agree</strong></td>
</tr>
<tr>
<td>The rationale for developing a clinical practice guideline, as stated in the “Choice of Topic” section of the report, is clear.</td>
<td>44 (97.8%)</td>
</tr>
<tr>
<td>There is a need for a clinical practice guideline on this topic.</td>
<td>39 (84.8%)</td>
</tr>
<tr>
<td>The literature search is relevant and complete.</td>
<td>39 (84.8%)</td>
</tr>
<tr>
<td>The results of the trials described in the report are interpreted according to my understanding of the data.</td>
<td>44 (95.7%)</td>
</tr>
<tr>
<td>The draft recommendations in this report are clear.</td>
<td>45 (97.8%)</td>
</tr>
</tbody>
</table>
Approved Practice Guideline Recommendations

These practice guideline recommendations reflect the integration of the draft recommendations with feedback obtained from the external review process. They have been approved by the Lung DSG and the Practice Guidelines Coordinating Committee (PGCC).

Recommendation

- For patients who have achieved complete response after induction therapy, PCI is recommended at a dose of 30 to 36 Gy in 2 to 3 Gy per fraction or a biologically equivalent dose.

Qualifying Statement

- There is insufficient evidence to make recommendations concerning the optimal timing of PCI in relation to the administration of chemotherapy. Lung Cancer DSG members generally felt that it should be given as soon as possible after completion of chemotherapy.

Update

After the practice guideline was approved by the PGCC, a reformatted version was submitted for publication. As part of its peer-review process, the journal had the manuscript reviewed, and the comments of the external reviewers were sent to the guideline authors. As a result of the reviewers’ comments, the authors modified the guideline recommendations. The revisions, as detailed below, were reviewed and approved by the members of the Lung DSG and sent to the PGCC for information.

The Lung DSG also consulted Dr. Peter Raaphorst (Medical Physicist, Ottawa Regional Cancer Centre) for advice on the equivalence on PCI doses. He indicated that 30 Gy in three weeks has a greater biologic effect on brain tissue than 25 Gy in two weeks, by approximately five percent, but this would not be expected to have a significant clinical impact (personal communication).

Recommendation

- For patients who have achieved complete response after induction therapy, PCI is recommended. There is insufficient evidence to make a definitive recommendation with respect to dose. There is some indication that 30 to 36 Gy in 2 to 3 Gy per fraction or a biologically equivalent dose may produce a better outcome than a lower dose or less aggressive fractionation regimen.

Qualifying Statements

- The schedule commonly used in Canada is 25 Gy in 10 fractions over two weeks. Data from further research, including a trial currently ongoing that compares 25 Gy in 10 fractions with 36 Gy in 18 fractions, will be required to determine optimal dose of PCI.
• There is insufficient evidence to make recommendations concerning the optimal timing of PCI in relation to the administration of chemotherapy. Lung Cancer Disease Site Group members generally felt that it should be given as soon as possible after completion of chemotherapy.

IX. PRACTICE GUIDELINE

This practice guideline reflects the most current information reviewed by the Lung DSG.

Target Population

These recommendations apply to adult patients with limited- or extensive-stage small cell lung cancer who have achieved complete remission in response to induction therapy (chemotherapy or chemoradiotherapy).

Recommendations

• For patients who have achieved complete response after induction therapy, PCI is recommended. There is insufficient evidence to make a definitive recommendation with respect to dose. There is some indication that 30 to 36 Gy in 2 to 3 Gy per fraction or a biologically equivalent dose may produce a better outcome than a lower dose or less aggressive fractionation regimen.

Qualifying Statements

• The schedule commonly used in Canada is 25 Gy in 10 fractions over two weeks. Data from further research, including a trial currently ongoing that compares 25 Gy in 10 fractions with 36 Gy in 18 fractions, will be required to determine optimal dose of PCI.
• There is insufficient evidence to make recommendations concerning the optimal timing of PCI in relation to the administration of chemotherapy. Lung DSG members generally felt that it should be given as soon as possible after completion of chemotherapy.

Related Guidelines

Practice Guidelines Initiative Practice Guideline Report:
• #7-13-1: The role of combination chemotherapy in the initial management of limited-stage small-cell lung cancer.
• #7-13-3: The role of thoracic radiotherapy as an adjunct to standard chemotherapy in limited-stage small cell lung cancer.

X. JOURNAL REFERENCE


XI. ACKNOWLEDGMENTS

The Lung DSG would like to thank Drs. Jaro Kotalik, Edward Yu, and William K. Evans and Ms. Barbara Markman and Ms. Jean Mackay for taking the lead in drafting and revising this practice guideline.

For a complete list of the members of the Lung DSG, please visit the Cancer Care Ontario web site at http://www.cancercare.on.ca/
REFERENCES

2. Wagner H. Radiation therapy in the management of limited small cell lung cancer: when, where, and how much? Chest 1998;113(1 Suppl):92S-100S.

Update

This section includes all references from the review and updating activities.

Evidence-based Series 7-13-2: Section 3

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Prophylactic Cranial Irradiation in Small Cell Lung Cancer: Document Summary and Review Tool

Document Summary and Review Tool

<table>
<thead>
<tr>
<th>Number and title of document under review</th>
<th>7-13-2 Prophylactic Cranial Irradiation in Small Cell Lung Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Report Date</td>
<td>November 2003</td>
</tr>
<tr>
<td>Clinical Expert</td>
<td>Dr. Edward Yu</td>
</tr>
<tr>
<td>Research Coordinator</td>
<td>Lesley Souter</td>
</tr>
<tr>
<td>Date Assessed</td>
<td>September 2011</td>
</tr>
<tr>
<td>Approval Date and Review Outcome (once completed)</td>
<td>21 Sept 2012 (UPDATE)</td>
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</table>

Original Question(s):
1. What is the role of prophylactic cranial irradiation in patients with small cell lung cancer who have achieved complete response/remission?
2. What dose and fractionation schedules of prophylactic cranial irradiation are optimal?
3. Does the use of prophylactic cranial irradiation in patients with small cell lung cancer in complete remission affect quality of life?

Target Population:
These recommendations apply to adult patients with limited-(LS) or extensive-stage (ES) small cell lung cancer (SCLC) who have achieved complete remission in response to induction therapy (chemotherapy or chemoradiotherapy).

Study Section Criteria:
Inclusion Criteria:
Articles were selected for inclusion in this overview of the evidence if they were the following:
3. Meta-analyses or individual randomized controlled trials that compared the administration of PCI with no administration of PCI to patients with SCLC who had achieved complete response to induction therapy (chemotherapy or chemoradiotherapy).
4. Abstracts of meta-analyses or trials were also considered.

Exclusion Criteria:
3. Phase I and II studies were not considered for inclusion in this report because of the availability of randomized controlled trials.
4. Papers published in a language other than English were not considered.

Search Details:
- Medline and Embase: January 2003 to March 2012, week 18
- Clinicaltrial.gov: January 2003 to June 2012
Brief Summary/Discussion of New Evidence:
Of 179 total hits from Medline and Embase and 11 total hits from clinicaltrials.gov, 14 references representing 5 clinical practice guidelines, 3 systematic reviews and meta-analyses and 6 randomized controlled trials were found evaluating the role of prophylactic cranial irradiation in small cell lung cancer. In addition, 1 on-going trial was identified from clinicaltrials.gov.

**Systematic Review**

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Literature Search Date</th>
<th>Brief Results</th>
<th>References</th>
</tr>
</thead>
</table>
| Systematic review to answer the question: What are the effects of treatments for small cell lung cancer? | Medline, Embase and Cochrane Library up to Oct 2009 | • PCI reduces the incidence of brain metastases and improves survival in patients with LS- and ES-SCLC  
• No difference in brain metastases at 2 years with high dose vs low dose PCI  
• Increase in 2 year incidence of chest relapses and decrease in 2 year overall survival with high dose PCI  
• Negative impact on patients’ health related quality of life: fatigue and hair loss | Neville, 2010 |
| Systematic review to answer the question: What are the effects of treatments for small cell lung cancer? | Medline, Embase and Cochrane Library up to May 2008 | • PCI improves survival at 3 years in patients with complete remission from SCLC  
• Clinical importance of cognitive impairment after PCI remains unclear | Neville, 2009 |
| Systematic review to answer multiple questions on management of SCLC. Addressed the effects of PCI | Medline through 12/21/04, Embase through 03/04/05, Cochrane Controlled Trials Register through 03/11/05 | • PCI improves survival of SCLC in complete remission after primary therapy  
• PCI decreases risk of brain metastases  
• PCI increases likelihood of disease-free survival  
• Acute toxicities seems tolerable in 8-40 Gy in 1.8 to 3 Gy fractions | Seidenfeld et. al., 2006 |

**RCTs**

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Name of trial (phase)</th>
<th>Population</th>
<th>Outcomes</th>
<th>Brief Results</th>
<th>References</th>
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<tbody>
<tr>
<td>PCI of 25 or 36 Gy</td>
<td>Intergroup Phase III (PCI99-01, EORTC 22003-08004, RTOG 0212 and IFCT 99-01)</td>
<td>Patients with LS-SCLC in complete remission after chemotherapy and TRT, n=720</td>
<td>Midterm and long-term repeated evaluation of neurocognitive functions and quality of life (QoL)</td>
<td>• No difference between the doses in any of the QoL and neurological and cognitive functions measured</td>
<td>Le Pechoux et. al., 2011</td>
</tr>
<tr>
<td>PCI of 25 or 36 Gy</td>
<td>RTOG 0212, Phase II</td>
<td>Patients with LS-SCLC who achieved a complete response after chemotherapy and TRT, n=265</td>
<td>Incidence of chronic neurotoxicity and changes in QoL</td>
<td>• Increased risk of developing chronic neurotoxicity with 36 Gy</td>
<td>Wolfson et. al., 2011</td>
</tr>
</tbody>
</table>
| PCI of 1) 25 Gy in 10 daily fractions of 2-5 Gy OR 2) 30 Gy in 18 daily fractions of 2 Gy OR 3) 30 Gy in 24 fractions over 16 days with 2-daily sessions of 1-5 | PCI99-01, EORTC 22003-08004, RTOG 0212 and IFCT 99-01, phase III | Patients with LS-SCLC in complete remission after chemotherapy and TRT, n=720 | Incidence of brain metastases                                                                                                                     | • No difference in 2-year incidence of brain metastases  
• Increase in mortality with 30 Gy PCI                                                                                                           | Le Pechoux et. al., 2009 |
<table>
<thead>
<tr>
<th>Gy</th>
<th>PCI or no PCI</th>
<th>Phase III (NCT0016211)</th>
<th>Patients with ED-SCLC and any response to chemotherapy, n=286</th>
<th>Health-related quality of life (HRQoL) and patient-reported symptoms</th>
<th>• Negative impact of PCI on functioning scales, but limited • Increased fatigue and hair loss with PCI</th>
<th>Slotman et. al., 2009</th>
</tr>
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<tbody>
<tr>
<td>PCI or no PCI</td>
<td>Phase III (NCT00016211)</td>
<td>Patients with ED-SCLC and any response to chemotherapy, n=286</td>
<td>Time to symptomatic brain metastases</td>
<td>• PCI reduced incidence of symptomatic brain metastases • PCI prolonged disease-free and overall survival</td>
<td>Slotman et. al., 2007</td>
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<tr>
<td>PCI or no PCI</td>
<td>Phase III</td>
<td>Patients with LS-SCLC in complete remission, n=51</td>
<td>Survival rate and incidence of cranial metastases</td>
<td>• PCI reduced incidence of brain metastases • No difference on survival rates, but authors attribute this to small sample size</td>
<td>Cao et. al., 2005</td>
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### Ongoing RCTs

<table>
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<th>Population</th>
<th>Outcomes</th>
<th>Study Status</th>
<th>ClinicalTrials.gov ID</th>
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<tr>
<td>PCI alone compared to PCI and consolidative extra-cranial irradiation</td>
<td>Phase II</td>
<td>Radiation Therapy Oncology Group and National Cancer Institute</td>
<td>ED-SCLC</td>
<td>Overall survival</td>
<td>Recruiting</td>
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### Practice Guidelines

<table>
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<tr>
<th>Title</th>
<th>Organization</th>
<th>Year of search</th>
<th>Summary of recommendations</th>
<th>Reference</th>
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<tr>
<td>Small cell lung cancer: Clinical practice guidelines in oncology</td>
<td>National Comprehensive Cancer Network (NCCN)</td>
<td>Guideline published in 2011, date of literature search not given</td>
<td>• PCI recommended for patients with LS or ES SCLC who attain complete or partial response • Total dose: 25 Gy in 10 fractions or 30 Gy in 15 fractions • For ES, 20 Gy in 5 fractions may be considered • PCI should not be given concurrently with systemic chemotherapy</td>
<td>Kalemkerian et. al., 2011</td>
</tr>
<tr>
<td>Small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up</td>
<td>European Society for Medical Oncology (ESMO)</td>
<td>Guideline published in 2010, date or literature search not given</td>
<td>• Patients with any response to first-line treatment should be offered PCI after completion of first-line • No recommendation on specific PCI schedule</td>
<td>Sorensen et. al., 2010</td>
</tr>
<tr>
<td>Management of small cell lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition)</td>
<td>American College of Chest Physicians (ACCP)</td>
<td>Medline 2004, Embase 2005, Cochrane Controlled Trials Register 2005</td>
<td>• Patients with LS-SCLC achieving a complete response or resected patients with stage I disease should be offered PCI • Patients with ES-SCLC achieving a complete response should be offered PCI</td>
<td>Simon and Turrisi, 2007</td>
</tr>
<tr>
<td>ESMO minimum clinical recommendation for diagnosis, treatment and follow-up of small-cell lung cancer (SCLC)</td>
<td>ESMO</td>
<td>Recommendations published in 2005, date of literature search not given</td>
<td>• PCI recommended in patients with complete remissions from LS-SCLC</td>
<td>Felip et. al., 2005</td>
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<tr>
<td>Small cell lung cancer</td>
<td>ACCP</td>
<td>Guideline published in 2003, date of</td>
<td>• Patients achieving complete remission should be offered PCI</td>
<td>Simon and Wagner, 2003</td>
</tr>
<tr>
<td>Section 3: Document Summary &amp; Review Tool</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1.</td>
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</tr>
<tr>
<td><strong>Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed?</strong> Answer Yes or No, and explain if necessary, citing newly identified references:</td>
<td>1. No</td>
<td></td>
<td></td>
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<td><strong>If Yes, the document will be immediately removed from the PEBC website, and a note as to its status put in its place. Go to 2.</strong></td>
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<tr>
<td>2.</td>
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</table>
| **On initial review,**  
  a. Did the newly identified evidence support the existing recommendations?  
  b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary? **Answer Yes or No to each, and explain if necessary:** | 2. No |
| **If both are Yes, the document can be ENDORSED. If either is No, go to 3.** |  |
| 3.  |  |
| **Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline?** Answer Yes or No, and explain if necessary: | 3. No |
| **If Yes, a final decision can be DELAYED up to one year. If No, go to 4.** |  |
| 4.  |  |
| **Do the PEBC and the DSG/GDG responsible for this document have the resources available to write a full update of this document within the next year?** | 4. Yes |
| **If Yes, the document needs an UPDATE. It can be listed on the website as IN REVIEW for one year. If a full update is not started within the year, it will be automatically ARCHIVED. If NO, go to 5.** |  |
| 5.  |  |
| If Q2, Q3, and Q4 were all answered NO, this document should be ARCHIVED with no further action. |  |

**New References Identified (alphabetical order):**


Literature Search Strategy:
Medline
1. meta-analysis as topic/
2. meta analysis.pt.
3. (meta analy$ or metaanaly$).tw.
4. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes$ or quantitative overview).tw.
5. (systematic adj (review$ or overview$)).tw.
6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. or/1-6
8. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
9. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
10. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
14. 12 and 13
15. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
16. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
17. random allocation/ or double blind method/ or single blind method/
18. (random$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
19. or/15-18
20. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
21. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
22. (20 or 21) and random.tw.
23. (clinical$ adj trial$1).tw.
24. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
25. placebos/
26. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
27. (allocated adj2 random).tw.
28. or/23-27
29. practice guidelines/
30. practice guideline?.tw.
31. practice guideline.pt.
32. or/29-31
33. 7 or 8 or 9 or 14 or 19 or 22 or 28 or 32
34. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
35. 33 not 34
36. limit 35 to english
37. animal/
38. human/
39. 37 not 38
40. 36 not 39
41. small cell lung cancer?.tw.
42. exp carcinoma, small cell/
43. exp cranial irradiation/
44. prophylactic cranial irradiation.tw.
45. whole brain irradiation.tw.
46. elective brain irradiation.tw.
47. prophylactic brain irradiation.tw.
48. prophylactic whole brain irradiation.tw.
49. whole brain radiation.tw.
50. 41 or 42
51. 43 or 44 or 45 or 46 or 47 or 48 or 49
52. 40 and 50 and 51
53. limit 52 to yr="2003-2012"

Embase
1. exp meta analysis/ or exp systematic review/
2. (meta analy$ or metaanaly$).tw.
3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summa$ or mathematical summa$ or quantitative synthes$ or quantitative synthes$ or quantitative overview).tw.
4. (systematic adj (review$ or overview$)).tw.
5. exp review/ or review.pt.
6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7. (study adj selection).ab.
8. 5 and (6 or 7)
9. or/1-4,8
10. (cochrane or embase or psychlit or psychlit or psychinfo or csinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
11. (reference list$ or bibliography$ or hand-search$ or relevant journals or manual search$).ab.
12. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
13. randomization/ or single blind procedure/ or double blind procedure/
14. (random$ control$ trial? or rct or phase III or phase IV).tw.
15. or/12-14
16. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
17. 16 and random$tw.
18. (clinical$ adj trial$1).tw.
19. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
20. placebos/
21. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
22. (allocated adj2 random).tw.
23. or/18-22
24. practice guidelines/
25. practice guideline?.tw.
27. or/24-26
28. 9 or 10 or 11 or 15 or 17 or 23 or 27
29. (editorial or letter or erratum or short survey).pt. or abstract report/ or letter/ or case study/
30. 28 not 29
31. limit 30 to english
32. animal/
33. human/
34. 32 not 33
35. 31 not 34
36. exp small cell carcinoma/
37. exp lung small cell cancer/
38. lung.tw.
39. 37 or 38
40. small cell lung.tw.
41. exp lung non small cell cancer/
42. 36 or 39 or 40
43. 42 not 41
44. exp cranial irradiation/
45. prophylactic cranial irradiation.tw.
46. whole brain irradiation.tw.
47. elective brain irradiation.tw.
48. prophylactic brain irradiation.tw.
49. prophylactic whole brain irradiation.tw.
50. whole brain radiation.tw.
51. 44 or 45 or 46 or 47 or 48 or 49 or 50
52. 43 and 51
53. 52 and 35
54. limit 53 to yr="2003-2012"


OUTCOMES DEFINITIONS

1. ARCHIVED - An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of the Web site and each page is watermarked with the phrase “ARCHIVED”.

2. ENDORSED - An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. DELAY - A Delay means that there is reason to believe new, important evidence will be released within the next year that should be considered before taking further action.

4. UPDATE - An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.