Evidence-based Series 7-14-2 Version 2

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

Surgical Management of Malignant Pleural Mesothelioma

Members of the Lung Cancer Disease Site Group

An assessment conducted in December 2016 deferred the review of Evidence based Series 7-14-2 Version 2, which means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

EBS 7-14-2 document consists of:
Section 1: Clinical Practice Guideline ENDORSED
Section 2: Systematic Review
Section 3: Guideline Development & External Review
Section 4: Document Review Summary & Tool

and is available on the CCO website on the PEBC Lung Cancer DSG page.

Release Date: May 15, 2012

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


Evidence-based Series 7-14-2 Version 2 ENDORSED

Surgical Management of Malignant Pleural Mesothelioma

Guideline Report History

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Question
What is the role of surgery (pleurectomy or extrapleural pneumonectomy) in the treatment of adults with malignant pleural mesothelioma?

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

Recommendations
Because of the lack of sufficient high-quality evidence on the surgical management of mesothelioma, the Lung Cancer Disease Site Group opinion is that:

- The role of surgery in the management of malignant pleural mesothelioma cannot be precisely defined. Specifically, the lack of randomised controlled clinical trials makes it impossible to determine whether the use of extrapleural pneumonectomy or pleurectomy improves the survival of patients with malignant pleural mesothelioma or effectively palliates the symptoms of the disease.
- In patients who undergo surgery, combined with chemotherapy and/or radiotherapy, multivariate analysis shows that longer survival is associated with small, epithelial-type, node-negative pleural mesotheliomas.
- This Evidence Summary is confined to the surgical management of malignant pleural mesothelioma. Please refer to Evidence Summary Report #7-14-1 and the Evidence-based
Series #7-14-3, to be released shortly, for opinions on the use of systemic therapy and radiation therapy in this disease.

- There is a need for future studies of the role of surgery in the treatment of mesothelioma to include evaluations of quality of life

**Key Evidence**

- This series is based on eighteen studies involving both extrapleural pneumonectomy and pleurectomy (eight prospective and ten retrospective), four studies examining extrapleural pneumonectomy only (two retrospective and two including both retrospective and prospective data), and twelve studies examining pleurectomy only (four prospective and eight retrospective). All but three studies also included adjuvant chemotherapy, radiotherapy or photodynamic therapy as part of the therapeutic regimen, making the assessment of the role of surgery impossible.

- Three prospective studies that involved both extrapleural pneumonectomy and pleurectomy, along with adjuvant chemotherapy, radiotherapy, or photodynamic therapy, directly compared the two surgical treatments (1-5). Longer survival was reported with pleurectomy in all three studies; however, caution must be exercised in interpreting those comparisons because the patients were not randomly allocated to the surgical procedure, and thus survival outcomes may have been influenced by pre-surgery patient characteristics.

- Operative mortality for both types of surgery was reported in two non-controlled, comparative prospective studies (3-5) and in two non-controlled, non-comparative prospective studies (6,7). Operative mortality ranged from 0% (two studies) to 3% (one study) following pleurectomy and from 4% to 14% following extrapleural pneumonectomy. In one study, operative morbidity was 5% following pleurectomy and 18% to 36% following extrapleural pneumonectomy (1); in a second study, the rates were 39% and 71%, respectively (6).

- Median survival was reported in four non-controlled, non-comparative prospective studies examining pleurectomy combined with intrapleural chemotherapy (13 to 27 patients per study) and was 9 months, 11.5 months, and 18.3 months in those four studies (8-11). Three of those studies also reported two-year survival (12% to 40%) and local recurrence rates (75% to 80%) for this combined-modality approach. Operative mortality was similar in two trials (one patient death in each study), although morbidity varied between 8% and 44% and included hemorrhage, renal toxicity, cardiac events, air leaks, and wound infections.

- Seven non-controlled prospective (1,2,4-7,12,13) and five retrospective case-series studies (14-18) explored the effect of prognostic factors on survival using multivariate analyses. Of the prospective studies, three were non-comparative studies (6,7,13), one had comparison groups that were not of interest (2), and three had relevant comparison groups but they assigned patients based on disease characteristics (1,4,5,12). Seven of those studies included treatment type as a potential prognostic variable; three specifically examined the type of surgery. The factors most commonly associated with longer survival included epithelial-type mesothelioma (five studies), earlier stage of disease (five studies), use of adjuvant or combined modality treatment (five studies), and good performance status (four studies). Factors adversely associated with survival included high pre-treatment platelet count (three studies), positive nodal status (two studies), larger preoperative tumour volume (two studies), and larger postoperative residual tumour volume (one study). The type of surgery did not have a significant impact on survival in any of the three studies that examined that association.
Two prospective and two retrospective non-comparative surgical studies, three including adjuvant chemotherapy or radiotherapy, reported the palliation of signs or symptoms of malignant mesothelioma following treatment (9,19-21). Pleural fluid control improved in 98% of 50 patients and 96% of 54 patients; the recurrence of pleural effusion was prevented in 80% of 20 patients; dyspnea improved in 47% of 20 patients and 100% of 37 patients; and pain improved in 21% of 19 patients and 85% of 71 patients. However, none of the studies described the methods of symptom assessment in detail.

Future Research
Future trials for malignant pleural mesothelioma should consist of randomized controlled trials examining extrapleural pneumonectomy for patients with good prognosis, pleurectomy for patients with poorer prognosis, pleurodesis for patients with pleural effusions, and pleurectomy versus pleurodesis for palliation of symptoms of malignant pleural mesothelioma. Quality of life as an outcome should also be included in future surgical trials involving this disease.

Related Guidelines
- PEBC Evidence Summary #7-14-1 Chemotherapy for Mesothelioma (posted on the CCO Web site);
- PEBC Evidence-based Series #7-14-3 Radiotherapy for Mesothelioma (currently under development).

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

The following references pertain to Section 1: A Clinical Practice Guideline. They are also referenced in Section 2: A Systematic Review; the citation number of each reference within Section 2 is shown in parentheses.

16. Sugarbaker DJ, Flores RM, Jaklitsch MT, Richards WG, Strauss GM, Corson JM, et al. Resection margins, extrapleural nodal status, and cell type determine postoperative long-


Surgical Management of Malignant Pleural Mesothelioma: 
A Systematic Review

D.E. Maziak, A. Gagliardi, A.E. Haynes, J.A. Mackay, W.K. Evans, and members of the Lung Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care


Section Date: August 9, 2005

QUESTION
What is the role of surgery (pleurectomy or extrapleural pneumonectomy) in the treatment of adults with malignant pleural mesothelioma?

INTRODUCTION
Mesotheliomas are neoplasms of the serosal membranes. As 80% of mesotheliomas originate in the pleural space, pleural mesothelioma is the most common primary tumour of the pleural cavity (1). Each year, approximately 100 Canadians will be diagnosed with malignant mesothelioma (2), with an estimated median survival of between four and 12 months if the disease is untreated (3). Mesotheliomas are classified into three general categories (diffuse malignant, localized benign, and localized malignant), although most clinical studies do not specifically report these disease categories. Since diffuse malignant pleural mesothelioma was first described as a distinct form, its treatment has been associated with controversy. Treatment has consisted of surgery, radiation, and chemotherapy in some form at some point during the course of the disease. The two main surgical approaches for the treatment of this disease are pleurectomy (PL) and extrapleural pneumonectomy (EPP). The former procedure generally involves the excision of sections of the pleura, and the latter, more aggressive approach involves the removal of all or part of a lung as well as the parietal pleura and ipsilateral pericardium and diaphragm. This review will focus on the role of surgery, specifically PL and EPP, in the treatment of diffuse and localized malignant mesothelioma, for which there is currently no widely accepted standard of care.

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 (4).
Evidence was selected and reviewed by one member of the PEBC’s Lung Disease Site Group (Lung DSG) and methodologists. This systematic review is a convenient and up-to-date source of the best available evidence on surgery for malignant pleural mesothelioma. The body of evidence in this review is primarily comprised of mature randomized controlled trial data. That evidence forms the basis of a clinical practice guideline developed by the Lung DSG. The systematic review and 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**

MEDLINE and CANCERLIT databases were searched from 1985 through July 2005, using the Medical Subject Headings “mesothelioma/surgery” and “lung neoplasms/surgery” and the keyword or text word “mesothelioma” in combination with “surgery”, “pleurectomy”, “decortication”, “pneumonectomy”, and “resection”. Similar terms were used to search the Cochrane Library 2002, Issue 4 for additional clinical trials. These terms were then combined with the search terms for the following study designs: practice guidelines, meta-analyses, systematic reviews, randomized controlled trials, and clinical trials. The search was limited to 1985 onwards because the classification and staging of pleural mesothelioma have varied tremendously over time, and it is difficult to compare data from early trials with that of trials that are more recent.

Ongoing clinical trials were identified using the Physician Data Query (PDQ) database at [http://www.cancer.gov/search/clinical_trials/](http://www.cancer.gov/search/clinical_trials/). Relevant articles were selected and reviewed by two reviewers, and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guidelines Clearinghouse (http://www.guideline.gov/index.asp) were searched for existing evidence-based practice guidelines.

**Inclusion Criteria**

Articles were selected for inclusion in this systematic review of the evidence if they were:

1. Randomized controlled trials (RCTs), systematic reviews (including meta-analyses or practice guidelines), phase II trials, or prospective or retrospective cohort studies examining the role of surgical resection for malignant pleural mesothelioma.
2. Trials reporting clinical or sub-clinical adverse effects on the topics mentioned above.

**Exclusion criteria**

1. Trials where the majority of patients were being treated for conditions other than malignant pleural mesothelioma.
3. Abstract publications.
4. Letters and editorials describing trial results.
5. Papers published in a language other than English.

**Synthesizing the Evidence**

A statistical synthesis of the evidence was not conducted because no randomized trials involving surgical treatment for mesothelioma were identified and the prospective and retrospective studies included a variety of adjuvant treatments.
RESULTS

Literature Search Results

No RCTs comparing PL with EPP or comparing surgery with an alternative treatment in patients with malignant pleural mesothelioma were identified. Studies that met the evidence-based series inclusion criteria are shown in Table 1 and include the following: 18 studies (eight non-controlled prospective, of which only four were comparative, and 10 retrospective case series) involving both PL and EPP (5-24); four studies (two retrospective case series and two including both retrospective and prospective case-series data) examining EPP only (25-28); and four prospective non-comparative studies plus eight retrospective case series studies examining PL only (29-40). Only 12 of the 34 studies reported the type of mesothelioma examined: 11 involved diffuse mesothelioma (15,16,18-20,26,27,30,34,35,39), and one involved localized disease (10).

Meta-analyses and RCTs would provide the best evidence of the relative effectiveness of different types of surgery or surgery in comparison with other treatment options for malignant pleural mesothelioma. However, none of the identified prospective studies was randomized, and none was designed to directly compare different treatments. Therefore, the overall level of evidence for the surgical treatment of mesothelioma is limited.

Some prospective studies did conduct statistical comparisons of the different treatments (7,9-12,30), although patients were not randomized. Given that patients were selected for a specific treatment rather than randomly assigned to a treatment, it is not appropriate and may be misleading to draw conclusions or inferences in favour of a particular intervention. Patient selection criteria, rather than the interventions themselves, may provide an alternative explanation for differences that emerge between the interventions.

The prospective studies were mostly small phase II trials or case series reports (median number of surgical patients, 40; range, 19 to 174) that included a variety of treatments in addition to surgery; therefore, it is difficult to separate the effect of surgery from other interventions. The retrospective studies meeting the evidence-based series inclusion criteria consisted of either case series reports or summaries of registry data. Although the retrospective data may provide potentially useful information on prognostic factors for survival, those studies constitute quite a low level of evidence and will not be the focus of this evidence-based series.

No evidence-based clinical practice guidelines were identified, although the British Thoracic Society (BTS) published a statement in 2001 intended to guide the management of malignant mesothelioma (41). The statement was developed through a review of the literature and expert consensus. However, a comprehensive review of the literature was not attempted, and the BTS indicated that limitations on the quality of evidence did not allow for the development of recommendations.

Table 1. Studies included in this evidence-based series report.

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Type of Study</th>
<th>Number of Fully Published Studies</th>
<th>Reference Number(s)</th>
<th>Further Information Found in Table</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleurectomy and extrapleural</td>
<td>Prospective, non-controlled</td>
<td>8</td>
<td>(5-14);</td>
<td>Table 2a</td>
</tr>
<tr>
<td>pneumonectomy</td>
<td>Retrospective</td>
<td>10</td>
<td>(15-24)</td>
<td>Table 2b</td>
</tr>
<tr>
<td>Extrapleural pneumonectomy</td>
<td>Prospective, non-controlled /</td>
<td>2</td>
<td>(25,28)</td>
<td>Table 3</td>
</tr>
<tr>
<td></td>
<td>retrospective</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Retrospective</td>
<td>2</td>
<td>(26,27)</td>
<td></td>
</tr>
<tr>
<td>Pleurectomy</td>
<td>Prospective, non-controlled</td>
<td>4</td>
<td>(29-32)</td>
<td>Table 4a</td>
</tr>
<tr>
<td></td>
<td>Retrospective</td>
<td>8</td>
<td>(33-38)</td>
<td>Table 4b</td>
</tr>
</tbody>
</table>
Outcomes
1. Studies Involving both Extrapleural Pneumonectomy and Pleurectomy
1a. Prospective, non-controlled studies

Eight prospective studies (Table 2a) included both EPP and PL as treatment options (5-14). None of the studies were randomized or provided similar, concurrent comparison groups, resulting in a relatively low level of available evidence on which to draw conclusions for or against surgical intervention.

Calavrezos et al did prospectively assign eligible patients to one of two treatments, supportive care or combined modality therapy including surgery (5). However, assignment was according to patient preference, and there was an imbalance in the resulting treatment groups by age, performance status, tumour histology, and tumour operability, in favour of the combined modality treatment group. All the prospective studies included a variety of treatments in addition to surgery. In the study by Calavrezos et al, combined modality therapy included surgery, chemotherapy, and radiotherapy, but only 42 of the 57 patients assigned to combined modality therapy underwent surgery (5). Rice et al adopted an aggressive treatment plan including surgery, postoperative intrapleural chemotherapy, and adjuvant chemotherapy (6).
<table>
<thead>
<tr>
<th>Study (Ref)</th>
<th>Patients</th>
<th>Operative Morbidity</th>
<th>Operative Mortality</th>
<th>Recurrence</th>
<th>Survival (m = months)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calavrezos, 1988 (5) Non-controlled comparative study</td>
<td>57 combined modality (34 PL, 8 EPP, 15 not resected) 75 supportive care (39 ineligible for surgery) 132 patients, 54 epithelial</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Median/2-yr 13m/11% (for 57 combined modality pts) Supportive care: 7m/3% (36 pts) Ineligible: 5m/7% (39 pts)</td>
<td>Minimum 22m follow-up Adjuvant treatment: CT for 54 surgical candidates + RT for responding pts Combined modality group better performance status (KPS 80-100, 84% vs. 36%) and younger (median, 53 vs. 64 years) than supportive care group Assignment to PL or EPP vs supportive care determined by patient choice</td>
</tr>
<tr>
<td>Rice, 1994 (6) Single-arm phase II trial</td>
<td>9 PL 10 EPP 19 patients, 10 epithelial</td>
<td>6 complications reported: reoperations, 3 (16%) including 2 for prosthetic replacement of diaphragm; supraventricular arrhythmias, 2 (11%); and vocal cord augmentation, 1 (5%)</td>
<td>1/19 (5%) presumed arrhythmia or pulmonary embolus + 1 CT-related death Local/distant combined 4/1/1 3/1/2</td>
<td></td>
<td>Median/3-yr for all 19 pts overall, 13m/17% disease-free, 11m/22%</td>
<td>Adjuvant treatment: intra-pleural CT for all pts and adjuvant CT for 15 pts Complete resection in 16 pts (10 EPP, 6 PL) Stage: I (68%), III (32%) Good to excellent palliation of symptoms in 84% of pts Adjuvant CT - not well tolerated; intrapleural CT - no serious complications Longer survival with epithelial-type disease</td>
</tr>
<tr>
<td>Pass, 1997 (7) Non-controlled comparative study</td>
<td>39 PL, 33 epithelial 39 EPP, 27 epithelial + 17 unresectable 95 patients</td>
<td>Ventricular arrhythmias, 2/39 (5%) Ventricular arrhythmias, 14/39 (36%); bronchopleural fistulas, 7/39 (18%) Overall, 61/95 (64%) free of morbidity</td>
<td>Overall, 2/95 post-operative hemorrhage (2%) with additional mortality due to 3 suicides and 1 aspiration total, 31/39 (79%) with 28 locoregional local, 27/39 (69%) with 17 locoregional PL vs. EPP for locoregional, p=0.013 Overall/ Progression-free Median 14.5m/7.4m Median 9.4m/7.0m PL vs. EPP, p=0.012/p=NS (Median for unresectable, 5.0m)</td>
<td></td>
<td>Median potential follow-up, 33.7m Adjuvant treatment: intra-operative PDT or postoperative immunotherapy EPP longer operative time (p=0.06) and greater blood loss (p&lt;0.001) EPP lower local recurrence but similar overall recurrence due to distant metastases</td>
<td></td>
</tr>
<tr>
<td>Moskal, 1998 (8) Single-arm phase II trial</td>
<td>28 PL 7 EPP 5 PL + lobectomy 40 of 43 patients</td>
<td>39% 71% 40% Overall 18/40 (45%): atrial</td>
<td>1/7 (14%) EPP pts - due to bronchopleural fistula NR</td>
<td>For 37 pts surviving postoperatively: median, 15m 2-y, 23%</td>
<td>Adjuvant treatment: intra-operative PDT at 20-30 J/cm² Complete resection in 16 pts Postoperative disease stage³: I (30%), II (2.5%), III (62.5%), IV (5%) On disease recurrence, 7 pts received palliative CT and 7 received palliative</td>
<td></td>
</tr>
</tbody>
</table>

Table 2a. Prospective studies involving both extrapleural pneumonectomy and pleurectomy.
were resectable, 25 epithelial fibrillation, (38%); sepsis (28%); respiratory insufficiency, (25%), bronchopleural fistula, (8% of all EPP pts)  

<table>
<thead>
<tr>
<th>Study</th>
<th>Surgery Type</th>
<th>Histology</th>
<th>Complications</th>
<th>Follow-up</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pass, 1997 &amp; 1998 (9,10)</td>
<td>23 PL, 25 EPP</td>
<td>33 of 48 pts had epithelial histology</td>
<td>Of 48 surgical pts - arrhythmia, 8%; bronchopleural fistula, 8%; cardiac herniation, bleeding, and pancreatitis, each 2%.</td>
<td>Median 22m</td>
<td>RT</td>
</tr>
</tbody>
</table>
| | | | 0/25 (4%) | 11m | ▪ Median potential follow-up, 23.1m  
▪ Adjuvant treatment: CT + randomization to intra-operative PDT. No survival difference associated with PDT randomization  
▪ Postoperative disease stage among 48 surgical pts: I (8%), II (8%), III (79%), IV (4%) |
| Rusch, 1991 & 1999 (11,12) | 59 PL, 115 EPP | 231 total, 164 epithelial histology | Arrhythmia, 8/20 (40%); bronchial stump leak and empyema, 4/20 (20%) | Median 2-yr/5-yr: 18.5m/40%/9% | Adjuvant treatment: 142 PL/EPP pts received adjuvant therapy - 106 RT, 29 CT, 7 CT+RT  
▪ Longer survival with epithelial than non-epithelial histology (p<0.01)  
▪ Disease stage among 231 pts: I (9%), II (16%), III (44%), IV (30%) |
| Maggi, 2001 (13) | 9 PL, 23 EPP | Of 32 pts - Major: total, 31.3%; bleeding, 19%; acute respiratory insufficiency, 6%; bronchopleural fistula & vocal cord paralysis, both 3% Minor: total, 12.8%; atrial fibrillation, 6%; transitory nerve paralysis & subcutaneous seroma, both 3% | Total, 2/32 (6%); 1 acute respiratory insufficiency with ARDS, 1 pneumonia | Total, 21 pts alive with median follow-up of 12.5m | ▪ Median follow-up, 11.5m for 27/30 survivors  
▪ Adjuvant treatment: CT at 4-6 wks postoperatively followed by RT to 55 Gy + additional CT  
▪ Preoperative disease stage (Brigham) for 32 pts: I (19%), II (31%), III (50%) |
| Rusch, 2001 | 5 PL | Total, 33/88 (38%) | 0 | Median/3-yr | ▪ Adjuvant treatment: PL pts received... |
(14)

### Single-arm phase II trial

<table>
<thead>
<tr>
<th></th>
<th>62 EPP</th>
<th>7/62 (11%) primarily related to pulmonary difficulties</th>
<th>2 local, 30 distal, 5 local &amp; distal for the 54 EPP pts receiving RT (69%)</th>
<th>NR</th>
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<tbody>
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<td>7/62 (11%) primarily related to pulmonary difficulties</td>
<td>2 local, 30 distal, 5 local &amp; distal for the 54 EPP pts receiving RT (69%)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>+ 21 exploratory surgery only</td>
<td>7/62 (11%) primarily related to pulmonary difficulties</td>
<td>2 local, 30 distal, 5 local &amp; distal for the 54 EPP pts receiving RT (69%)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>88 total, 60 epithelial</td>
<td>7/62 (11%) primarily related to pulmonary difficulties</td>
<td>2 local, 30 distal, 5 local &amp; distal for the 54 EPP pts receiving RT (69%)</td>
<td>NR</td>
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<tr>
<td></td>
<td></td>
<td>7/62 (11%) primarily related to pulmonary difficulties</td>
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<tr>
<td></td>
<td></td>
<td>7/62 (11%) primarily related to pulmonary difficulties</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>7/62 (11%) primarily related to pulmonary difficulties</td>
<td>2 local, 30 distal, 5 local &amp; distal for the 54 EPP pts receiving RT (69%)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7/62 (11%) primarily related to pulmonary difficulties</td>
<td>2 local, 30 distal, 5 local &amp; distal for the 54 EPP pts receiving RT (69%)</td>
<td>NR</td>
</tr>
</tbody>
</table>

**IORT @ 15 Gy; 54 EPP and 4 PL pts received 54 Gy in 30 fr to hemithorax at 3-5 wks postoperatively**
- EPP IORT changed to external RT
- Tumour histology had no effect on survival but stage, tumour, and nodal status did
- Disease stage for 88 pts: I (2%), II (19%), III (52%), IV (26%)

#### Notes:
- ARDS - acute respiratory distress syndrome, CT - chemotherapy, EPP - extrapleural pneumonectomy, fr - fractions, Gy - gray(s), IORT - intraoperative RT, KPS - Karnofsky performance status, m - month(s), NR - not reported, NS - not statistically significant, PDT - photodynamic therapy, PL - pleurectomy, pt(s) - patient(s), Ref - reference, RT - radiotherapy, vs. - versus, wks - weeks, yr - year(s).

a. Patients assigned to treatment groups based on personal choice.
b. Doxorubicin 60 mg/m² + vindesine 3 mg/m² + cyclophosphamide 650 mg/m² every 3 wks +/- 45-60 Gy radiotherapy.
c. Postoperative intrapleural CT was administered over 4 hours following PL (cisplatin 100 mg/m² and mitomycin-C 8 mg/m²), and within 1-2 wks postoperatively following EPP (cisplatin 100 mg). Adjuvant CT was 2 monthly injections of cisplatin 50-100 mg/m² in the first 3 pts and, in the remaining pts, mitomycin-C 8 mg/m² weeks 1 and 6 with cisplatin 50 mg/m² weeks 1-4 and 6-9.
d. Patients assigned to groups based on patient and disease characteristics.
e. American Joint Committee on Cancer staging system.
f. Tamoxifen 20 mg orally twice daily for 35 days (2 cycles), interferon-a2b 5mU/m² 3 times/week, and cisplatin 25 mg/m² days 8, 15, 22, and 29.
g. International Mesothelioma Interest Group staging system.
h. Data taken from 1991 report (11), EPP=20 patients, PL=26 patients.
i. Median, 2-year, and 5-year survival estimated from the survival curves.
j. Paclitaxel 200 mg/m² + carboplatin (area under the curve, 6) x 2 cycles every 3 weeks.
k. Paclitaxel 60 mg/m² weekly, given concurrently with radiotherapy and followed by 2 more cycles of paclitaxel-carboplatin.
<table>
<thead>
<tr>
<th>Study (Ref)</th>
<th>Patients</th>
<th>Operative Morbidity</th>
<th>Operative Mortality</th>
<th>Survival</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chailleux, 1988 (15) Case series</td>
<td>29 PL or EPP 14 CT + PL or EPP 167 patients, 81% epithelial histology</td>
<td>NR</td>
<td>NR</td>
<td>1-yr/2-yr surgery without CT, 54%/25% Surgery with CT, 64%/29% Non-surgical treatment (41 pts), 31-42%/9-21% Supportive care (79 pts), 28%/2%</td>
<td>Single centre with data from 1955 to 1985 4 pts total underwent EPP Adjuvant treatment: CT (varied regimens) Non-surgical treatment included talc poudrage (17 pts) and chemotherapy (24 pts)</td>
</tr>
<tr>
<td>Ruffie, 1989 (16) Case series</td>
<td>63 PL, epithelial NR 23 EPP, 12 epithelial 246 CT, RT or supportive care 332 patients</td>
<td>NR</td>
<td>NR</td>
<td>Median/2-yr 9.8m/NR 9.3m/17% No surgery, median 8m p&gt;0.23</td>
<td>Multi-centre analysis of data from 1965 to 1984 Adjuvant treatment: some patients also received RT or CT Disease stage (Butchart) for 332 pts: I (17%), II (29%), III (6%), IV (4%), unknown (44%) PL prevented recurrence of pleural effusions in 86% pts</td>
</tr>
<tr>
<td>Harvey, 1990 (17) Case series from registry data</td>
<td>9 PL, 2 epithelial 7 EPP, 2 epithelial 76 supportive care 92 patients</td>
<td>NR</td>
<td>0</td>
<td>Median 12m &lt;6m (1 pt survived 7 yrs and 1 pt, 8 yrs) supportive care, median 7.6m</td>
<td>California centres with data from 1965 to 1988 Adjuvant treatment: for PL, 4 pts CT, 1 RT; for EPP, 1 pt CT+RT</td>
</tr>
<tr>
<td>Branscheid, 1991 (18) Case series</td>
<td>82 PL 76 EPP 143 CT, exploratory thoracotomy, or supportive care 301 patients, 50% epithelial</td>
<td>NR</td>
<td>2/82 (2.4%) 9/76 (11.8%)</td>
<td>Median 10.4m 9.3m overall, 7.8m Reported significant survival advantage for PL/EPP (p=NR)</td>
<td>German study with data from 1978 to 1989 Adjuvant treatment: CT for 49 pts receiving PL or EPP Longer median survival for epithelial than sarcomatous or mixed biphasic histology (p&lt;0.001) Preoperative/intraoperative disease stage for 301 pts I (2%), II...</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Type</td>
<td>No. of Patients</td>
<td>Histology</td>
<td>Major Complications</td>
</tr>
<tr>
<td>-------</td>
<td>------</td>
<td>------</td>
<td>----------------</td>
<td>-----------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Allen, 1994</td>
<td>19</td>
<td>Case series</td>
<td>56 PL, 28 epithelial, 40 EPP, 26 epithelial</td>
<td>96 patients</td>
<td>Major complications: air leak, arrhythmia, bronchopleural fistula, vocal cord paralysis, tracheostomy, chylothorax, MI, effusion, splenectomy</td>
</tr>
<tr>
<td>Huncharek, 1996</td>
<td>20</td>
<td>Case series</td>
<td>17 PL or EPP, 21 CT + PL or EPP, 11 CT, 4 RT, 26 supportive care</td>
<td>49% of patients had epithelial histology</td>
<td>NR</td>
</tr>
<tr>
<td>Lampl, 1999</td>
<td>21</td>
<td>Case series</td>
<td>19 PL, 23 EPP, 11 exploratory surgery only</td>
<td>53 patients</td>
<td>NR</td>
</tr>
<tr>
<td>Aziz, 2002</td>
<td>22</td>
<td>Case series</td>
<td>191 SC, 47 PL, 13 EPP, 51 EPP + CT</td>
<td>NR</td>
<td>Major complications: EPP: ARDS (5pts); bleeding (4pts); pneumonia/empyema (4pts); reintubation and ventilation (2pts)</td>
</tr>
<tr>
<td>Study</td>
<td>Patients</td>
<td>Minor Complications EPP*</td>
<td>Chemotoxicity</td>
<td>Median/1 year</td>
<td>Survival **</td>
</tr>
<tr>
<td>-------</td>
<td>----------</td>
<td>--------------------------</td>
<td>---------------</td>
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<td>-------------</td>
</tr>
<tr>
<td>De Vries 2003 (23)</td>
<td>46 patients</td>
<td>18/64 (28%) dysrhythmia (8pts); wound infection (4pts); sputum retention (3pts); pneumothorax (1pt)</td>
<td>Nausea (63%), Anaemia (32%), leucopenia (21%), Thrombocytopenia (9%).</td>
<td>PL - 1/29 (3.8%)</td>
<td>EPP - 1/17 (5.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemotoxicity</td>
<td>Nausea (63%), Anaemia (32%), leucopenia (21%), Thrombocytopenia (9%).</td>
<td>Median/1 year</td>
<td>EPP - 12m/ 42% (3pts &gt;7 years)</td>
</tr>
<tr>
<td>Stewart, 2004 (24)</td>
<td>3 chest wall tumour resection</td>
<td>Non-radical surgery group - 7/132 (5%)</td>
<td>EPP - 4/132 (3%)</td>
<td>EPP - 16m</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>132 patients</td>
<td>EPP - 16m</td>
<td>8pts in the EPP group had neoadjuvant CT, maximum 3 cycles or cisplatin and gemcitabine.</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- CT = chemotherapy, EPP = extrapleural pneumonectomy, m = month(s), MI = myocardial infarction, NR = not reported, PL = pleurectomy, pt(s) = patient(s), Ref = reference, RT = radiotherapy, vs. = versus, yr = year(s), SCT = systemic chemotherapy, ARDS = adult respiratory distress syndrome, SC = supportive care.
- a Staging system adapted from the UICC classification for bronchial carcinoma.
- b Classified according to the International Mesothelioma Interest Group staging system.
- c Operative mortality reported for all EPP patients overall.
- d Survival rate determined from published survival curve.
Median survival ranged from less than six months in seven patients (17) to 16 months in 23 patients (21) following EPP and from nine months in 56 patients (19) to 14 months in 19 patients (21) following PL. One study reported a median survival of 4.5 months in 26 patients undergoing supportive care compared with 23.9 months in 21 patients undergoing surgery combined with chemotherapy with or without radiotherapy (p<0.01 Wilcoxon) (20). Four studies also reported a median survival of between 4.5 and eight months for non-surgical patients (16,17,20-22), although in two studies unresected patients were likely to have more advanced disease than were surgical patients (21,22).

Ruffie et al included 118 of 332 patients in a multivariate analysis and found that later disease stage (p<0.001), a high platelet count (p=0.001), and asbestos exposure (p=0.02) were negatively associated with survival (16). In the study by Allen et al, the lack of postoperative adjunctive therapy (p=0.0001) and sarcomatous tumours (p=0.0007) were adversely associated with survival (19). In the same study, the presenting combined symptoms of surgical procedure, age, sex, mediastinal nodal metastases, and pain were not associated with survival. For 301 patients with pleural mesothelioma, 158 treated surgically, Branscheid et al conducted univariate analyses and reported longer median survival for patients with epithelial tumours compared with sarcomatous or biphasic tumours (9.8 versus 3.0 versus 5.8 months, respectively, p<0.001), although it is unclear if that outcome was affected by other confounding factors (18). Other prognostic variables adversely affecting survival included age >40 years (p<0.05), weight loss (p<0.05), and the presence of chest wall pain (p<0.01); the latter was also associated with sarcomatous histology (18).

Operative mortality was similar for PL and EPP in two of the five studies reporting outcomes for both treatments (0% to 7.5%), and cause of death included pulmonary embolism, myocardial infarction, organ failure, intraoperative bleeding, and pneumonia (19,21). The operative period was not defined in either study. In the three studies, 30-day mortality was between 3% to 11.8% following EPP and 2.4% to 5% following PL, although the cause of death was not reported (18,23,24). Morbidity for both PL and EPP was reported in one study, and the overall rates were similar, 27% and 30%, respectively (19). Arrhythmia, tracheostomy, and pneumonia occurred following both surgeries; air leak and renal failure occurred following PL. Similar complications occurred in the report by DeVries et al, with 41% operative morbidities. (23) Bronchopleural fistula, vocal cord paralysis, chylothorax, myocardial infarction, effusion, and splenectomy occurred following EPP (19) Ruffie et al and Aziz et al reported similar complications following EPP, with an overall morbidity rates 21% to 26% (16,22). None of the retrospective studies reported on symptom palliation; however, results reported by Ruffie et al suggested that PL prevented the recurrence of pleural effusions in 86% of 63 patients (16).

2. Studies Involving Extrapleural Pneumonectomy

Four studies reported outcomes following EPP for malignant pleural mesothelioma (25-28). One small, retrospective case series study of five patients provided limited outcome data and is not discussed further (27). The other three studies examined survival in patients undergoing EPP, with or without adjuvant therapy (25,26,28) (Table 3). One of those studies was an updated case series report of 183 patients undergoing surgery as part of a trimodality therapy program. Data were collected retrospectively for the period 1980 to 1997, although the authors indicated that all surviving patients were contacted at the time of the latest update (26). The study did not include a comparison group but, given the relative recency of the data and the larger sample size, the analysis of possible prognostic factors provides useful information. The other study included both retrospective data collected between 1965 and 1978 and prospective registry data collected from 1978 to 1985 (25). Patients in the early period of that study underwent pleurectomies, while patients recruited more recently...
underwent pleuropneumonectomies; however, the number of patients undergoing each procedure was not reported separately. Although survival rates were reported by treatment group in that study, the allocation of patients to a specific treatment appeared to be dependent on patient and disease characteristics, which would likely differentially impact outcomes (25). The final study by Stewart et al reviewed retrospective data from a prospective database registry between August 1999 and July 2004. (28)

Median survival for patients undergoing extrapleural pneumonectomy, with or without adjuvant chemotherapy, was similar in both studies at 18 to 19 months (25,26). The results of a multivariate analysis (Cox model) reported by Antman et al suggested that good performance status (0 to 1, p<0.001), epithelial tumour histology (p<0.001), and pleuropneumonectomy with adjuvant chemotherapy (p=0.018) were associated with longer survival, but chest pain at diagnosis (p<0.001) and less than six months between the appearance of symptoms and diagnosis (p=0.010) were associated with shorter survival (25). Sugarbaker et al also conducted a multivariate analysis (proportional hazards regression model) and found that survival was adversely affected by the presence of positive resection margins (odds ratio, 1.7; 95% confidence interval, 1.2 to 2.6; p=0.0082), sarcomatous or mixed tumour histology (odds ratio, 3.0; 95% confidence interval, 2.0 to 4.5; p<0.0001), and metastatic extrapleural nodes (odds ratio, 2.0; 95% confidence interval, 1.3 to 3.2; p=0.0026).

For 183 patients, Sugarbaker et al reported 3.8% postoperative mortality, defined as death within 30 days of surgery, and 24.5% major morbidity, defined as untoward events that prolonged hospitalization (26). Adverse events that occurred in at least five patients postoperatively included: cardiac arrest, aspiration, pulmonary failure or pulmonary embolism, bleeding or suspected cardiac tamponade, and vocal cord paralysis, with fatalities due to pulmonary embolism, myocardial infarction, cardiac herniation, and respiratory failure (26). Stewart et al also defined operative mortality as less than 30 days postoperative; five patients (7%) expired in the given time frame. As for operative morbidity, patients experienced multiple adverse events. Twenty-two patients (30%) experienced technical difficulties, 35 patients (47%) had cardiovascular episodes, 15 patients (20%) had respiratory difficulties, four patients (5%) had gastrointestinal problems, and three patients (4%) had infections (28).
# Table 3. Studies examining extrapleural pneumonectomy.

<table>
<thead>
<tr>
<th>Study (Ref)</th>
<th>Patients</th>
<th>Operative Morbidity</th>
<th>Operative Mortality</th>
<th>Survival</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>92 CT only</td>
<td></td>
<td></td>
<td>▪ Data collected retrospectively on 31 pleural pts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19 EPP+CT</td>
<td></td>
<td></td>
<td>▪ Adjuvant treatment: CT&lt;sup&gt;b&lt;/sup&gt; +/- RT for pts without progression following CT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>56% epithelial</td>
<td></td>
<td></td>
<td>▪ Disease stage of 136 pleural pts: I (58%), II (24%), III (18%); IV (1%)</td>
</tr>
<tr>
<td>Sugarbaker, 1999 (26)</td>
<td>183 pts</td>
<td>Overall, 92/183 (50%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>major&lt;sup&gt;d&lt;/sup&gt;: 45/183 (24.5%) minor: 75/183 (41%)</td>
<td>Median/2-yr/5-yr</td>
<td>▪ Single-centre data from 1980 to 1997</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7/183 (3.8%): pulmonary embolism, 3 pts; myocardial infarction, 2 pts; cardiac herniation and respiratory failure, 1 pt each</td>
<td>19m/38%/15% For subgroup of 103 pts with epithelial histology: 26m/52%/21%; p=0.0001 compared with survival for sarcomatous or mixed histology</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>▪ Median follow-up, 13m (range, 0.2-100m)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>▪ Adjuvant treatment: CT started 4 to 6 wks post-surgery&lt;sup&gt;e&lt;/sup&gt; + RT 30 Gy (1.5 Gy per fr) to hemi-thorax; mediastinum received 40 Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>▪ Disease stage (Sugarbaker) for 183 pts: I (36%), II (22%), III (38%), NR (4%)</td>
</tr>
<tr>
<td>Takahashi, 2001 (27)</td>
<td>5 pts</td>
<td>Atrial fibrillation, 2/5 patients</td>
<td>0</td>
<td>NR</td>
<td>▪ Single-centre data from 1989 to 1995</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>▪ All stage Ia or Ib</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>▪ Adjuvant treatment: RT in 1 pt</td>
</tr>
<tr>
<td>Stewart, (2005) (28)</td>
<td>59 pts</td>
<td>Postoperative&lt;sup&gt;f&lt;/sup&gt;: Technical 22/74 (30%) Cardiovascular 35/74 (47%) Respiratory 15/74 (20%) Gastro-intestinal 4/74 (5%) Infection 3/74 (4%)</td>
<td>&lt; 30 days post operative 5/74 (7%) rt ventricular failure 2pts, MI 1pt, pulmonary embolism 1pt, perforate oesophagus 1pt</td>
<td>N/R</td>
<td>▪ Single centre data from August 1999 - July 2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>▪ Adjuvant treatment CT: 9pts with gemcitabine, pemetrexed 5pts, vinorelbine 1pt</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>▪ Overall re-operation rate 18pts (24%)</td>
</tr>
</tbody>
</table>

**Notes:** CT - chemotherapy, EPP - extrapleural pneumonectomy, fr - fraction(s), Gy - gray(s), m - month(s), NR - not reported, pt(s) - patient(s), Ref - reference, RT - radiotherapy, wks - weeks, yr(s) - year(s), rt - right, MI - myocardial infarction.

<sup>a</sup> Survival data for CT includes patients with the following disease type: 92 pleural, 29 peritoneal, and 5 other.

<sup>b</sup> Cyclophosphamide 600 mg/m<sup>2</sup> + doxorubicin 60 mg/m<sup>2</sup> every 3 weeks (to a total doxorubicin dose of 450 mg/m<sup>2</sup>).

<sup>c</sup> Overall morbidity is less than the sum of major and minor morbidities because patients could have both major and minor events.

<sup>d</sup> Major complications: cardiac arrest, ventricular failure, aspiration, pulmonary failure, pulmonary embolus, contralateral pneumothorax, sepsis, wound infection, empyema, upper GI bleeding, vocal cord paralysis, seizure, deep vein thrombosis, acute renal failure, bacteremia, perforated duodenal ulcer, colectomy, Ogilvie’s syndrome, pancreatitis. Minor complications: atrial and ventricular arrhythmias.

<sup>e</sup> 1980-1985: cyclophosphamide 600 mg/m<sup>2</sup> + doxorubicin 50-60 mg/m<sup>2</sup> for 4-6 cycles (9 pts); 1985-1994, as 1980-1985 + cisplatin 70 mg/m<sup>2</sup> (80 pts); 1995-1997, carboplatin (area under the curve, 6) + paclitaxel 200 mg/m<sup>2</sup> (94 pts).

<sup>f</sup> Multiple perioperative morbidities.
3. Studies Involving Pleurectomy

Four prospective studies and eight retrospective studies examined survival, morbidity, and mortality in patients undergoing PL for malignant mesothelioma (29-40). Data from those studies are summarized in Tables 4a and 4b.

### Table 4a. Prospective studies examining pleurectomy.

<table>
<thead>
<tr>
<th>Study (Ref)</th>
<th>Patients</th>
<th>Operative Morbidity</th>
<th>Operative Mortality</th>
<th>Survival</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rusch, 1994 (29) Single-arm phase II trial</td>
<td>27 PL + CT, 70% epithelial</td>
<td>12/27 (44.4%): hemorrhage, renal toxicity, myocardial infarction, prolonged air leaks, atrial arrhythmias, wound infection</td>
<td>1/27 (3.7%): upper GI hemorrhage from duodenal ulcer</td>
<td>Median, 18.3 m&lt;sup&gt;a&lt;/sup&gt; 1-yr 69% (95% CI, 54%-90%) 2-yr 40% (95% CI, 25%-65%)</td>
<td>▪ Adjuvant treatment: intrapleural +/- systemic CT&lt;sup&gt;b&lt;/sup&gt; ▪ Disease stage (modified UICC): I (33%), III (67%) ▪ 16/20 (80%) recurred locally ▪ Complete resection possible in 20/27 (74%) ▪ Epithelial type had longer survival than non-epithelial (p=0.0375)</td>
</tr>
<tr>
<td>Sauter, 1995 (30) Two trials: 1) Single-arm phase II trial 2) Prospective case-series</td>
<td>13 subtotal PL + CT Other prospective: 7 subtotal PL (4 with RT) 10/20 epithelial</td>
<td>1/13 (8%): wound complication from PL CT caused nephrotoxicity (grade 2, 2pts; grade 4, 1 pt) and thrombocytopenia (1 pt)</td>
<td>1/20 (5%): grade 4 nephrotoxicity followed by sepsis and respiratory failure</td>
<td>Median/2-yr PL + CT (13 pts): 9m/15% PL +/- RT (7 pts): overall, 21m/43%; with RT, 38m/50%; without RT, 13m/33% For all 20 pts: 12m/25% PL + CT vs. PL +/- RT, p=0.04.</td>
<td>Median time to progression: PL + CT, 6m PL +/- RT, 12m (p=0.01)</td>
</tr>
<tr>
<td>Colleoni, 1996 (31) Non-controlled case series</td>
<td>20 PL + CT, 50% epithelial</td>
<td>Grade 3-4 side effects: anemia (1pt), renal toxicity (2 pts)</td>
<td>NR</td>
<td>Median survival, 11.5 m Median time to progression, 7.4m</td>
<td>▪ Median follow-up, 11m ▪ Adjuvant treatment: intrapleural +/- systemic CT&lt;sup&gt;c&lt;/sup&gt; ▪ Disease stage (TNM): I (40%), II (20%), III (40%) ▪ Survival better with minimal residual disease (24.5 vs. 10 m)</td>
</tr>
<tr>
<td>Lee, 1995 (32) Prospective case-series</td>
<td>17 enrolled&lt;sup&gt;d&lt;/sup&gt; 15 PL + CT&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Grade 3/4 - Arrhythmia (1pt), renal failure and chest tube infection (1pt)</td>
<td>No treatment related mortality</td>
<td>Median - 1/2year 11.5m - 30%/12&lt;sup&gt;f&lt;/sup&gt;</td>
<td>▪ 11/15 pts also received RT dose ▪ 3pts expired &lt;6m post treatment ▪ recurrence rate 12/15 pts median 7.5m (80%) ▪ Local recurrence in a 15pts</td>
</tr>
</tbody>
</table>

**Notes:** CI - confidence interval, CT chemotherapy, GI - gastrointestinal, Gy - gray(s), m - month(s), NR - not reported, PL - pleurectomy, pt(s) - patient(s), Ref - reference, RT - radiotherapy, UICC - International Union against Cancer, vs. vs. versus, wks - weeks, yr(s) - year(s).

1. Survival data from the text is recorded in the table. Survival data reported in the abstract differs slightly for median (17 months) and one-year survival (68%).
2. Intrapleural cisplatin 75-100 mg/m<sup>2</sup> and mitomycin 8 mg/m<sup>2</sup>, followed by cisplatin 50 mg/m<sup>2</sup> days 1, 8, 15, 22, 36, 43, 50, and 57 and mitomycin 8 mg/m<sup>2</sup> days 1 and 36, starting 3-5 weeks postoperatively.
3. Only 13/20 patients had a definitive diagnosis of malignant pleural mesothelioma pre-thoracotomy and were eligible for the phase II trial. The remaining 7 patients were also followed for the period of the study.
4. Intrapleural chemotherapy administered in operating room (cisplatin 100 mg/m<sup>2</sup> and cytosine arabinoside 1200 mg) and systemic chemotherapy administered 3-5 weeks postoperatively (cisplatin 50 mg/m<sup>2</sup>/week x 8 and mitomycin-C 8 mg/m<sup>2</sup> days 1 and 36).
5. Intrapleural cisplatin 100 mg/m<sup>2</sup> and cytarabine 1,000 mg/m<sup>2</sup> followed by systemic chemotherapy starting 21-35 days postoperatively (epirubicin 60 mg/m<sup>2</sup> and mitomycin-C 10 mg/m<sup>2</sup>) and administered every 28 days for 4 cycles.
6. 2 pts diagnosed with metastatic pleural adenocarcinoma.
Cisplatin (100mg/m²) and cytosine arabinoside (1,200 mg) mixed together in 250ml normal saline were poured into the hemithorax after pleurocotomy/decortication.

Survival rate determined from published survival curve.
### Table 4b. Retrospective studies examining pleurectomy.

<table>
<thead>
<tr>
<th>Study (Ref)</th>
<th>Patients</th>
<th>Operative Morbidity</th>
<th>Operative Mortality</th>
<th>Survival</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Alberts, 1988 (33) | 26 PL, 54% epithelial 262 total received CT and/or RT and/or surgery | NR                  | NR                  | Median: 10.9m  
For all 262 pts, median, 9.6m | ▪ Data from two South African centres between 1965 and 1985  
▪ Adjuvant treatment: CT³ + RT 45 Gy over 6 wks for PL pts  
▪ Epithelial cell type was not prognostic for survival in entire group of 262 pts  
▪ Disease stage (Butchart) for 262 pts: I (77%), II (13.4%), III (5%), IV (4.6%) |
| Achatzy, 1989 (34) | 46 PL  
72 subtotal PL  
82 other surgery⁶  
245 total with 45 no surgery | 2/46 (4.3%)  
8/72 (11.1%)  
All surgery, 12/200 (6%) | 1/50 (2%) due to hemorrhage | Median: 10.1m for surgical pts and 6m for non-surgical pts  
5-yr: 2.2% of 178 surgical pts and 11.4% of 44 non-surgical pts  
For all 245 pts: median, 9.2m; 1-yr, 36%; 3-yr, 6.3%; 5-yr, 4.1%  
2 pts lived >10 yrs | ▪ Single centre with data from 1969 to 1985  
▪ Adjuvant treatment: some surgical pts received postoperative CT and RT alone or in combination  
▪ Postoperative CT/RT did not improve prognosis |
| Ball, 1990 (35)   | 13 PL  
22 no PL (radical or palliative RT +/- CT)  
38 total (35 with disease confined to hemithorax) | NR                  | NR                  | Median: PL, 17m (13 pts)  
No PL, 9m (22 pts)  
For all 38 pts: median, 9m; estimated 2-yr, 16% | ▪ Single centre with data from 1981 to 1985; pts given variety of treatments  
▪ Adjuvant treatment: some PL pts received radical or palliative RT +/- CT³  
▪ Two deaths due to RT |
| Brancatisano, 1991 (36) | 45 subtotal PL  
50 total had thoracotomy | 8/50 (16%): air leak, pneumonia, respiratory insufficiency, empyema, hemorrhage | 1/50 (2%) due to hemorrhage | For 49 pts (excluding the one postoperative death): median, 16m; 2-yr, 21% | ▪ Data from two Australian centres between 1984 and 1989  
▪ Adjuvant treatment: NR  
▪ Concluded that pleurectomy is good for diagnosis and palliation |
### EBS 7-14-2 V2 SURGICAL MANAGEMENT MALIGNANT PLEURAL MESOTHELIOMA

#### Section 2: Systematic Review

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>No.</th>
<th>Procedure</th>
<th>Complications</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
</table>
| Soysal, 1997   | Case series  | 56  | PL        | 22/100 (22%): air leak, empyema, pleural effusion, wound infection | median, 17m (range 3 to 63m) For pts also receiving RT +/- CT: median, 22m | • Single centre with data from 1974 to 1992 and focus on diagnosis and palliative care  
  • Adjuvant treatment: 31 pts RT, 24 pts CT, and 20 pts CT + RT  
  • 89% pts stage I or II disease  
  • Concluded PL provided good palliation to control pleural fluid |
| Ceresoli, 2001 | Case series  | 38  | PL        | NR            | NR                              | • Single centre with data from 1986-1999  
  • Median follow-up, 22m  
  • Adjuvant treatment: CT and palliative RT (<45 Gy) for some pts  
  • Good performance status and combined modality treatment associated with longer survival  
  • Disease stage (Butchart) for 121 pts: I (64%), II (24%), III (3%), IV (9%) |
| Lee, 2002      | Case series  | 26  | PL        | Post operative complications: Atrial fibrillation 3/26 (11%), Persistent air leak 1/26 (4%), RT induced pneumonitis 4/26 (17%) | No deaths as a result of surgery or therapy | • Single centre with data from 1995 - 2000  
  • Median follow-up, 70m  
  • Progression free survival: 1yr - 50%, 2yr - 22%  
  • EBRT median dose: 41.4 Gy (range 30.1-48.8 Gy)  
  • CT was given 1-2m post RT for 2 to 3 cycles |
| Phillips, 2003 | Case series  | 15p | Group I²  | Post operative complications: Acute renal failure 1/70 (1%), air leaks 2/70 (3%) | Group II (3%) and III (7%) - 1pt from each group with respiratory failure | • Single centre with data from 1989 - 1999  
  • 2pts from group III thoracotomy could not diagnose; had Ct guided needle biopsy  
  • All pts received RT post operative at chest drain sites to prevent tumour recurrence  
  • Survival was longer in pts with epithelioid histological subtype (median 10m) compared to biphasic (6m) or sarcomatous (4m) |
|                |              | 40p | Group II² | post operative complications: |                              |                                                                      |
|                |              | 15p | Group III²| Postoperative complications: |                              |                                                                      |

Notes: CT - chemotherapy, Gy - gray(s), m - month(s), NR - not reported, PL - pleurectomy, pt(s) - patient(s), Ref - reference, RT radiotherapy, wks - weeks, yr(s) - year(s), IORT - Intraoperative radiation therapy, EBRT - external beam radiotherapy, Ct - computed tomography.

a  Chemotherapy involved a variety of three- to five-drug combination regimens.

b  Among the 82 patients undergoing ‘other’ surgery, there were 78 diagnostic thoracotomies, 2 extended pleuropneumonectomies, 1 partial removal of the diaphragm, and 1 total pleurectomy with upper lobectomy.

c  Most common chemotherapies were doxorubicin, cisplatin, cyclophosphamide, and vincristine (protocols NR).

d  defined as > 7 days

e  Group I - diagnostic direct pleural biopsy only, Group II - pleural biopsy through VAT followed by talc pleurodesis, Group III - and pleurectomy
3a. Prospective, non-controlled studies

The four prospective studies provided the study inclusion criteria, and one indicated that consecutive patients meeting the inclusion criteria were enrolled in the study (30). All four trials were small (15 to 27 patients), and three did not include a concurrent comparison group (29,31,32). Therefore, those three studies contained only limited evidence. One of the latter studies excluded nine of 36 enrolled patients from the analysis because they were subsequently found to be unresectable (eight patients) or misdiagnosed (one patient) (29), and the other study reported data for 20 evaluable patients with the aim of assessing the feasibility of a multimodality treatment approach (31). In the third trial, 13 of 20 patients were diagnosed preoperatively and enrolled in a phase II trial of pleurectomy with intrapleural chemotherapy (30). The seven remaining patients were diagnosed post-thoracotomy and underwent surgery without chemotherapy, although some did receive radiotherapy. However, the comparison of those two groups was limited by the small numbers in each group and because, as noted by the study authors, there might be fundamental differences between patients who are or are not diagnosable preoperatively. Lee et al enrolled 17 patients; however, after biopsy it was discovered that two patients were diagnosed with metastatic pleural adenocarcinoma. Along with chemotherapy, 11 patients also received radiotherapy (32). All four prospective studies administered intrapleural chemotherapy during either a total or a subtotal PL, and most patients also received systemic chemotherapy following surgery (29-32).

The results from the four prospective studies are summarized in Table 4a. Survival duration was assessed from the date of the thoracotomy (29), from the date of study entry (31,32), or from an undefined time (30). Median survival was 18.3 months, 11.5 months, and 9 months, respectively. Two-year survival was also reported in three studies at 40% (29), 15% (30), and 12%, estimated by using the published survival curve. (32). In one study, tumours were considered completely resected in 20 of 27 patients (29). In the other two studies, gross residual disease remained after surgery (30,31).

Local recurrence was reported as common in two studies, at 80% (29) and 75% (30). One patient died in the postoperative period in each of two studies (29,30), although reported postoperative morbidity was more common in the study by Rusch et al (29) and included the following major morbidities: intrathoracic hemorrhage (one patient) and renal failure (two patients). Colleoni et al also reported the following grade 1-4 side effects associated with surgery and intrapleural chemotherapy: renal toxicity (50%), hematological (35%), fever (30%), pain (15%), infection (10%), cardiac toxicity (10%), and hepatic toxicity (10%) (31). None of the studies defined the period considered postoperative.

Sauter et al assessed the palliative effects of pleurectomy combined with intrapleural and adjuvant chemotherapy in 20 patients (30). They reported improvements in dyspnea (47%) and pain (21%) and no recurrence of pleural effusions (80% of patients). The five-grade National Cancer Institute Common Toxicity Criteria was used to assess dyspnea, with a reduction of ≥1 grade considered an improvement. Pain was assessed on an undefined patient-report measure.

3b. Retrospective studies

In the eight retrospective studies, all case series reports, data was collected over periods varying from five years (35,36,39) to 21 years (33), with a median of between 45 and 54 patients undergoing PL [range 13 patients (35) to 118 patients (34)]. Those studies are subject to the same limitations as the retrospective studies mentioned in a previous section of this report. Seven of the eight retrospective studies reported the use of adjuvant treatment involving chemotherapy and/or radiotherapy (33-35,37-40).
Median survival for patients undergoing PL was reported in seven of the eight retrospective studies and varied between 10.9 months among 26 patients (33) and 17 months among 13 (35) and 100 (37) patients (Table 4b). Achatzy et al reported a median survival of 10.1 months for 178 patients undergoing some form of surgery, including 118 patients who underwent a total or subtotal PL (34). Three studies assessed survival from date of diagnosis (33,35,38), and four did not define the period of assessment (34,36,40) and one determined survival from the date of surgery. (39) Two retrospective studies reported two-year survival for surgical patients. Brancastisano et al reported a 21% survival for 45 patients who underwent a subtotal pleurectomy and four patients who underwent thoracotomy (36). The second study by Phillips et al reported a 40% survival for 15 patients who underwent a pleurectomy. (40)

In a multivariate analysis (Cox model), Alberts et al found longer survival was associated with good performance status (p<0.0001), duration of symptoms >6 months (p=0.0079), and earlier disease stage (p=0.0285) (33). Good performance status (p=0.001) and combined modality treatment with palliative pleurectomy and chemotherapy (p=0.003) were also associated with improved survival in the Cox multivariate analysis reported by Ceresoli et al (38). Postoperative mortality was reported in four studies and ranged from 1% of 100 patients undergoing either a total or a subtotal PL (37) to 11% of 72 patients undergoing a subtotal PL (34). The latter study defined the postoperative period as 30 days. Postoperative morbidity was reported in four studies at 1% among 70 patients (40) and 22% among 100 patients (37). Patients in both of the latter studies experienced empyema and/or air leak; other complications included respiratory failure, pleural effusion, hemorrhage, and wound infection.

Two retrospective studies reported that PL offered good palliation (36,37). In one study, lifelong control of pleural fluid was achieved in 49 of 50 patients who had presented with unilateral pleural effusion that was unsuccessfully treated with thoracocentesis (36). In the second study, symptom palliation was achieved for up to six months for cough (100% of 40 patients), dyspnea (100% of 37 patients), pleural fluid control (96% of 54 patients), chest pain (85% of 71 patients), pleural mass/thickening (55% of 70 patients), and constriction of the hemithorax (40% of 30 patients) (37). The method of symptom assessment was not reported in that study (37).

**DISCUSSION**

Diffuse malignant mesothelioma, a very insidious neoplasm that is relatively rare, is associated with exposure to asbestos, is typically diagnosed many years after exposure, and is aggressive in its spread to local structures (3)). Ideally, the impact of surgery on this disease would be assessed through RCTs that compare different types of surgery or compare surgery with other treatment modalities. However, given the rarity of the disease, only non-controlled studies have been conducted to date, and those are generally case series and non-comparative phase II studies, which constitute a relatively low level of evidence. In addition, the classification, staging, and treatment of this disease have varied tremendously throughout the years, making it very difficult to compare the data from trials and the results of treatment. In limiting the search to the role of surgery in mesothelioma from 1985, we hoped to eliminate some of the confusion. Although this helped to focus the work, the quality of evidence was still limited. Many studies incorporated data from earlier years, particularly retrospective case series reports that frequently included data from the 1960’s and 1970’s. Some authors republished old data or extracted data from other studies, further complicating the interpretation of the results. This evidence-based series has, therefore, focused mainly on the results of prospective studies and included only the latest publications of ongoing case series reports.
What can be clearly stated is that the evidence for the role of surgery is very poor for this rare disease. Even if surgery is very aggressive, patients usually succumb to their disease within two years. Data from non-controlled studies, both prospective and retrospective, suggest that aggressive surgery, with adjuvant chemotherapy and radiotherapy, may have a role for patients with small, epithelial-type, node-negative mesotheliomas, but the role of aggressive surgery alone compared to other treatments, including best supportive care, has not been directly assessed.

There are few data concerning symptom control and palliation, which may be particularly important outcomes for a disease with limited survival prospects, and limited data on disease-free survival. While this evidence-based series has focused on the role of surgery in the treatment of mesothelioma, we did not find in these studies any evaluation of the quality of life of patients receiving surgical treatment.

ONGOING TRIALS

<table>
<thead>
<tr>
<th>Protocol ID</th>
<th>Title and details of trial</th>
</tr>
</thead>
</table>

CONCLUSIONS

Following practitioner feedback and review by the PGCC, the Lung DSG decided that changes were necessary in the ‘Recommendations’ section of this evidence-based series. The opinions of the Lung DSG have been modified to the following:

- The role of surgery in the management of malignant pleural mesothelioma cannot be precisely defined. Specifically, the lack of randomised controlled trials makes it impossible to determine whether the use of extrapleural pneumonectomy or pleurectomy improves the survival of patients with malignant pleural mesothelioma or effectively palliates the symptoms of the disease.
- In patients who undergo surgery, combined with chemotherapy and/or radiotherapy, multivariate analysis shows that longer survival is associated with small, epithelial-type, node-negative pleural mesotheliomas.
- This evidence-based series is confined to the surgical management of malignant pleural mesothelioma. Please refer to Evidence Summary Report #7-14-1 and Evidence-based Series #7-14-3, to be released shortly, for opinions on the use of systemic therapy and radiation therapy in this disease.
- There is a need for quality of life evaluation to assess the role of surgery in the treatment of mesothelioma.

CONFLICT OF INTEREST

The members of the Lung DSG disclosed potential conflicts of interest relating to the topic of this evidence-based series. No potential conflicts were declared.

JOURNAL REFERENCE

This evidence-based series was submitted as an evidence summary on June 28, 2004 and accepted for publication on September 14, 2004 by the journal Lung Cancer.

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For a complete list of the Lung Cancer Disease Site Group members, please visit the CCO website at: http://www.cancercare.on.ca/access_PEBC.htm.

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For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at: Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca
REFERENCES


Surgical Management of Malignant Pleural Mesothelioma:
Guideline Development and External Review: Methods and Results

D.E. Maziak, A. Gagliardi, A.E. Haynes, J.A. Mackay, W.K. Evans, and members of the Lung Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)
Developed by the Lung Disease Site Group


Section Date: August 9, 2005

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 consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians in the province 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: A New Look to the PEBC Practice Guidelines

Historically all the components and methodologies of the practice guidelines were packaged into one report. However, in response to feedback from Ontario clinicians and members of the PEBC panels, the end product has been restructured to better meet the information needs and preferences of that core audience. The high-quality methods and the credible development process are now part of 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 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 surgery for malignant pleural mesothelioma, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

External Review by Ontario Clinicians

Following review and discussion of the original evidence summary report, the Lung DSG circulated the report 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 June 6 2003.) |
|--------------------------|--------------------------|
| **Target Population**    |                           |
| • This evidence summary applies to adult patients with diffuse or localized malignant pleural mesothelioma. 8 |
| **Recommendations**      |                           |
| • Definitive recommendations cannot be made because of the lack of sufficient high-quality evidence. Instead, the Lung DSG offers the following opinions based on the evidence reviewed: |
| • The role of surgery for malignant pleural mesothelioma is unclear. There is insufficient data to support the use of extrapleural pneumonectomy or pleurectomy to improve the survival of patients with malignant pleural mesothelioma or for palliation of symptoms of the disease. |
| • There is some evidence to suggest that if surgery is performed, it is more effective when combined with chemotherapy and/or radiotherapy in the treatment of small, epithelial-type, node-negative pleural mesotheliomas. |
| • There is a need for quality-of-life evaluation to assess the role of surgery in the treatment of mesothelioma. |
Practitioner Feedback

A draft evidence summary version of this series was reviewed by Ontario practitioners. Any changes made to the report as a result of practitioner feedback are described in the ‘Modifications’ section below.

Methods

Practitioner feedback was obtained through a mailed survey of 111 practitioners in Ontario (31 surgeons, 36 medical oncologists, 23 radiation oncologists, 20 respirologists, and 1 hematologist). The survey consisted of items evaluating the methods, results, and interpretive summary. Written comments were invited. The practitioner feedback survey was mailed out on June 5, 2003. Follow up reminders were sent out at two weeks (postcard) and four weeks (complete package mailed again). The Lung DSG reviewed the results of the survey.

Results

Sixty-one responses were received out of the 111 surveys sent (55% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 43 indicated that the report was relevant to their clinical practice and completed the survey. Two respondents left that question blank but completed the rest of the survey, and one respondent who indicated that the report was not relevant completed the survey, but the data from the latter respondent was not included in the analysis below. Results of the practitioner feedback survey are summarized in Table 5.

Table 5. Results of the practitioner feedback survey.

<table>
<thead>
<tr>
<th>Item</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<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>Strongly agree or agree 40 (89%)  Neither agree nor disagree 4 (9%)  Strongly disagree or disagree 1 (2%)</td>
</tr>
<tr>
<td>There is a need for an evidence summary on this topic.</td>
<td>Strongly agree or agree 37 (82%)  Neither agree nor disagree 7 (16%)  Strongly disagree or disagree 1 (2%)</td>
</tr>
<tr>
<td>The literature search is relevant and complete in this evidence summary.</td>
<td>Strongly agree or agree 36 (82%)  Neither agree nor disagree 8 (18%)  Strongly disagree or disagree 0</td>
</tr>
<tr>
<td>I agree with the methodology used to summarize the evidence.</td>
<td>Strongly agree or agree 40 (91%)  Neither agree nor disagree 4 (9%)  Strongly disagree or disagree 0</td>
</tr>
<tr>
<td>I agree with the overall interpretation of the evidence in the evidence summary.</td>
<td>Strongly agree or agree 41 (91%)  Neither agree nor disagree 4 (9%)  Strongly disagree or disagree 0</td>
</tr>
<tr>
<td>The Opinions of the Disease Site Group section of this evidence summary is useful.</td>
<td>Strongly agree or agree 33 (75%)  Neither agree nor disagree 8 (18%)  Strongly disagree or disagree 3 (7%)</td>
</tr>
<tr>
<td>An evidence summary of this type will be useful for clinical decision making.</td>
<td>Strongly agree or agree 31 (69%)  Neither agree nor disagree 10 (22%)  Strongly disagree or disagree 4 (9%)</td>
</tr>
<tr>
<td>At present, there is insufficient evidence to develop a practice guideline on this topic.</td>
<td>Strongly agree or agree 36 (80%)  Neither agree nor disagree 2 (4%)  Strongly disagree or disagree 7 (16%)</td>
</tr>
<tr>
<td>There is a need to develop an evidence-based practice guideline on this topic when sufficient evidence becomes available.</td>
<td>Strongly agree or agree 38 (88%)  Neither agree nor disagree 1 (2%)  Strongly disagree or disagree 4 (9%)</td>
</tr>
<tr>
<td>How likely would you be to consider surgery as a treatment option for patients with malignant pleural mesothelioma in your practice?</td>
<td>Strongly agree or agree 18 (41%)  Neither agree nor disagree 8 (18%)  Strongly disagree or disagree 18 (41%)</td>
</tr>
</tbody>
</table>

*One practitioner did not respond to these questions

b Two practitioners did not respond to this question
Summary of Written Comments

Sixteen respondents (36%) provided written comments. The main points contained in the written comments were:

1. There was general agreement that the lack of evidence precluded definitive recommendations. Two practitioners commented that prospective randomized trials were unlikely to be forthcoming with such an uncommon form of cancer and that mesothelioma cases should be managed in larger teaching hospitals, where multidisciplinary modes of management are available. One practitioner felt that it is unrealistic to state that future research should include RCTs of surgery.

2. Four practitioners commented that the decision to refer patients to a surgeon is made on a case-by-case basis and that surgery may be useful in selected patients. One practitioner noted that he/she considers age a primary factor in whether to recommend surgery. This practitioner suggested that in otherwise-healthy patients aggressive surgical treatment could be recommended, whereas in older patients with comorbidities, the focus should be on palliative treatment.

3. One practitioner challenged the usefulness of median survival time as a measure of benefit and suggested that a more appropriate outcome criterion would be long-term survival (i.e., 5 years).

4. One respondent disagreed with the classification of mesothelioma as diffuse, benign, or malignant localized. He/she noted that none of the studies dealt with localized fibrous tumour of the pleura.

5. One practitioner suggested examining the studies more thoroughly to look at the natural history of untreated or palliatively treated mesothelioma compared to surgical outcomes.

6. One practitioner felt that pleurodesis provided as good a survival as more radical therapy.

7. One practitioner commented that the indolent nature of some of these tumours makes assessment of the treatment very difficult. This practitioner also cautioned that some studies excluded operative deaths from median survival figures.

8. One respondent suggested that although initial extrapleural pneumonectomy results were promising, they were not able to reproduce them, and therefore their centre resorted to using surgery only for diagnosis and then treated these patients palliatively.

Modifications/Actions

1. We feel hopeful that an RCT would be possible through a cooperative group with many countries involved.

2. We agree that as the evidence is not present to support surgical resection, each case should be individualized, considered for a trial if one exists, and managed in a center that has the support.

3. We agree with the comment about median survival; however, we have simply reported the results as quoted in the papers. If median, mean, and long-term survivals were reported, we have quoted them.

4. The problem of tumour classification was addressed in the ‘Interpretive Summary’. We have not classified the tumours as such, but simply quoted the papers in their descriptions and attempted to differentiate between them.

5. The question of the evidence summary was the role of surgery in mesothelioma, and therefore the natural history, although very important, was not included so as to retain the focus of the summary.

6. We do not have the evidence in this summary to refute or agree with this comment.

7. We agree that these tumours may be indolent and as such, no treatment may be appropriate. We agree with the practitioner’s comment about extracting data from
survival curves and have explicitly stated how survival was determined throughout the evidence-based series.

8. The role of palliative treatment alone compared to surgery for mesothelioma is an important point and is addressed in Section 1, Future Research and Section 2, Conclusions.

**Practice Guidelines Coordinating Committee Approval Process**

The evidence summary report was circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Eight of thirteen members of the PGCC returned ballots. Three PGCC members approved the evidence-based series report as written, and five members approved the report conditional on the Lung DSG addressing specific concerns.

**Summary of Comments**

Two members of the PGCC were concerned that the statement, “the role of surgery is unclear” was not supported by the following comment, “data to support the use of surgery to improve survival or palliation.” There was also concern that, given the complications reported in the literature, the data appears to support limited use of surgery. A third member was concerned that the opinion on histological type, nodal status, and combination chemotherapy and/or radiation therapy was misleading as it was written. Specifically, the member suggested that surgery was not more effective in those settings, just that those factors, when present, were potential prognostic factors. A fourth member requested that opinions be added regarding the type of chemotherapy and palliative care approach. Finally, a fifth member provided suggestions related to how the trials were described in the report. Specifically, descriptions or summary statements describing the quality and methodology of the trials would enhance the systematic review of this evidence-based series.

**Modifications/Actions**

In response to the first two PGCC members’ comments, it is impossible to determine if the use of pleurectomy or extrapleural pneumonectomy in patients with malignant pleural mesothelioma improves survival or palliation, due to a lack of RCT’s. This point has been clarified in the evidence-based series and specifically in the first opinion statement of the Section 2, Conclusions. The third member’s concern was warranted. The Lung DSG has rewritten the second opinion to clarify that the factors mentioned are potential prognostic factors, when present. In order to address the fourth member’s request, a bullet was added to the Conclusions opinions section stating: ‘In the management of malignant pleural mesothelioma, there is limited data to support the use of chemotherapy and/or radiotherapy for palliation in some patients. The role of these modalities will be elaborated on further in Evidence Summary Report #7-14-1 and Evidence-based Series #7-14-3.’ Finally, the Lung DSG agreed with the fifth member’s suggestions regarding the trial descriptions. Summary statements and descriptions regarding the quality and methodology of the trials were added, where appropriate.

**Peer Review Feedback**

Two reviewers from *Lung Journal* provided feedback from the manuscript based on this series. One of the reviewers felt that the conclusion in the original manuscript that suggested “...aggressive surgery, with adjuvant chemotherapy and radiotherapy, may have a role for patients with small, epithelial-type, node-negative mesotheliomas...” was not supported by the evidence given in the report. The fact that there was a lack of uniformity in reporting the data between the studies and that numerous studies did not report data on
selection criteria, operative morbidity, or operative mortality was noted. The other reviewer was not certain what was meant by the term “small, epithelial-type pleural mesothelioma”. He/she further noted that “UR”, “could not be debulked”, “palliative PL/exploration”, and “exploratory” all seemed to mean the same and suggested that the importance of the new American Joint Committee on Cancer/International Union Against Cancer staging system should be emphasized. Furthermore, it was noted that the median survival from the Pass et al (10) was reported as an intention-to-treat survival and that data was missing from table 4a regarding the Rusch et al (29) paper.

Finally, it was indicated by a reviewer for the Annals of Thoracic Surgery that a study by Aziz et al (22) had not been included in as a reference.

**Modifications/Actions**

The authors of the report responded to the comments and agreed that there was little evidence to support the conclusion, and therefore made changes in the revised manuscript to indicate that “Multivariate analyses from several non-comparative studies indicate that longer survival is associated with small, epithelial-type, node-negative pleural mesotheliomas in patients who undergo aggressive surgery combined with adjuvant chemotherapy and/or radiotherapy. However, no conclusions could be made regarding the role of aggressive surgery combined with adjuvant chemotherapy and/or radiotherapy as none of those studies were randomized.”

The authors also agreed that uniformity of patient selection across clinical trials was important, and therefore all centres should use only one staging system. However, suggesting one pleural mesothelioma staging system over another falls outside of the scope of this evidence-based series. Changes were made to the manuscript to reflect this position.

There was agreement by the authors that there was great variability in the data reported between the studies, especially in terms of selection criteria and operative morbidity and mortality. The authors added a section to the revised manuscript that concluded, “All future studies should report data on selection criteria and operative morbidity and mortality...”. Even though some of the terms used in the document had the same meaning, the authors did not change the terms indicated in the review summary as these were the terms used by the authors of the included studies.

In regard to the outstanding data and reference, the median survival from Pass et al (10) was added to the table for the total patient group as was the data from the Aziz et al study (23). The inclusion of that data did not produce any changes in the results of the review.

**RELATED PRINT AND ELECTRONIC PUBLICATIONS**
- PEBC Evidence Summary #7-14-1 *Chemotherapy for mesothelioma* (posted on the CCO Web site);
- PEBC Evidence-based Series #7-14-3 *Radiotherapy for mesothelioma* (currently under development).
REFERENCES


Surgical Management of Malignant Pleural Mesothelioma

Guideline Review Summary

Review Date: April 2012

The 2012 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making.

OVERVIEW
Evidence-based Series History
   This guidance document was originally released by the PEBC, CCO in 2005. In April 2012, the PEBC guideline update strategy was applied and the new updated document released in May 2012. The Clinical Practice Guideline and Systematic Review in this version are the same as the August 2005 version.

Update Strategy
   Using the Document Review Tool (at the end of this report), the PEBC update strategy includes an updated search of the literature, review and interpretation of the new eligible evidence by clinical experts from the authoring guideline panel, and consideration of the guideline and its recommendations in response to the new available evidence.

DOCUMENT ASSESSMENT AND REVIEW RESULTS
Question Considered
   What is the role of surgery (pleurectomy or extrapleural pneumonectomy) in the treatment of adults with malignant pleural mesothelioma?

Literature Search and New Evidence
   The new search (August 2005 to March 2012) yielded 9 references representing 2 guidelines, 2 systematic reviews & meta-analysis, 1 RCT (has 2 publications), 2 single-arm clinical trials and 1 retrospective study were found evaluating the effect of surgery on malignant pleural mesothelioma. A single on-going study was identified from
clinicaltrials.gov. Brief results of these publications are shown in the Document Review Tool at the end of this report.

Impact on Guidelines and Its Recommendations

The new data supports existing recommendations. Hence, the Lung Cancer DSG ENDORSED the 2005 recommendations on surgical management of malignant pleural mesothelioma.
**Original Question(s)**
What is the role of surgery (pleurectomy or extrapleural pneumonectomy) in the treatment of adults with malignant pleural mesothelioma?

**Target Population**
Adult patients with diffuse or localized malignant pleural mesothelioma.

**Inclusion criteria**
Articles were selected for inclusion if they were:
1. Randomized controlled trials (RCTs), systematic reviews (including meta-analyses or practice guidelines), phase II trials, or prospective or retrospective cohort studies examining the role of surgical resection for malignant pleural mesothelioma.
2. Trials reporting clinical or sub-clinical adverse effects on the topics mentioned above.

**Exclusion criteria**
1. Trials where the majority of patients were being treated for conditions other than malignant pleural mesothelioma.
3. Abstract publications.
4. Letters and editorials describing trial results.
5. Papers published in a language other than English.

**Search Period**
- August 2005 to April 2012 (Medline March wk 3 + Embase week 13)
- August 2005 to April 2012 (clinicaltrials.gov)

**Brief Summary/Discussion of New Evidence**
Of 1236 total hits from Medline + Embase and 26 total hits from clinicaltrials.gov, 9 references representing 2 guidelines, 2 systematic reviews & meta-analysis, 1 RCT (has 2 publications), 2 single arm clinical trial and 1 retrospective study were found evaluating the effect of surgery on malignant pleural mesothelioma. A single on-going study was identified from clinicaltrials.gov.

<table>
<thead>
<tr>
<th>Surgical intervention</th>
<th>N of studies</th>
<th>Population</th>
<th>Outcomes</th>
<th>Brief result</th>
<th>References</th>
</tr>
</thead>
</table>
| Extrapleural pneumonectomy (EPP) | 34 non-RCTs | Patients with malignant pleural mesothelioma (n=2462) | Overall survival & QOL | - The median overall survival varied from 9.4 to 27.5 months.  
- 1-, 2-, and 5-year survival rates ranged from 36 to 83%, 5 to 59%, and 0 to 24%, respectively.  
- Overall perioperative mortality rates ranged from 0 to 11.8%, and the perioperative morbidity rates ranged from 22 to 82%.  
- Quality of life assessments from three studies reported improvements in nearly all domains at 3 months. | Cao et al 2010 |
### EBS 7-14-2 V2 SURGICAL MANAGEMENT MALIGNANT PLEURAL MESOTHELIOMA

<table>
<thead>
<tr>
<th>Lung-sparing extirpative surgery</th>
<th>26 non-RCTs</th>
<th>Patients with malignant pleural mesothelioma (n=1270)</th>
<th>Overall survival</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Patients with histologically confirmed MPM (n=50)</td>
<td>Total, 12 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Survival &amp; QOL</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 30 deaths occurred (EPP= 17, No EPP= 13). Four were perioperative deaths (EPP= 3, No EPP= 1).</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 12-month survival rates were EPP= 52.2% (95% CI: 30.5 70.0), No EPP= 73.1% (95% CI: 51.7 86.2).</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• A Cox model for survival adjusted for gender, histological subtype, stage and age gave a hazard ratio of 2.75 (95% CI: 1.21 6.26; p= 0.02) in favour of No EPP.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Global QOL was lower for EPP, with the nadir 6 weeks after randomization. Median QOL score did not return to baseline levels.</td>
<td></td>
</tr>
</tbody>
</table>

### Randomized control trial

<table>
<thead>
<tr>
<th>Surgical intervention</th>
<th>Population</th>
<th>Follow-up</th>
<th>Outcomes</th>
<th>Brief result</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPP Vs. No EPP</td>
<td>Patients with histologically confirmed resectable MPM</td>
<td>Median, 9 months</td>
<td>Survival &amp; QOL</td>
<td>• Histology was epithelioid in 14 patients and mixed or sarcomatoid in five patients.</td>
<td>Treasure et al 2009 &amp;2011 (feasibility study)</td>
</tr>
<tr>
<td></td>
<td>Pretreatment disease stage III or IV disease</td>
<td>Median age, 60yrs (n=21)</td>
<td></td>
<td>• Pretreatment disease stage was III in 13 patients and IV in six patients.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median, 21.7 months</td>
<td>Survival, morbidity &amp; mortality</td>
<td>• Eight of nine patients undergoing surgical exploration had EPP.</td>
<td>• The median survival of all patients was 19 months.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patients with histologically confirmed MPM</td>
<td>Median age, 65yrs (n=35)</td>
<td></td>
<td>• Patients who had an EPP had a median survival of 33.5 months.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tramodality treatment; Chemotherapy +EPP + radiotherapy</td>
<td></td>
<td></td>
<td>• Patients with unresectable tumors had a median survival of 9 months (p = 0.01)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tramodality treatment; Chemotherapy +EPP + radiotherapy</td>
<td></td>
<td></td>
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</tbody>
</table>

### Single arm clinical trial

| Tramodality treatment; Chemotherapy +EPP + radiotherapy | Patients with histologically confirmed MPM | Median, 9 months | Survival & QOL | • Tumor histology was epithelioid in 27 patients (77.1%). Macroscopic complete resection could be achieved in 18 patients (51.4%). | Flores et al 2006 (feasibility study) |
|--------------------------------------------------------|-------------------------------------------|------------------|-----------------| • Surgical morbidity/mortality and trimodality treatment-related mortality were 20.0%, 2.9% and 5.8%, respectively. |  |
|                                                        | Median age, 60yrs (n=21)                  |                  | Survival, morbidity & mortality | • Thirty-three patients completed the trimodality therapy. |  |
|                                                        | Median, 21.7 months                      |                  |                  | • Overall median survival was 30.0 months. One-, 2-, and 3-year-survival were 69%, 50% and 31%, respectively. |  |
|                                                        | Patients with histologically confirmed MPM |                  |                  | • Advanced stages III/IV (p=0.06), macroscopic incomplete resections (p=0.001), non-epithelial histology (p=0.35) and nodal metastases (p=0.19) were associated with poorer survival. | Bülükbas et al 2011 |

### Retrospective study

| EPP Vs. No EPP | Patients with untreated epithelioid MPM that was surgically resectable (n=36) | Median, 27 months | Survival | • Median and 1-year survival did not differ between the 18 EPP patients and 18 non-EPP patients (20.4 versus 20.7 months and 76 versus 78%, respectively; p = NS). | Hasani et al 2009 |
|----------------|--------------------------------------------------------------------------------|-----------------|----------| • There was one death in hospital six days’ post-EPP and another death post discharge and 28 days post-EPP (30-day mortality 11%). |  |
|                |                                                                                 |                  |          | • Pathologic analysis of the 18 resected EPP specimens revealed N2 disease in seven patients (39%) and nonepithelioid subtype in six patients (33%). |  |
|                |                                                                                 |                  |          | • Local recurrence did not occur among EPP survivors; however, 56% (9 of 16 patients) developed distant recurrence. |  |

### Ongoing study 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>Observational</td>
<td>Tramodality Therapy for Malignant Pleural Mesothelioma: Radical Pleurectomy, Followed by Adjuvant Chemotherapy With Cisplatin/Pemetrexed and Radiotherapy</td>
<td>Recruiting</td>
<td>NCT01343264</td>
<td>December 2012</td>
<td>April 26, 2011</td>
</tr>
</tbody>
</table>
### Instructions

Beginning at question 1, below, answer the questions in sequential order, following the instructions in the black boxes as you go.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is the volume and content of the new evidence so extensive such that a simple update will be difficult?</td>
<td>No</td>
<td>If Yes, then the document should be ARCHIVED with no further action; go to 11. If No, go to 2.</td>
</tr>
<tr>
<td>2. On initial review, does the newly identified evidence support the existing recommendations? 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:</td>
<td>Newly identified evidence still support existing guideline so document 7-14-2 should be ENDORSED</td>
<td>If Yes, the document can be ENDORSED. If No, go to 3.</td>
</tr>
<tr>
<td>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:</td>
<td>Not Applicable</td>
<td>If Yes, a WARNING note will be placed on the website. If No, go to 4.</td>
</tr>
<tr>
<td>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:</td>
<td>Not applicable</td>
<td>If Yes, the document update will be DEFERRED, indicating that the document can be used for decision making and the update will be deferred until the expected evidence becomes available. If No, go to 5.</td>
</tr>
<tr>
<td>5. An update should be initiated as soon as possible. List the expected date of completion of the update:</td>
<td>Not applicable</td>
<td>An UPDATE will be posted on the website, indicating an update is in progress.</td>
</tr>
<tr>
<td>6. Circulate this form to the appropriate Disease Site Group for their approval. Once approved, a copy of this form should be placed behind the cover page of the current document on the website. Notify the original authors of the document about this review.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**DSG/ GDG Approval Date:** 20 April, 2012

**Comments from DSG/GDG members:** None
New References Identified (alphabetical 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 metaanaly$).tw.
4. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or Quantitative synthes?s or quantitative overvi
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 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$).ab.
10. (selection criteria or data extraction or quality assessment or Jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
14. 12 and 13
15. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/ or exp randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
16. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
17. random allocation/ or double blind method/ or single blind method/
18. (random$ 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$1).tw.
24. ((sing$ 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. 41 or 42
44. (surgery? or pleurectomy? or decortication? or pneumonectomy? or resection?).tw.
45. 43 and 44
46. 40 and 45
48. 46 and 47

EMBASE
1. exp meta analysis/ or exp systematic review/
2. (meta analy$ or metanaly$).tw.
3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative syntheses$ or quantitative overview).tw.
4. (systematic adj (review$ or overview$)).tw.
5. exp review/ or review.pt.
6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7. (study adj selection).ab.
8. 5 and (6 or 7)
9. or/1-4,8
10. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scienscan or bids or sigle or cancerlit).ab.
11. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
12. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
13. randomization/ or single blind procedure/ or double blind procedure/
14. (randomi$ 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$.tw.
18. (clinical$ 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 mesothelioma/
38. 36 or 37
39. (surgery? or pleurectomy? or decortication? or pneumonectomy? or resection?).tw.
40. 38 and 39
41. 35 and 40
42. (200529$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$).ew.
43. 41 and 42

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 “ARCHIVED”.

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.