Evidence-based Series #7-14-3 ARCHIVED 2013

The Role of Radiation Therapy in Malignant Pleural Mesothelioma

Members of the Lung cancer Disease Site Group

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

An Assessment conducted in November 2013 ARCHIVED Evidence-based Series 7-14-3. This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes.

The reviewed EBS report, consists of

- Section 1: Clinical Practice Guideline
- Section 2: Systematic Review
- Section 3: EBS Development Methods and External Review Process and Results
- Section 4: Document Review Summary and Tool

and is available on the CCO Web site (http://www.cancercare.on.ca) PEBC Lung Cancer DSG page at: https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/lung-ebs/

Release Date: May 16, 2013

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Phone: 905-527-4322 ext. 42822  Fax: 905-526-6775  E-mail: ccopgi@mcmaster.ca

# Guideline Report History

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Evidence-Based Series #7-14-3: Section 1

The Role of Radiation Therapy in Malignant Pleural Mesothelioma:
A Clinical Practice Guideline

YC Ung, E Yu, C Falkson, AE Haynes, D Stys-Norman, WK Evans,
and the Lung Cancer Disease Site Group

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

The 2006 guideline recommendations requires 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 4: Document Review Tool for a summary of updated evidence published between 2005 and 2012.

Report Date: February 6, 2006

Question
What is the role of radiation therapy (RT) in the management of malignant pleural mesothelioma?

Target Population
This evidence-based series applies to adult patients with malignant pleural mesothelioma.

Recommendations
The lack of sufficient high-quality evidence precludes definitive recommendations being made. Instead, the Lung Cancer Disease Site Group (Lung DSG) offers the following opinions based on the evidence reviewed:

- There is limited evidence for the role of radiotherapy in the management of patients with malignant pleural mesothelioma.
- There is inconsistent evidence and no consensus among the radiation oncologist in the Lung DSG for the use of prophylactic external beam radiation therapy to tracts caused by thoracic drainage tubes or thoracic diagnostic procedures. For this reason, a
recommendation could not be made for this treatment. The decision to use prophylactic external beam radiation therapy to tracts must therefore be based on an individualized case assessment.

- Radical radiation therapy alone should not be offered as a curative treatment option to patients with malignant pleural mesothelioma, based on the currently available evidence.
- Palliative radiation therapy may offer short-term symptom control in terms of chest pain; however, long-term control has not been demonstrated to date.
- Future studies including radiotherapy for the treatment of patients with malignant pleural mesothelioma should include formal measures of quality of life (QOL) and symptom control.

**Key Evidence**

- There are no randomized trials comparing radical or palliative radiation therapy to the primary (pleural) lesion to no treatment or best supportive care for patients with malignant pleural mesothelioma.
- Three small randomized controlled trials compared prophylactic external beam radiation therapy (EBRT) to no radiation therapy for patients with thoracic tracts caused by drainage tubes or diagnostic procedures. One randomized trial reported a significant reduction in the frequency of malignant seeding of tracts for the radiation therapy arm (0% of 20 patients) compared to the control arm (40% of 20 patients), p<0.001. A second randomized trial reported preliminary results from 12 patients and found more procedure tract metastases in the EBRT arm than the control arm, however no p-value was reported. The third randomized trial did not detect a statistically significant difference in procedure tract metastases between treatment arms. A pooled analysis found no significant reduction in the frequency of procedure tract metastases. None of those trials reported any serious adverse effects due to radiation therapy.
- A poll was conducted among the radiation oncologist in the Lung DSG to determine the pattern of practice for prophylactic RT to drainage sites. There was no consistent consensus on the use of prophylactic RT, a reflection of the lack of high-quality data from the small randomized trials available.
- Four noncomparative studies have shown that hemithoracic irradiation alone resulted in significant toxicity, including radiation-induced pulmonary fibrosis, radiation pneumonitis, and bronchopleural fistula, without any survival benefit. Median survival ranged from seven months to 17 months.
- Few of the identified studies reported on symptom control, and no studies included formal measures of QOL.

**Related Guidelines**

- Evidence Summary Report #7-14-1: *The Use of Chemotherapy in Patients with Malignant Pleural Mesothelioma*.
- Evidence Summary Report #7-14-2: *Surgical Management of Malignant Pleural Mesothelioma*.
Funding
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Contact Information
For further information about this series, please contact
Dr. William K. Evans, Co-Chair, Lung Cancer Disease Site Group, McMaster University and Juravinski Cancer Centre, 699 Concession Street, Hamilton ON L8V 5C2; TEL (905) 387-9711 ext. 63001; FAX (905) 575-6323
or
Dr. Yee C. Ung, Co-Chair, Lung Cancer Disease Site Group, Toronto-Sunnybrook Regional Cancer Centre, 2075 Bayview Avenue, Toronto, ON, M4N 3M5; TEL (416) 480-4951; FAX (416) 480-6002.

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Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca
The Role of Radiation Therapy in Malignant Pleural Mesothelioma: A Systematic Review

YC Ung, E Yu, C Falkson, AE Haynes, D Stys-Norman, WK Evans, and the Lung Cancer Disease Site Group

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

Report Date: February 6, 2006

QUESTION
What is the role of radiation therapy (RT) in the management of malignant pleural mesothelioma?

INTRODUCTION
Malignant pleural mesothelioma (MPM) is a rare malignancy with approximately 100 new cases diagnosed in Canada per year (1). Patients with MPM generally present with advanced symptomatic disease for which there is no standard treatment. The prognosis for those patients is poor, with several early retrospective studies reporting five-year survival rates of 1% or less (2-4) and median survivals of 7.6 months or less (2-5) for patients receiving best supportive care. The quality of life (QOL) for MPM patients can be significantly affected by pain, shortness of breath, and cough. The role of radiation therapy in the treatment of MPM has not been well defined. However, radiation therapy may offer those patients palliation of symptoms and improvements in QOL. The Lung Cancer Disease Site Group (Lung DSG) felt it was timely to review the available literature and conduct a systematic review to address the role of radiation therapy in the management of MPM.

METHODS
This systematic review was developed by Cancer Care Ontario’s Program in Evidence-Based Care (PEBC) using the methods of the Practice Guidelines Development Cycle (6). Evidence was selected and reviewed by three members of the Lung DSG and methodologists.

This systematic review is a convenient and up-to-date source of the best available evidence on the role of radiation therapy in malignant mesothelioma of the pleura. The body of evidence in this review is comprised of data primarily from small randomized trials or from non-comparative studies. The level of evidence precludes the development of definitive recommendations, and, instead, opinions of the Lung DSG are offered. The systematic review...
and the companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-term Care.

**Literature Search Strategy**

Evidence was identified through a systematic search of the databases MEDLINE (1966 to October 2005), EMBASE (1980 to October 2005), CANCERLIT (1975 through September 2001), and the Cochrane Library (2005, Issue 3). “Mesothelioma” (Medical Subject Heading (MeSH) and Excerpta Medica Tree (EMTREE)), “pleural neoplasms” (MeSH), “pleura mesothelioma” (EMTREE), “malignant mesothelioma” (EMTREE), and “mesothelioma” as a text word were combined with “radiotherapy” (MeSH, EMTREE), and the following text words: “radiotherapy”, “radiation”, and “irradiation”. Those terms were then combined with search terms for the following publication types and study designs: practice guidelines, systematic reviews, meta-analyses, reviews, randomized controlled trials, controlled clinical trials, clinical trials, multicenter studies, comparative studies, and prospective studies.

In addition, conference proceedings of the American Society of Clinical Oncology (ASCO) (1995-2005) and the American Society for Therapeutic Radiation and Oncology (ASTRO) (2000-2005) were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guidelines Clearinghouse (http://www.guideline.gov/index.asp) were also searched for existing evidence-based practice guidelines. The reference lists from those sources were searched for additional trials, as were the reference lists from relevant review articles.

**Study Selection Criteria**

Articles published as full reports or as abstracts were included if they focused on radiotherapy (radical, adjuvant or palliative) for patients with MPM; reported data on survival, QOL, or toxicity; and were:

a) randomized trials comparing radiation therapy alone or as part of a planned combined modality regimen to no radiation therapy or best supportive care; or

b) non-randomized prospective studies of radiation therapy, alone or as part of a planned combined modality regimen involving more than 40 patients; or

c) meta-analyses or systematic reviews.

Trials that focused on a modality other than radiation therapy, except when radiation was part of a planned combined modality regimen, were excluded. Trials published in a language other than English were also not considered.

**Synthesizing the Evidence**

A post-hoc meta-analysis was conducted to explore the impact of radiotherapy on procedure tract metastases. This analysis was based on the number of patients with procedure tract metastases in each treatment arm compared with the number of patients randomized. Trials were pooled using Review Manager 4.2.7, which is available through the Cochrane Collaboration (Review Manager [RevMan] Version 4.2 for Windows. Oxford (England): The Cochrane Collaboration, 2003). Pooled results are expressed as a relative risk ratio (RR) with 95% confidence intervals (CI) using the random effects model. The Lung DSG did not statistically pool data for the primary outcomes of interest (survival, adverse events, and QOL) from the randomized trials as it was not always possible to isolate the details or effects of radiation therapy. Also, the trials spanned many years and did not use a consistent radiotherapy regimen. Pooling of data from the non-randomized prospective trials was not considered due to the heterogeneity of these trials.
RESULTS

Literature Search Results

No meta-analyses were found for this topic. Three randomized trials (7-9) and four non-randomized, prospective trials (10-13) met the eligibility criteria for this systematic review. The randomized trials compared prophylactic radiation therapy with no radiation therapy after thoracoscopy (7); thoracic drainage tube removal (8,14); or fine needle aspiration, Abrams needle biopsy, thoracoscopy, or thoracic drainage tube removal (9). Twelve non-randomized prospective trials included less than 40 patients and were considered ineligible (15-27).

Survival was the primary outcome of interest. Toxicity and QOL were also considered. For studies reported in more than one paper, only the most recent paper was referenced.

Outcomes

Randomized Controlled Trials

Three randomized trials of prophylactic radiation therapy after thoracoscopy or thoracic drainage tube removal were identified (Table 1) (7-9). Those trials randomized patients to prophylactic radiation therapy or no radiation therapy (control group) after thoracoscopy, thoracic drain, fine needle aspiration, or Abrams needle biopsy. All three trials contained small sample sizes. A sample size calculation was reported in one trial, which was based on detecting a 20% reduction in procedure tract metastases (9).

Table 1. Randomized controlled trials of radiation therapy for MPM.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Diagnostic/ palliative procedures</th>
<th>Prophylactic EBRT (dose &amp; fx)</th>
<th>N</th>
<th>Median survival</th>
<th>Procedure tract metastases</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boutin, 1995 (7)</td>
<td>Thoracoscopy</td>
<td>21 Gy in 3 fx</td>
<td>20</td>
<td>14 mo</td>
<td>0% a</td>
<td>No patients with inflammation or edema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No EBRT</td>
<td>20</td>
<td>8 mo</td>
<td>40% a</td>
<td>NA</td>
</tr>
<tr>
<td>O'Rourke, 2000 (8)</td>
<td>Thoracic drain, pleural biopsy or thoracoscopy</td>
<td>21 Gy in 3 fx</td>
<td>31</td>
<td>8 mo</td>
<td>50% a</td>
<td>NR</td>
</tr>
<tr>
<td>2005 (14) [abstracts]</td>
<td></td>
<td>No EBRT</td>
<td>30</td>
<td></td>
<td>17% b</td>
<td>NA</td>
</tr>
<tr>
<td>Bydder, 2004 (9)</td>
<td>FNA, Abrams needle biopsy, thoracoscopy, or thoracic drain</td>
<td>10 Gy in 1 fx</td>
<td>43</td>
<td>8.7 mo</td>
<td>7% c,d</td>
<td>No patients with RTOG/EORTC Grade 2-4 toxicities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>total c</td>
<td>1 year: 35%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: EBRT – external beam radiation therapy, EORTC – European Organization for Research and Treatment of Cancer, FNA – fine needle aspiration, fx – fraction, Gy – Grays, NA – not applicable, N – number of patients, NR – not reported, RTOG – Radiation Therapy Oncology Group

a p<0.001
b Data reported from 2000 abstract which only reported on 6 patients per treatment arm
c Data reported based on the number of procedure sites (58 procedure sites from 43 patients).
d p=0.53

Survival

The randomized trials were not designed to detect differences in survival; rather, they were designed to determine if the frequency of thoracic procedure tract metastases could be reduced through the use of prophylactic radiation therapy. Median survival was 8.7 and 14 months for the two trials that reported data for patients in the prophylactic external beam radiation therapy (EBRT) group (7,9) and eight months for the single trial that reported data for patients in the control group (7). O’Rourke et al did not report survival by treatment arm, but reported that the median survival for all patients in the trial was eight months (8). One study
reported a one-year survival rate of 35% (9). No statistical analyses for survival were reported in any of the identified trials.

**Adverse effects**

Data on adverse effects were reported in only two trials (Table 1) (7,9). Boutin et al noted that tolerance to radiation therapy was excellent, with no patients exhibiting inflammation or edema (7). However, all patients had skin discoloration due to radiation therapy. Bydder et al reported that no patients experienced Radiation Therapy Oncology Group (RTOG) or European Organization for Research and Treatment of Cancer (EORTC) grade 2-4 toxicities following radiation therapy (9). Overall, the doses of prophylactic external beam radiation therapy were well tolerated with no serious adverse effects experienced by any patients.

**Quality of life**

None of the trials included measures of QOL or symptom control.

**Procedure tract metastases**

O’Rourke et al reported in 2000 that 50% of six patients in the radiation therapy group had procedure tract metastases compared to only 17% of six patients in the control group; however, no statistical analysis was reported (8). In the updated 2005 abstract (14), those data were not further reported. Bydder et al reported that 7% of 28 procedure sites in the radiation therapy group had metastases compared to 10% of 30 procedure sites in the control group; however, that difference was not statistically significant (p=0.53) (9). Boutin et al reported that none of 20 patients in the radiation therapy group had procedure tract metastases compared to 40% of 20 patients in the control group, with that difference found to be statistically significant (p<0.001) (7).

Two trials (7,8) reported conflicting results regarding the benefit of treatment for procedure tract metastases. The data were pooled and the pooled analysis did not find a significant difference in overall effect (RR 0.47, 95% CI, 0.01 – 30.90, p=0.72). The trial by Bydder (9) was not included in the meta-analysis as the results were reported by the number of tract sites and not by patient.

**Non-Randomized Prospective Studies**

Four non-randomized prospective studies were identified that investigated the use of adjuvant or palliative radiation therapy for patients with MPM (10-13). The studies were non-comparative and were either case series or small single-arm phase I or II trials.

Characteristics of the identified studies and results are found in Table 2. Three of the studies included radiation therapy as part of a combined modality regimen (10,12,13). Treatments that were combined with radiation therapy included extrapleural pneumonectomy, pleurectomy, decortication, and chemotherapy (systemic and intracavitary), in various combinations. One study reported on patients who received no specific regimen; rather, patients received various combinations of surgery, chemotherapy, or radiation therapy (11).

**Survival**

Survival was generally well reported among the studies (Table 2); however, survival rates showed great variability. Median survival ranged from seven to 17 months, one-year overall survival from 34% to 56%, and five-year overall survival from 0% to 9%. Three studies treated patients with a regimen including either a pleurectomy or an extrapleural pneumonectomy combined with radiation therapy (10,12,13), with two studies also including chemotherapy (10,12). In those studies, median survival ranged from 12.6 to 17 months. One study treated patients with a combination of only chemotherapy and radiation therapy and
median survival for this study was 7 months (11). No comparisons of survival could be made between the identified studies due to the variability of treatment.

**Adverse effects**

All the studies included data on adverse effects for the treatment being examined. However, it was difficult to isolate the adverse effects of radiation therapy as most of the studies included a variety of additional treatments. Holsti et al. reported that no patients who were treated at a dose of 20Gy had any adverse effects due to radiation therapy (12). However, most of the patients who received total doses of 38.5Gy to 71Gy had severe radiation-induced injury to the irradiated lung that started within one month of treatment and subsequently progressed (12). One study examined hemithoracic EBRT combined with chemotherapy and reported that 100% of 47 patients experienced radiation-induced pulmonary fibrosis, 23.4% experienced radiation pneumonitis, and 4.3% experienced bronchopleural fistula (11). However, if extrapleural pneumonectomy was performed, the rate of pulmonary complications was low (13).

**Quality of life**

None of the identified studies included formal measures of QOL. However, one study did measure symptom control due to radiation therapy (11). Linden et al. reported on changes in the Karnofsky performance status (KPS), body weight, and pain score (11). For 41 patients who survived one month after radiation therapy, the mean KPS and body weight decreased (p<0.005, each), and the mean pain score increased (p<0.05). For 28 patients who survived from one to six months after radiation therapy, the mean body weight did not decrease (p=0.11) and the mean pain score did not increase (p=0.18); however, the mean KPS continued to decrease (p<0.0005).
<table>
<thead>
<tr>
<th>Reference</th>
<th>Treatment(s)</th>
<th>Type and dose of radiotherapy</th>
<th>N</th>
<th>Median survival</th>
<th>Overall survival</th>
<th>Adverse Effect (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mychalsak, 1989 (10)</td>
<td>Tx + Pl + IOBT + EBRT</td>
<td>IOBT followed by hemithoracic EBRT: dose NR, IOBT (54pts) with either: A) permanent I-125 (n=46) – dose NR, or; B) temporary Ir-192 (n=14) – dose NR</td>
<td>105</td>
<td>12.6 mo</td>
<td>1 year: 52% 2 year: 23%</td>
<td>Radiation pneumonitis – 11.4% Pericardial tamponade – 7.6%</td>
</tr>
<tr>
<td>Linden, 1996 (11)</td>
<td>EBRT ± CT</td>
<td>Hemithoracic EBRT: 40Gy in 20fx 5 days a week for 4 weeks</td>
<td>47</td>
<td>7 mo</td>
<td>1 year: 34% 2 year: 10.8% 5 year: 0%</td>
<td>Radiation pneumonitis – 23.4% Bronchopleural fistula – 4.3% Radiation-induced fibrosis – 100%</td>
</tr>
<tr>
<td>Holsti, 1997 (12)</td>
<td>Tx ± Pl/ Dc/ EPP + CT + EBRT</td>
<td>Hemithoracic EBRT: 20-71Gy²</td>
<td>57</td>
<td>NR</td>
<td>1 year: 53% 2 year: 21% 5 year: 9%</td>
<td>None in patients with dose = 20Gy Most patients with dose &gt; 20Gy had severe radiation-induced injury</td>
</tr>
<tr>
<td>Rusch, 2001 (13)</td>
<td>EPP + EBRT or Pl/ Dc + IOBT + EBRT</td>
<td>IOBT (with Ir) to diaphragm and mediastinum: 15Gy + EBRT to perimeter of remaining lung tissue, chest wall, diaphragm, and mediastinum: 45-54Gy</td>
<td>62</td>
<td>17 mo</td>
<td>1 year: 56% 2 year: 41%</td>
<td>Grade 3/4: fatigue – 11.9%, nausea – 6.0%, vomiting – 4.5%, esophagus – 4.5%, lung – 1.5%, skin – 4.5%, Grade 4/5: WBC – 1.5%, platelets – 1.5%</td>
</tr>
</tbody>
</table>


² Patients were divided into six groups based on radiation doses received – see Appendix 2 for fractionation and doses
DISCUSSION

Patients with MPM generally have a poor prognosis, and most will succumb to their disease within three to five years of diagnosis. Therefore, it is important to examine not only treatments administered with a curative intent but also those given with a palliative intent.

At the present time, there is no evidence to support the use of radical radiation therapy alone, administered with curative intent, in the management of patients with MPM. The only randomized trials of radiation therapy for patients with MPM conducted to date have investigated the use of prophylactic EBRT to reduce the frequency of malignant seeding of tracts caused by thoracic drainage tubes or thoracic diagnostic procedures. One randomized trial reported a significant reduction in the frequency of malignant seeding of tracts caused by thoracic drainage tube removal and thoracic diagnostic procedures such as thorascopy for the EBRT group compared to the no EBRT group (7). However, a second randomized trial reported more procedure tract metastases in the EBRT group than the no-EBRT group (p=not reported) (8), although these were preliminary results and were based on only 12 patients. The third randomized trial found no statistically significant differences in procedure tract metastases (9). Although the frequency of procedure tract metastases after prophylactic radiation was not stated initially as an outcome of interest in this systematic review, the consensus of the authors was that the three randomized trials were the best available evidence for the use of radiation therapy for patients with MPM. Based on the consensus and the evidence analyzed in this systematic review, the authors concluded that there is insufficient evidence to definitively recommend prophylactic radiation to thoracic diagnostic tracts, and the decision to use prophylactic EBRT for patients with thoracic tracts must be based on an individualized case assessment.

Several non-randomized prospective trials have shown that radical radiation therapy can be integrated into a combined modality regimen including surgery and chemotherapy. However, the same studies showed that hemithoracic radiation, without extrapleural pneumonectomy, resulted in significant toxicity including radiation pneumonitis, lung fibrosis, and bronchopleural fistula without any survival benefit.

Palliative radiation therapy may offer symptom control and increased QOL for these patients. Of note is the fact that no studies have included formal measures of QOL, and few studies have reported on the methods used to measure symptom control.

CONCLUSIONS

Based on the lack of evidence for the use of radical radiation therapy alone in the management of patients with MPM, radical radiation should not be offered as a curative treatment option to patients with MPM. Palliative radiation therapy may offer short-term symptom control; however, long-term control has not been demonstrated. This lack of evidence is particularly disappointing considering the poor prognosis of this disease and the need for therapies that can improve the survival and quality of life of these patients. Future studies including radiotherapy for the treatment of patients with MPM should include formal measures of QOL and symptom control.
ONGOING TRIALS

The National Cancer Institute’s Clinical Trials (PDQ) (http://www.cancer.gov/search/clinical_trials/) and the Current Controlled Trials (CCT) database (http://www.controlled-trials.com) databases on the Internet were searched for reports of new or ongoing trials. Any ongoing trials found in MEDLINE, EMBASE, The Cochrane Library, ASCO, or ASTRO were also included here.

<table>
<thead>
<tr>
<th>Protocol ID(s)</th>
<th>Title and details of trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCO: 2000 Abstract #2279 (28)</td>
<td>2279: Induction chemotherapy, extrapleural pneumonectomy (EPP) and adjacent fast neutron radiation therapy (FNRT) for pleural mesothelioma (DMM). No survival, toxicity, or QOL data have been reported.</td>
</tr>
<tr>
<td>CCT - ISRCTN22296481</td>
<td>A randomised study to assess whether radiotherapy prevents skin lumps at sites where needles or tubes have been inserted in patients with malignant mesothelioma. Last modified: November 21, 2005. Available at: <a href="http://www.controlled-trials.com/isrctn/trial/MESOTHELIOMA/0/22296481.html">http://www.controlled-trials.com/isrctn/trial/MESOTHELIOMA/0/22296481.html</a></td>
</tr>
</tbody>
</table>

CONFLICT OF INTEREST

The members of the Lung DSG were asked to disclose potential conflicts of interest relating to the topic of this systematic review. The authors of this guideline declared that there were no conflicts of interest.

JOURNAL REFERENCE


ACKNOWLEDGEMENTS

The Lung DSG would like to thank Drs. Yee Chung Ung, Edward Yu, Conrad Falkson, and William K. Evans, Mr. Adam E. Haynes, and Mrs Denise Stys-Norman for taking the lead in drafting and revising this evidence-based series.
**Funding**

The PEBC is supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding agencies.

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**Contact Information**

For information about this series, please contact

**Dr. William K. Evans**, Co-Chair, Lung Cancer Disease Site Group, McMaster University and Juravinski Cancer Centre, 699 Concession Street, Hamilton ON L8V 5C2;
TEL (905) 387-9711 ext. 63001; FAX (905) 575-6323

or

**Dr. Yee C. Ung**, Co-Chair, Lung Cancer Disease Site Group, Toronto-Sunnybrook Regional Cancer Centre, 2075 Bayview Avenue, Toronto, ON, M4N 3M5;
TEL (416) 480-4951; FAX (416) 480-6002.

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REFERENCES


Appendix 1. In conjunction with Table 2: Dose, fractionation, and number of patients per treatment group reported by Holsti et al (12).

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>N</th>
<th>Dose and fractionation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemithorax irradiation I</td>
<td>8</td>
<td>2Gy/fx x 10fx over 12d</td>
</tr>
<tr>
<td>Hemithorax irradiation II&lt;sup&gt;a&lt;/sup&gt;</td>
<td>17</td>
<td>2.2Gy/fx x 25fx over 7w with a 2w rest midway</td>
</tr>
<tr>
<td>Hemithorax irradiation III&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6</td>
<td>1.25Gy/fx x 56fx given twice daily at 6h intervals over 7w with a 10d rest at halfway</td>
</tr>
<tr>
<td>Hemithorax irradiation IV&lt;sup&gt;d&lt;/sup&gt;</td>
<td>11</td>
<td>1.25Gy/fx x 28fx given twice daily at 6h intervals over 3w followed by 4Gy/fx x 9fx q 2d over 3w</td>
</tr>
<tr>
<td>Hemithorax irradiation V&lt;sup&gt;d&lt;/sup&gt;</td>
<td>5</td>
<td>3.5Gy/fx x 9fx over 15d</td>
</tr>
<tr>
<td>Hemithorax irradiation VI&lt;sup&gt;d&lt;/sup&gt;</td>
<td>10</td>
<td>2Gy/fx x 10fx over 2w to hemithorax, followed by 3Gy/fx x 10fx over 2w to bulky tumour areas</td>
</tr>
</tbody>
</table>

Notes:  d – day(s), fx – fraction(s), Gy – Gray, h – hour, N – number of patients, q – every, w – week(s).
<a> Irradiated with 8 MV photons from a linear accelerator.

<sup>b</sup> Irradiated with 24 MV photons from a linear accelerator.
Evidence-Based Series #7-14-3: Section 3

The Role of Radiation Therapy in Malignant Pleural Mesothelioma:
Guideline Development and Review - Methods and Results

YC Ung, E Yu, C Falkson, AE Haynes, D Stys-Norman, WK Evans,
and the Lung Cancer Disease Site Group

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

Report Date: February 6, 2006

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs) mandated to develop the PEBC products. These panels are comprised of clinicians, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and a consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the routine periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.

The Evidence-Based Series

Each evidence-based series is comprised of three sections.

- **Section 1: Clinical Practice Guideline.** This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review by Ontario practitioners.

- **Section 2: Systematic Review.** This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.

- **Section 3: Guideline Development and External Review – Methods and Results.** This section summarizes the guideline development process and the results of the formal external review by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.
DEVELOPMENT OF THIS EVIDENCE-BASED SERIES
Development and Internal Review

This evidence-based series was developed by the Lung Cancer Disease Site Group (Lung DSG) of CCO’s PEBC. The series is a convenient and up-to-date source of the best available evidence on the role of radiation therapy in malignant pleural mesothelioma (MPM), developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

Disease Site Group Consensus

The lack of sufficient high-quality evidence precludes definitive recommendations from being made, and, instead, the Lung DSG offers the following opinions. There is limited evidence for the role of radiotherapy in the management of patients with MPM. Furthermore, prophylactic external beam radiation therapy to tracts caused by thoracic drainage tubes or thoracic diagnostic procedures can be used to reduce the frequency of malignant seeding. In addition, radical radiation therapy alone should not be offered as a curative treatment option to patients with MPM. Finally, palliative radiation therapy may offer short-term symptom control in terms of chest wall pain; however, long-term control is not achieved.

External Review by Ontario Clinicians

Following the review and discussion of Sections 1 and 2 of this evidence-based series, the Lung DSG circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Box 1 summarizes the draft clinical recommendations and supporting evidence developed by the panel.

BOX 1: DRAFT RECOMMENDATIONS (approved for external review May 20 2005)

Target Population
- This evidence summary report applies to adult patients with MPM

Recommendations and Key Evidence
- There is limited evidence for the role of radiotherapy in the management of patients with MPM. There are no randomized controlled trials comparing radical or palliative radiation therapy to the primary (pleural) lesion to no treatment or best supportive care for patients with MPM.
- Prophylactic external beam radiation therapy to tracts caused by thoracic drainage tubes or thoracic diagnostic procedures can be used to reduce the frequency of malignant seeding. Three small randomized controlled trials compared prophylactic external beam radiation therapy to no radiation therapy for patients with thoracic tracts caused by drainage tubes or diagnostic procedures. One randomized controlled trial reported a significant difference in the frequency of procedure tract metastases for the radiation therapy arm (0% of 20 patients) compared to the control arm (40% of 20 patients), p<0.001. One remaining trial did not detect a significant difference between the two treatments arms, and the last trial, the smallest, did not report a p-value; however, more metastases were detected in the radiation therapy arm. None of those trials reported any serious adverse effects due to radiation therapy.
- Radical radiation therapy alone should not be offered as a curative treatment option to patients with MPM based on the currently available evidence. Several noncomparative studies have shown that hemithoracic irradiation alone, resulted in significant toxicity, including radiation-induced pulmonary fibrosis, radiation pneumonitis, and bronchopleural fistula, without any survival benefit.
- Palliative radiation therapy may offer short-term symptom control in terms of chest pain; however, long-term control has not been demonstrated to date. One noncomparative study reported that palliative radiation therapy offered significant short-term symptom control. The duration of symptom control was only three to five months. However, median survival for that patient population ranged from four months to 18 months. Therefore, palliative radiation therapy may be reasonable for short-term duration of pain relief for a patient population with limited survival.
- Future studies including radiotherapy for the treatment of patients with MPM should include formal measures of quality of life (QOL) and symptom control. Few of the identified studies reported on symptom control, and no studies included formal measures of quality of life.

Methods
Feedback was obtained through a mailed survey of 135 practitioners in Ontario and included medical and radiation oncologists, surgeons, and respirologists. 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. The survey was mailed out on May 20 2005. 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**

Fifty-eight responses were received out of the 135 questionnaires sent (43% response rate). Responses include returned completed surveys as well as phone, fax and email responses. Of the practitioners who responded, 39 indicated that the guideline was relevant to their clinical practice. Key results of the practitioner feedback survey are summarized in Table 1.

Table 1. Responses to eight items on the practitioner feedback survey.

<table>
<thead>
<tr>
<th>Item</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Strongly agree or agree</td>
</tr>
<tr>
<td>The rationale for developing a guideline, as stated in the &quot;Introduction&quot; section of this draft report, is clear.</td>
<td>33 (85%)</td>
</tr>
<tr>
<td>There is a need for a guideline on this topic.</td>
<td>26 (67%)</td>
</tr>
<tr>
<td>The literature search is relevant and complete (e.g., no key trials were missed nor any included that should not have been) in this draft guideline.</td>
<td>31 (80%)</td>
</tr>
<tr>
<td>The results of the trials described in this draft guideline are interpreted according to my understanding of the data</td>
<td>37 (95%)</td>
</tr>
<tr>
<td>The draft recommendations in this report are clear.</td>
<td>33 (85%)</td>
</tr>
<tr>
<td>I agree with the draft recommendations as stated.</td>
<td>34 (87%)</td>
</tr>
<tr>
<td>The draft recommendations are suitable for the patients for whom they are intended.</td>
<td>34 (87%)</td>
</tr>
<tr>
<td>This draft report should be approved as a practice guideline.</td>
<td>30 (77%)</td>
</tr>
</tbody>
</table>

If this draft report were to be approved as a practice guideline, how likely would you be to make use of it in your own practice?  

<table>
<thead>
<tr>
<th>Very likely or likely</th>
<th>Unsure</th>
<th>Not at all likely or unlikely</th>
</tr>
</thead>
<tbody>
<tr>
<td>31 (80%)</td>
<td>4 (10%)</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

a Two practitioners did not respond to this question  
b One practitioner did not respond to this question
Summary of Written Comments
Eleven practitioners (19%) provided written comments. The main comments focused on the following points:
1. One practitioner commented that there was very little evidence for a practice guideline. There were no RCTs; so why do it?
2. One practitioner questioned why one area omitted was the radial radiation therapy post-induction chemo, and extra pleural pneumonectomy for selected patients.
3. One practitioner challenged the figures that stated the incidence of MPM was low by a factor of 3. Cancer Surveillance On-Line (Public Health Agency of Canada [PHAC]) states that in year 2000 there were 310 reported cases in Canada.
4. One practitioner suggested that given the toxicity of controlled studies, it would be potentially beneficial to search for studies reported in languages other than English.

Modifications/Actions
1. In fact, there were three RCTs included in this evidence-based series. Unfortunately, the studies were underpowered due to sample size and could not be used to solidify recommendations regarding MPM.
2. This evidence series focused solely on radiation therapy for MPM. The topic in question is discussed further in the PEBC Evidence-Based Series #7-14-2 Surgical Management of Malignant Pleural Mesothelioma.
3. After further investigation to determine if, in fact, the figures had changed, BC Cancer maintained the original figures of 100 cases per year in Canada for MPM, and the Cancer Surveillance On-Line site had no direct information regarding the incidence of MPM in Canada.
4. The decision to focus on English articles only was due to limited funding for translation.

Report Approval Panel
The final evidence-based series report was reviewed and approved by the PEBC Report Approval Panel in February 2006. The Panel consists of two members, including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the Panel included the following three:
1. The Panel suggested the DSG provide an explicit discussion of the value of the different levels of evidence included in the document. If a specific evidence base (e.g., retrospective studies, small prospective studies of combined modality treatment) does not inform the recommendations, the DSG should consider excluding it.
2. Given the limited and contrasting evidence for the main recommendation on prophylactic EBRT for drainage tracts, a more explicit description of the DSG consensus process relating to this recommendation is important and could be included in the Discussion section of the document. The importance of the DSG consensus could also be acknowledged in the Recommendations section.
3. The DSG may want to consider conducting a meta-analysis for the three RCTs of tract seeding.

Modifications/Actions
1. All studies that provided little or no new evidence (small numbers–less than 40 patients and retrospective) to the body of evidence were removed from the guideline and a post hoc comment was added in the Exclusion Criteria section to address this issue.
   A poll was conducted among the radiation oncologists in the Lung DSG to determine the pattern of practice for prophylactic radiation therapy to drainage sites. There was no consistent consensus on the use of prophylactic radiation therapy. This is a reflection of the lack of high-quality data from the small randomized trials available. Therefore, a recommendation could not be made for this treatment. The decision to use prophylactic EBRT to tracts must therefore be based on an individualized case assessment.
2. The data was pooled but only for two of the studies, as one reported results on the number of sites affected and not the number of patients. There was no significant overall effect.

RELATED PRINT AND ELECTRONIC PUBLICATIONS
REFERENCES


OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario’s Program in Evidence-based Care 2006.

In September 2011, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature. A clinical expert reviewed and interpreted the new eligible evidence and proposed the existing recommendations require an update. The Lung Cancer Disease Site Group (DSG) agreed to update the recommendations found in Section 1 (Clinical Practice Guideline) in September 2012.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Question Considered

What is the role of radiation therapy (RT) in the management of malignant pleural mesothelioma?

Literature Search and New Evidence

The new search (November 2005 to April 2012) yielded 11 references representing 1 systematic review, 2 RCTs and 6 non-RCTs evaluating the role of radiotherapy in the management of malignant pleural mesothelioma either as part of a trimodality therapy or alone. Eight references are potentially new studies, of which 4 had full text publications and 4 were in abstract form. Furthermore, 2 ongoing studies were identified from clinicaltrials.gov. Brief results of these searches are shown in the Document Review Tool.

Impact on Guidelines and Its Recommendations

The new data does not contradict existing recommendations. However, there needs to be some modifications to the current recommendations due to the evidence available. Hence, the Lung Cancer DSG decided that the 2006 recommendations on the role of radiation therapy in malignant pleural mesothelioma require an UPDATE.
## Document Review Tool

<table>
<thead>
<tr>
<th>Number and title of document under review</th>
<th>7-14-3 The Role of Radiation Therapy in Malignant Pleural Mesothelioma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of current version</td>
<td>6 February, 2006</td>
</tr>
<tr>
<td>Clinical reviewer</td>
<td>Dr. Conrad Falkson</td>
</tr>
<tr>
<td>Research coordinator</td>
<td>Nofisat Ismaila</td>
</tr>
<tr>
<td>Date screened</td>
<td>September 2011</td>
</tr>
<tr>
<td>Date and final results/outcomes</td>
<td>Sept 24, 2012 [TO BE UPDATED]</td>
</tr>
</tbody>
</table>

**Original Question(s):**

What is the role of radiation therapy (RT) in the management of malignant pleural mesothelioma?

**Target Population:**

Adult patients with malignant pleural mesothelioma.

**Inclusion criteria:**

Articles published as full reports or as abstracts were included if they focused on radiotherapy (radical, adjuvant or palliative) for patients with MPM; reported data on survival, QOL, or toxicity; and were:

- Randomized trials comparing radiation therapy alone or as part of a planned combined modality regimen to no radiation therapy or best supportive care; or
- Non-randomized prospective studies of radiation therapy, alone or as part of a planned combined modality regimen involving more than 40 patients; or
- Meta-analyses or systematic reviews.

**Exclusion criteria:**

- Trials that focused on a modality other than radiation therapy, except when radiation was part of a planned combined modality regimen, were excluded.
- Trials published in a language other than English were also not considered.

**Search Period:**

- November 2005 to April 2012 (Medline April wk 1 + Embase week 15)
- November 2005 to April 2012 (ASCO Annual Meeting)
- November 2005 to April 2012 (ASTRO Annual Meeting)
- November 2005 to April 2012 (Clinicaltrials.gov)

**Brief Summary/Discussion of New Evidence:**

Of 1586 total hits from Medline + Embase and 85 total hits from ASCO + 50 total hits from ASTRO conference abstract searches + 34 total hits from clinicaltrials.gov, 11 references representing 1 systematic review, 2 RCTs (1 RCT had 2 protocol abstract publications) and 6 non-RCT (1 study had an abstract publication) were found evaluating the role of radiotherapy in the management of malignant pleural mesothelioma either as part of a trimodality therapy or alone. Eight references are potentially new studies, of which 4 had full text publications and 4 were in abstract form. Furthermore, 2 ongoing studies were identified from clinicaltrials.gov.
### IMRT after EPP

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Type of studies</th>
<th>Population</th>
<th>Outcomes</th>
<th>Brief results</th>
<th>References</th>
</tr>
</thead>
</table>
| Trimodality therapy | 15 studies on   | Patients with histologically proven MPM | local and locoregional failure after EPP and adjuvant RT, OS, Toxicity | - Local control remains poor despite the inclusion of conventional adjuvant radiation therapy in trimodality therapy and this can be improved by the delivery of adjuvant IMRT.  
- However, IMRT can be associated with severe pulmonary toxicity if the radiation dose to the remaining lung is not kept to a very low level.  
- New advances in technology can allow for lower doses to the contralateral lung, decreased treatment delivery time, and improved target dose coverage. | Chi et al, 2011     |
| 7 studies on toxicity of adjuvant IMRT | 12 studies on techniques of adjuvant IMRT |                        |         |                                                                                                                                                                                                           |                    |

### XRT Vs. BSC

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Population</th>
<th>Follow-up</th>
<th>Outcome</th>
<th>Brief results</th>
<th>References</th>
</tr>
</thead>
</table>
| XRT Vs. BSC   | Patients with a histological diagnosis of pleural mesothelioma and an invasive procedure within the preceding 21 days Median age, 70 yrs (n=61) | Median, 8 months | Tract metastasis | - Seven patients developed tract metastases associated with the drain site (four XRT arm, three BSC)  
- Four developed metastases associated with subsequent procedures at other sites (three XRT, one BSC)  
- Two patients each developed two tract metastases.  
- Of the 12 metastases, nine overlay the previous drain site but three were adjacent to the site.  
- No statistically significant difference was found in the risk of tract metastasis associated with the drain site between the arms (p = 0.748) | O'Rourke et al, 2007 |

### PET-guided dose escalation tomotherapy (A two-step dose escalation study)

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Population</th>
<th>Follow-up</th>
<th>Outcome</th>
<th>Brief results</th>
<th>References</th>
</tr>
</thead>
</table>
| PET-guided dose escalation tomotherapy (A two-step dose escalation study) | Patients with histologically proven MPM  
Group 1 (no SIB), n=12  
Group 2 (SIB), n=12  
Median age, 65yrs | Median, 13 months | Survival, toxicity | - First group of 12 consecutive MPM patients were treated with 56 Gy/25 fractions to the planning target volume (PTV)  
- The second group of 12 consecutive patients were treated with the same dose to the whole pleura adding a simultaneous integrated boost of 62.5 Gy to the FDG-PET/CT positive areas (BTV)  
- No grade 3 (RTOG/EORTC) acute or late toxicities were reported in the first group, while 3 cases of grade 3 late pneumonitis were registered in the second group: the duration of symptoms was 2–10 weeks.  
- Median overall survival was 8 months (1.2–50.5 months) and 20 months (4.3–33.8 months) from the beginning of radiotherapy, for groups I and II, respectively (p = 0.19).  
- A significant impact on local relapse from radiotherapy was seen (median time to local relapse: 8 vs 17 months; 1-year local relapse-free rate: 16% vs 81%, p = 0.003) | Fodor et al, 2010 & 2011 |

### Chemotherapy + EPP + XRT

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Population</th>
<th>Follow-up</th>
<th>Outcome</th>
<th>Brief results</th>
<th>References</th>
</tr>
</thead>
</table>
| Chemotherapy + EPP + XRT | Patients with histologically confirmed MPM  
Median age, 65yrs (n=35) | Median, 21.7 months | Survival, morbidity & mortality | - The percutaneous radiotherapy regimen varied from 21 Gy over 3 days, which is equivalent to 45 Gy over 4.5 weeks, to 50 Gy over 6 weeks.  
- Surgical morbidity/mortality and trimodality treatment-related mortality were 20.0%, 2.9% and 5.8%, respectively.  
- Thirty-three patients completed the trimodality therapy.  
- Overall median survival was 30.0 months. One-, 2-, and 3-year-survival were 69%, 50% and 31%, respectively.  
- Advanced stages III/IV (p=0.06), macroscopic incomplete resections (p=0.001), non-epithelial histology (p=0.55) and nodal metastases (p=0.19) were associated with poorer survival. | Bolukbas et al, 2011 |

### Chemotherapy + EPP + EBRT

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Population</th>
<th>Follow-up</th>
<th>Outcome</th>
<th>Brief results</th>
<th>References</th>
</tr>
</thead>
</table>
| Chemotherapy + EPP + EBRT | Patients with MPM and stage III or IV disease  
Median age, 60yrs (n=21) | Median, 9 months | Survival | - All patients completing EPP began EBRT within 6 weeks postoperatively and received the predetermined dose of 54 cGy except one patient who refused treatment after receiving 5040 Gy. | Flores et al, 2006 (feasibility study) |
- Hematologic toxicity occurred in one patient with anemia.
- Low-grade complications included esophagitis and weight loss.
- Two patients developed upper-extremity deep venous thromboses requiring anticoagulation
- The median survival of all patients was 19 months.
- The trial was stopped prematurely because of a new competing protocol.

### Abstracts

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patient Population</th>
<th>Toxicity, survival, tumor control rates</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIT (21 Gy/3 fractions) Vs. Observation</td>
<td>Patients with MPM (n=374)</td>
<td>NR</td>
<td>This 2-arm multicentre randomised trial</td>
</tr>
<tr>
<td></td>
<td>Chest wall metastasis</td>
<td></td>
<td>Patients will receive monthly telephone follow-up from a dedicated research nurse and be asked to attend a clinic at 6, 12 and 26 weeks post-randomisation.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>The trial will open for accrual early 2012</td>
</tr>
<tr>
<td>Chemotherapy +EPP + HTR</td>
<td>Patients with MPM (T3-3, N0-2) Median age, 63yrs (n=54)</td>
<td>Total, 90 days EFS</td>
<td>The total dose of HTR given at first was 54 Gy, but this was later reduced to 50.4 Gy after 2 patients died due to cardiopulmonary failure.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Of the 54 pts enrolled, 52 (96.3%) completed chemotherapy (CT), 45 (83.3%) underwent S, 22 (40.7%) completed the whole treatment.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>The median EFS was 6.9 months (95%CI: 5.0–10.5) and the median progression-free survival was 8.6 months (95%CI: 6.3-14.4).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A total of 18 (33.3%) and 13 (24.1%) pts were still event free after 1 and 2 years respectively.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Of the 54 pts, 16 (29.6%) showed partial response to CT, 31 (57.4%) showed stable disease, 4 (7.4%) showed progression, responses in 3 (5.6%) pts were unknown (overall response before S).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>During the whole study 36 (66.7%) pts experienced 1 grade 3-4 toxicity (the most frequent were hematological and gastrointestinal) but no statistically significant differences were observed before and after amendment.</td>
</tr>
<tr>
<td>Chemotherapy +EPP + IMRT</td>
<td>Patients with histologically confirmed MPM (n=41)</td>
<td>Median, 12 months</td>
<td>Median target dose was 50-54Gy in 2 Gy fractions.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean dose to the contralateral lung could be kept below 7 Gy in most cases.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Common adverse effects of the IMRT were low-grade skin erythema, nausea, and fatigue.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>One patient showed clinical symptoms of pneumonitis and fully recovered after steroid therapy (mean dose to contralateral lung in this case was 11 Gy).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No higher-grade radiation-induced side effects were observed.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2-yrs local control since the beginning of RT was 62% and 2-yrs progression free survival 33%.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median overall survival since the beginning of RT was 22 months.</td>
</tr>
<tr>
<td>EPP + RT</td>
<td>Patients with resectable epithelial or mixed MPM Median age, NR (n=37)</td>
<td>NR</td>
<td>Postoperative radiotherapy (40 Gy) was delivered through anterior and posterior fields, with a 10 to 20 Gy boost dose if necessary</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Overall hospital mortality was 5.7 %.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Major post operative complications were: 3 acute lung injury, 1 bronchopleural fistula, 1 stroke, 1 chylothorax and one diaphragmatic patch dehiscence.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Survival for the 35 patients with complete resection was 47 ± 8 % at 2 years.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median overall survival time was 22 months. Survival without recurrence was 37 ± 8 % at 2 years.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median time to progression was 15 months. Locoregional recurrence is the most common form of relapse</td>
</tr>
</tbody>
</table>

Bayman et al 2010 & 2012 (RCT protocol)
Rea et al 2011
Thieke et al, 2010
Peigaud et al, 2009
Abbreviations: Extrapleural Pneumonectomy (EPP); Intensity-modulated Radiotherapy (IMRT); Radiotherapy 21 Gy in three fractions (XRT arm) or Best Supportive Care (BSC); Simultaneous Integrated Boost (SIB); Radiation Therapy Oncology Group (RTOG); European Organization for Research and Treatment of Cancer (EORTC); Biological Target Volume (BTV); Event Free Survival (EFS); Hemithoracic Radiation (HTR)

Ongoing studies from Clinicaltrials.gov

<table>
<thead>
<tr>
<th>Study type</th>
<th>Official title</th>
<th>Status</th>
<th>Protocol ID</th>
<th>Completion Date</th>
<th>Last updated</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td>Neoadjuvant Chemotherapy and Extrapleural Pneumonectomy of Malignant Pleural Mesothelioma (MPM) With or Without Hemithoracic Radiotherapy. A Randomized Multicenter Phase II Trial</td>
<td>Recruiting</td>
<td>NCT00334594</td>
<td>December 2012</td>
<td>September 9, 2011</td>
</tr>
<tr>
<td>Observational</td>
<td>Phase II Toxicity Study Using Chemotherapy +/- Pleurectomy/Decortication Followed By Intensity Modulated Radiation Therapy to the Pleura in Patients With Locally Advanced Malignant Pleural Mesothelioma.</td>
<td>Recruiting</td>
<td>NCT00715611</td>
<td>July 2012</td>
<td>March 2, 2012</td>
</tr>
</tbody>
</table>

1. Is the volume and content of the new evidence so extensive that a simple update will be difficult?  
1. No. Adding a section regarding trimodality therapy would be appropriate and can be done as an update, the rest of the information is essentially still valid.

2. On initial review,  
   a. Does 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, and explain if necessary:

2. a. Yes, with the addition of a section on trimodality/EPP
   b. No need to add a section on trimodality and EPP + RT/IMRT

3. 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? Answer Yes or No, and explain if necessary, citing newly identified references:

3. No – however the current guideline suggested not enough evidence to comment on the ‘radical treatment’ – there is now enough evidence to make some recommendation and I believe we should

4. 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:

4. No

5. An update should be initiated as soon as possible. List the expected date of completion of the update:

5. Could be completed within 3m depending on PEBC support

An UPDATE will be posted on the website, indicating an update is in progress.

6. Circulate this form to the appropriate Disease Site Group for their approval. Once approved, a copy of this form should be placed as an appendix to the current document on the website. Notify the original authors of the document about this review.

DSG/ GDG Approval Date: 24 September 2012

Comments from DSG/GDG members:

2013 Document Review Summary and Tool – page 23
New References Identified (alphabetic order):


Literature Search Strategy:

Medline
1. meta-Analysis as topic.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
2. meta analysis.pt.
3. (meta analy$ or metanaaly$).tw.
4. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or Quantitative synthesis$ 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 bibliography$ or hand-search$ or relevant journals or manual search$).ab.

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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. exp lung neoplasms/
42. exp mesothelioma/
43. exp pleural neoplasms/
44. pleura mesothelioma.tw.
45. malignant mesothelioma.mp.
46. 41 or 42 or 43 or 44 or 45
47. (radiotherapy or radiation or irradiation).tw.
48. 46 and 47
49. 40 and 48
51. 49 and 50

**Embase**

1. exp meta analysis/ or exp systematic review/
2. (meta analys$ or metaanaly$).tw.
3. (systematic review$ or pooled analys$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes$ or quantitative overview).tw.
4. (systematic adj (review$ or overview$)).tw.
5. exp review/ or review.pt.
6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7. (study adj selection).ab.
8. 5 and (6 or 7)
9. or/1-4,8
10. (cochrane or embase or psychlit or psycolit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
11. (reference list$ or bibliograph$ 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 or phase 3 or phase 4).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$.tw.
18. (clinic$ adj trial$1).tw.
19. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
20. placebo/
21. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
22. (allocated adj2 random).tw.
23. or/18-22
24. practice guidelines/
25. practice guideline?.tw.
27. or/24-26
28. 9 or 10 or 11 or 15 or 17 or 23 or 27
29. (editorial or note or letter or erratum or short survey).pt. or letter/ or case study/
30. 28 not 29
31. limit 30 to english
32. Animal/
33. Human/
34. 32 not 33
35. 31 not 34
36. exp lung neoplasms/
37. exp pleural neoplasms/
38. exp mesothelioma/
39. malignant mesothelioma.tw.
40. pleura mesothelioma.tw.
41. 36 or 37 or 38 or 39 or 40
42. (radiotherapy or radiation or irradia
tion).tw.
43. 41 and 42
44. 35 and 43
45. (200542$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$).ew.
46. 44 and 45

**ASCO Annual Meeting** - searched [http://www.ascopubs.org/search](http://www.ascopubs.org/search) with keywords: Radiotherapy AND (Malignant Pleural Mesothelioma)

**ASTRO Annual Meeting** - searched [http://www.redjournal.org/content/astro_abstracts](http://www.redjournal.org/content/astro_abstracts) with keywords: Radiotherapy AND (Malignant Pleural Mesothelioma)

OUTCOMES DEFINITION

1. **ARCHIVE** – 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 our website, each page is watermarked with the phrase “Archived document, not for use in clinical decision making.”

2. **ENDORSEMENT** – An endorsed document is a document that has been reviewed by the DSG for currency and relevance, and the DSG believes it is still useful as guidance for clinical decision making. A document may be endorsed because the DSG 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. **DEFERRAL** – A Deferral means that the clinical reviewers feel that the document is still useful and the decision has been made to postpone further action due to a number of reasons. The reasons for deferral should be found in the DART form and on the document.

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.