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Evidence-based Series #7-14-2: Section 1

Surgical Management of Malignant Pleural Mesothelioma: A Clinical Practice Guideline

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

Report Date: August 9, 2005

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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Evidence-based Series #7-14-2: Section 2

Surgical Management of Malignant Pleural Mesothelioma: A Systematic Review

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A Quality Initiative of the
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Report 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 CANCELIT 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/. 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.
2. Papers published before 1985.
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.

Type of Surgery	Type of Study	Number of Fully Published Studies	Reference Number(s)	Further Information Found in Table
Pleurectomy and extrapleural pneumonectomy	Prospective, non-controlled	8	(5-14);	Table 2a
	Retrospective	10	(15-24)	Table 2b
Extrapleural pneumonectomy	Prospective, non-controlled / retrospective	2	(25,28)	Table 3
	Retrospective	2	(26,27)	
Pleurectomy	Prospective, non-controlled	4	(29-32)	Table 4a
	Retrospective	8	(33-38)	Table 4b

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 2a. Prospective studies involving both extrapleural pneumonectomy and pleurectomy.

Study (Ref)	Patients	Operative Morbidity	Operative Mortality	Recurrence	Survival (m = months)	Comments
Calavrezos, 1988 (5) Non-controlled comparative study ^a	57 combined modality (34 PL, 8 EPP, 15 not resected) 75 supportive care (39 ineligible for surgery) 132 patients, 54 epithelial	NR	NR	NR	<u>Median/2-yr</u> 13m/11% (for 57 combined modality pts) Supportive care: 7m/3% (36 pts) Ineligible: 5m/7% (39 pts)	<ul style="list-style-type: none"> • Minimum 22m follow-up • Adjuvant treatment: CT for 54 surgical candidates + RT for responding pts^b • 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
Rice, 1994 (6) Single-arm phase II trial	9 PL 10 EPP 19 patients, 10 epithelial	6 complications reported: reoperations, 3 (16%) including 2 for prosthetic replacement of diaphragm; supraventricular arrhythmias, 2 (11%); and vocal cord augmentation, 1 (5%)	1/19 (5%) presumed arrhythmia or pulmonary embolus + 1 CT-related death	<u>Local/distant combined</u> 4/1/1 3/1/2	<u>Median/3-yr for all 19 pts</u> overall, 13m/17% disease-free, 11m/22%	<ul style="list-style-type: none"> • Adjuvant treatment: intra-pleural CT for all pts and adjuvant CT^c 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
Pass, 1997 (7) Non-controlled comparative study ^d	39 PL, 33 epithelial 39 EPP, 27 epithelial + 17 unresectable 95 patients	Ventricular arrhythmias, 2/39 (5%) Ventricular arrhythmias, 14/39 (36%); bronchopleural fistulas, 7/39 (18%) Overall, 61/95 (64%) free of morbidity	Overall, 2/95 post-operative hemorrhage (2%) with additional mortality due to 3 suicides and 1 aspiration	total, 31/39 (79%) with 28 locoregional total, 27/39 (69%) with 17 locoregional PL vs. EPP for locoregional, p=0.013	<u>Overall/ Progression-free</u> Median 14.5m/7.4m Median 9.4m/7.0m PL vs. EPP, p=0.012/p=NS (Median for unresectable, 5.0m)	<ul style="list-style-type: none"> • 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<0.001) • EPP lower local recurrence but similar overall recurrence due to distant metastases
Moskal, 1998 (8) Single-arm phase II trial	28 PL 7 EPP 5 PL + lobectomy 40 of 43 patients	39% 71% 40% Overall 18/40 (45%): atrial	1/7 (14%) EPP pts – due to bronchopleural fistula	NR	For 37 pts surviving postoperatively: median, 15m 2-yr, 23%	<ul style="list-style-type: none"> • Adjuvant treatment: intra-operative PDT at 20-30 J/cm^b • Complete resection in 16 pts • Postoperative disease stage^e: I (30%), II (2.5%), III (62.5%), IV (5%) • On disease recurrence, 7 pts received palliative CT and 7 received palliative

	were resectable, 25 epithelial	fibrillation, (38%); sepsis (28%); respiratory insufficiency, (25%), bronchopleural fistula, (8% of all EPP pts)				RT
Pass, 1997 & 1998 (9,10) Non-controlled phase III trial ⁴	23 PL 25 EPP + 15 could not be debulked 33 of 48 surgical pts had epithelial histology	Of 48 surgical pts – arrhythmia, 8%; bronchopleural fistula, 8%; cardiac herniation, bleeding, and pancreatitis, each 2%.	0 1/25 (4%)	NR	Median 22m 11m p=0.07	<ul style="list-style-type: none"> Median potential follow-up, 23.1m Adjuvant treatment: CT^f + randomization to intra-operative PDT. No survival difference associated with PDT randomization Postoperative disease stage^g among 48 surgical pts: I (8%), II (8%), III (79%), IV (4%)
Rusch, 1991 & 1999 (11,12) Non-controlled, comparative study ^d	59 PL 115 EPP + 57 palliative PL /exploration 231 total, 164 epithelial histology	NR Arrhythmia, 8/20 (40%); bronchial stump leak and empyema, 4/20 (20%) ⁸	2/59 (3%) 6/115 (5%) Overall, 3.5%	local/distant/ combined ⁿ : 9/1/12 0/5/8 at last follow-up	Median/2-yr/5-yr ^l 18.5m/40%/9% 14.7m/30%/6% Overall, PL vs. EPP, p=0.3. Median for palliative, 8.7m Recurrence-free (2-yr), PL 15% vs. EPP 30%, p=0.03 ⁸	<ul style="list-style-type: none"> Median follow-up, 9.6m 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^g for 231 pts: I (9%), II (16%), III (44%), IV (30%)
Maggi, 2001 (13) Non-controlled case series ^d	9 PL 23 EPP 32 total, 26 epithelial histology	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	NR	Total, 21 pts alive with median follow-up of 12.5m	<ul style="list-style-type: none"> Median follow-up, 11.5m for 27/30 survivors Adjuvant treatment: CT^j at 4-6 wks postoperatively followed by RT to 55 Gy + additional CT^k Preoperative disease stage (Brigham) for 32 pts: I (19%), II (31%), III (50%)
Rusch, 2001	5 PL	Total, 33/88 (38%)	0	NR	Median/3-yr	<ul style="list-style-type: none"> Adjuvant treatment: PL pts received

(14) Single-arm phase II trial ^d	62 EPP + 21 exploratory surgery only 88 total, 60 epithelial		7/62 (11%) primarily related to pulmonary difficulties	2 local, 30 distal, 5 local & distal for the 54 EPP pts receiving RT (69%)	NR 17m/27% Median for stage I/II, 33.8m and for stage III/IV, 10m.	IORT @ 15 Gy; 54 EPP and 4 PL pts received 54 Gy in 30 fr to hemi-thorax at 3-5 wks postoperatively <ul style="list-style-type: none"> • EPP IORT changed to external RT • Tumour histology had no effect on survival but stage, tumour, and nodal status did • Disease stage^g for 88 pts: I (2%), II (19%), III (52%), IV (26%)
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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-α2B 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 2b. Retrospective studies involving both extrapleural pneumonectomy and pleurectomy.

Study (Ref)	Patients	Operative Morbidity	Operative Mortality	Survival	Comments
Chailleux, 1988 (15) Case series	29 PL or EPP 14 CT + PL or EPP 167 patients, 81% epithelial histology	NR	NR	<u>1-yr/2-yr</u> 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%	<ul style="list-style-type: none"> 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)
Ruffie, 1989 (16) Case series	63 PL, epithelial NR 23 EPP, 12 epithelial 246 CT, RT or supportive care 332 patients	NR 6/23 (26%): bronchopleural fistula, 9%; cardiac arrhythmia, respiratory failure, pneumonia with sepsis, and contralateral pneumothorax, 4% each	NR 3/23 (13%): acute respiratory syndrome, empyema, pulmonary embolus, 1 pt each	<u>Median/2-yr</u> 9.8m/NR 9.3m/17% No surgery, median 8m p>0.23	<ul style="list-style-type: none"> 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
Harvey, 1990 (17) Case series from registry data	9 PL, 2 epithelial 7 EPP, 2 epithelial 76 supportive care 92 patients	NR	0 NR	<u>Median</u> 12m <6m (1 pt survived 7 yrs and 1 pt, 8 yrs) supportive care, median 7.6m	<ul style="list-style-type: none"> California centres with data from 1965 to 1988 Adjuvant treatment: for PL, 4 pts CT, 1 RT; for EPP, 1 pt CT+RT
Branscheid, 1991 (18) Case series	82 PL 76 EPP 143 CT, exploratory thoracotomy, or supportive care 301 patients, 50% epithelial	NR	2/82 (2.4%) 9/76 (11.8%)	<u>Median</u> 10.4m 9.3m overall, 7.8m Reported significant survival advantage for PL/EPP (p=NR)	<ul style="list-style-type: none"> 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<0.001) Preoperative/intraoperative disease stage^a for 301 pts I (2%),

					II (11%), III (56%), IV (15%), unknown (16%)
Allen, 1994 (19) Case series	56 PL, 28 epithelial 40 EPP, 26 epithelial 96 patients	<u>Major complications</u> 15/56 (26.8%): air leak, 11%; arrhythmias, 9%; renal failure, 4%; tracheostomy, 4%; pneumonia, 2% 12/40 (30%): arrhythmia, 7.5%; bronchopleural fistula, vocal cord paralysis, tracheostomy, 5% each; chylothorax, MI, effusion, pneumonia, splenectomy, 2.5% each	3/56 (5.4%): MI, 1 pt; organ failure, 2 pts 3/40 (7.5%): pulmonary embolism, MI, intraoperative bleeding, 1 pt each	<u>Median/1-yr/2-yr/5-yr</u> 9.0m/30.4%/8.9%/5.4% 13.3m/52.5%/22.5%/10.0% p=0.20	<ul style="list-style-type: none"> Single centre with data from 1958 to 1993 Adjuvant treatment: 73% of each surgical group, CT +/- RT postoperatively (RT usually for recurrence) Surgical disease stage (Butchart) for 37 surviving EPP pts: I (51%), II (38%), III (8%), IV (3%)
Huncharek, 1996 (20) Case series	17 PL or EPP 21 CT + PL or EPP 11 CT 4 RT 26 supportive care 49% of patients had epithelial histology	NR	NR	<u>Median</u> 5.m 23.9m 6.0m 11.5m 4.5m CT + PL/EPP vs. supportive care, p<0.01 Wilcoxon	<ul style="list-style-type: none"> Single centre with data from 1978 to 1994 3 pts total underwent EPP Adjuvant treatment: CT mostly cisplatin or doxorubicin-based
Lampl, 1999 (21) Case series	19 PL 23 EPP 11 exploratory surgery only 53 patients	NR	0 1/23 (4.2%), pneumonia	<u>Median</u> 14m 16m Median for exploratory only, 6m	<ul style="list-style-type: none"> Single centre with data from 1986 to 1998 Adjuvant treatment: NR Disease stage^b: all PL pts were stage T1a or b; all EPP pts were stage T2 or T3
Aziz 2002 (22) case series	191 SC 47 PL 13 EPP 51 EPP + CT	<u>Major complications EPP^c</u> 14/64 (21%) ARDS (5pts); bleeding (4pts); pneumonia/empyema (4 pts); reintubation and ventilation (2pts)	EPP ^c 6/64 (9.1%) ARDS - 5 pts, MI - 1pt	<u>Median/ 1/3 year SC - 7m</u> <u>PL - 14m/ 39%^d</u> <u>EPP - 13m/ 48%/0%</u> <u>EPP + CT - 35m/ 84%/48%</u>	<ul style="list-style-type: none"> Single centre data 1989 – 1999 Adjuvant treatment: carboplatin and epirubicin Disease stage median survival: T1-43m, T2 – 31m, T3 – 14m.

	302 patients	Minor complications EPP ^c 18/64 (28%) dysrhythmia (8pts); wound infection (4pts); sputum retention (3pts); pneumothorax (1pt) Chemotoxicity Nausea (63%), Anaemia (32%), leucopenia (21%), Thrombocytopenia (9%).		(> 5yr 9pts)	
De Vries 2003 (23)	29 PL 17 EPP 46 patients	PL 12/29 (41%) – atelectasis (2pts), blood transfusion (3pts), air-leaks (3pts) with drainage (3pts), ventilation (1pt). EPP 1/46 (2%) – Empyema (1pt)	PL – 1/29 (3.8%) EPP – 1/17 (5.8%)	<u>Median/ 1 year</u> <u>PL – 9m/ 22%^b (4pts >5 years)</u> <u>EPP – 12m/ 42%^b (3 pts >7years)</u>	<ul style="list-style-type: none"> Single centre data 1976 – 2001 South Africa 2 EPP patients were diagnosed post operatively with adenocarcinoma Adjuvant treatment: PL CT+/-RT n=25; EPP CT+/-RT n=14
Stewart, 2004 (24)	53 EPP non-radical surgery 47 decortication 24 VATS 5 PL 3 chest wall tumour resection 132 patients	N/R	EPP – 4/132 (3%) Non-radical surgery group – 7/132 (5%)	<u>EPP – 16m</u> <u>Non-radical surgery group – 11m</u> <u>(p=0.079)</u>	<ul style="list-style-type: none"> Longer median survival for EPP epithelial than biphasic histology (538 v 237 days, p=0.008) Longer median survival for non radical surgery epithelial than biphasic and sarcomatous histology (475 v 324 and 128 days, p=0.0001) 8pts in the EPP group had neoadjuvant CT, maximum 3 cycles of cisplatin and gemcitabine.

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.

Study (Ref)	Patients	Operative Morbidity	Operative Mortality	Survival	Comments
Antman, 1988 (25) Retrospective/prospective case series	22 EPP 92 CT only 19 EPP+CT 136 pleural pts in total, 56% epithelial	NR	NR	Median 18m 16m ^a 18m	<ul style="list-style-type: none"> Single-centre data from 1965 to 1985 Data collected retrospectively on 31 pleural pts Adjuvant treatment: CT^b +/- RT for pts without progression following CT Disease stage of 136 pleural pts: I (58%), II (24%), III (18%); IV (1%)
Sugarbaker, 1999 (26) Retrospective case series	183 EPP total, 103 epithelial	Overall, 92/183 (50%) ^c major ^d : 45/183 (24.5%) minor: 75/183 (41%)	7/183 (3.8%): pulmonary embolism, 3 pts; myocardial infarction, 2 pts; cardiac herniation and respiratory failure, 1 pt each	Median/2-yr/5-yr For 176 pts surviving postoperatively, 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	<ul style="list-style-type: none"> Single-centre data from 1980 to 1997 Median follow-up, 13m (range, 0.2-100m) Adjuvant treatment: CT started 4 to 6 wks post-surgery^e + RT 30 Gy (1.5 Gy per fr) to hemi-thorax; mediastinum received 40 Gy Disease stage (Sugarbaker) for 183 pts: I (36%), II (22%), III (38%), NR (4%)
Takahashi, 2001 (27) Retrospective case series	5 EPP 3 epithelial	Atrial fibrillation, 2/5 patients	0	NR	<ul style="list-style-type: none"> Single-centre data from 1989 to 1995 All stage Ia or Ib Adjuvant treatment: RT in 1 pt
Stewart, (2005) (28) Retrospective/prospective case series	59 EPP 15 EPP + CT 74 patients	Post operative ^f : Technical 22/74 (30%) Cardiovascular 35/74 (47%) Respiratory 15/74 (20%) Gastro-intestinal 4/74 (5%) Infection 3/74 (4%)	< 30 days post operative 5/74 (7%) rt ventricular failure 2pts, MI 1pt, pulmonary embolism 1pt, perforate oesophagus 1pt	N/R	<ul style="list-style-type: none"> Single centre data from August 1999 – July 2004 Adjuvant treatment CT: 9pts with gemcitabine, pemetrexed 5pts, vinorelbine 1pt Overall re-operation rate 18pts (24%)

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.

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

^b Cyclophosphamide 600 mg/m² + doxorubicin 60 mg/m² every 3 weeks (to a total doxorubicin dose of 450 mg/m²).

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

^d 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.

^e 1980-1985, cyclophosphamide 600 mg/m² + doxorubicin 50-60 mg/m² for 4-6 cycles (9 pts);

1985-1994, as 1980-1985 + cisplatin 70 mg/m² (80 pts);

1995-1997, carboplatin (area under the curve, 6) + paclitaxel 200 mg/m² (94 pts).

^f 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.

Study (Ref)	Patients	Operative Morbidity	Operative Mortality	Survival	Comments
Rusch, 1994 (29) Single-arm phase II trial	27 PL + CT, 70% epithelial	12/27 (44.4%): hemorrhage, renal toxicity, myocardial infarction, prolonged air leaks, atrial arrhythmias, wound infection	1/27 (3.7%): upper GI hemorrhage from duodenal ulcer	Median, 18.3m ^a 1-yr 69% (95% CI, 54%-90%) 2-yr 40% (95% CI, 25%-65%) Median progression-free, 13.6m	<ul style="list-style-type: none"> Adjuvant treatment: intrapleural +/- systemic CT^b 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)
Sauter, 1995 (30) Two trials: 1) Single-arm phase II trial 2) Prospective case-series	Phase II ^c : 13 subtotal PL + CT Other prospective: 7 subtotal PL (4 with RT) 10/20 epithelial	1/13 (8%): wound complication from PL CT caused nephrotoxicity (grade 2, 2pts; grade 4, 1 pt) and thrombocytopenia (1 pt)	1/20 (5%): grade 4 nephrotoxicity followed by sepsis and respiratory failure	<u>Median/2-yr</u> 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. Median time to progression: PL + CT, 6m PL +/- RT, 12m (p=0.01)	<ul style="list-style-type: none"> Median potential follow-up, 53m Adjuvant treatment: for 13 pts in phase II trial, intrapleural +/- systemic CT^d; for 4 of the remaining 7 pts, RT @ 45-50 Gy, 6 to 20 wks postoperatively CT pts had poorer outcome 15/20 (75%) recurred locally Improvements in dyspnea (47% pts) and pain (21% pts); pleural effusion recurrence prevented in 80% pts Disease stage (Butchart): I (90%), II (10%)
Colleoni, 1996 (31) Non-controlled case series	20 PL + CT, 50% epithelial	Grade 3-4 side effects: anemia (1pt), renal toxicity (2 pts)	NR	Median survival, 11.5 m Median time to progression, 7.4m	<ul style="list-style-type: none"> Median follow-up, 11m Adjuvant treatment: intrapleural +/- systemic CT^e Disease stage (TNM): I (40%), II (20%), III (40%) Survival better with minimal residual disease (24.5 vs. 10 m)
Lee, 1995 (32) Prospective case-series	17 enrolled ^f 15 PL + CT ^g	Grade 3/4 – Arrhythmia (1pt), renal failure and chest tube infection (1pt)	No treatment related mortality	Median – 1/2year 11.5m – 30%/12% ^h	<ul style="list-style-type: none"> 11/15 pts also received RT dose 3pts expired <6m post treatment recurrence rate 12/15 pts median 7.5m (80%) Local recurrence in a 15pts

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. – 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/m² and mitomycin 8 mg/m², followed by cisplatin 50 mg/m² days 1, 8, 15, 22, 36, 43, 50, and 57 and mitomycin 8 mg/m² 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/m² and cytosine arabinoside 1200 mg) and systemic chemotherapy administered 3-5 weeks postoperatively (cisplatin 50 mg/m²/week x 8 and mitomycin-C 8 mg/m² days 1 and 36).

⁵ Intrapleural cisplatin 100 mg/m² and cytarabine 1,000 mg/m² followed by systemic chemotherapy starting 21-35 days postoperatively (epirubicin 60 mg/m² and mitomycin-C 10 mg/m²) and administered every 28 days for 4 cycles.

^f 2 pts diagnosed with metastatic pleural adenocarcinoma

^g Cisplatin (100mg/m²) and cytosine arabinoside (1,200 mg) mixed together in 250ml normal saline were poured into the hemithorax after pleurocotomy/decortication

^h Survival rate determined from published survival curve.

Table 4b. Retrospective studies examining pleurectomy.

Study (Ref)	Patients	Operative Morbidity	Operative Mortality	Survival	Comments
Alberts, 1988 (33) Case series	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	<ul style="list-style-type: none"> Data from two South African centres between 1965 and 1985 Adjuvant treatment: CT^a + 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) Case series	46 PL 72 subtotal PL 82 other surgery ^b 245 total with 45 no surgery	NR	2/46 (4.3%) 8/72 (11.1%) All surgery, 12/200 (6%)	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	<ul style="list-style-type: none"> 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) Case series	13 PL 22 no PL (radical or palliative RT +/- CT) 38 total (35 with disease confined to hemithorax)	NR	NR	<u>Median:</u> PL, 17m (13 pts) No PL, 9m (22 pts) For all 38 pts: median, 9m ; estimated 2-yr, 16%	<ul style="list-style-type: none"> Single centre with data from 1981 to 1985; pts given variety of treatments Adjuvant treatment: some PL pts received radical or palliative RT +/- CT^c Two deaths due to RT
Brancatisano, 1991 (36) Case series	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%	<ul style="list-style-type: none"> Data from two Australian centres between 1984 and 1989 Adjuvant treatment: NR Concluded that pleurectomy is good for diagnosis and palliation

Soysal, 1997 (37) Case series	56 PL 44 subtotal PL 100 total, 60% epithelial	22/100 (22%): air leak, empyema, pleural effusion, wound infection	1/100 (1%) following empyema, sepsis, and acute respiratory distress syndrome	median, 17m (range 3 to 63m) For pts also receiving RT +/- CT: median, 22m	<ul style="list-style-type: none"> • 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 (38) Case series	38 PL 16 PL + CT 37 CT 30 Supportive care 121 total, 73% epithelial	NR	NR	<u>Median/1-yr</u> 12.5m/50% 14m/62.5% 8m/36.5% 4m/20%	<ul style="list-style-type: none"> ▪ 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 (39) case series	26 PL 24 IORT + EBRT ± CT (12pts) 26 Total	Post operative complications: Atrial fibrillation 3/26 (11%), Persistent air leak ^a 1/26 (4%) RT induced pneumonitis 4/26 (17%)	No deaths as a result of surgery or therapy	<u>Median – 18m (post operative)</u> <u>1yr – 64%</u> <u>3yr – 18%</u> <u>5yr – 12.3%</u>	<ul style="list-style-type: none"> ▪ Single centre with data from 1995 - 2000 ▪ Median follow-up, 70m ▪ Progression free survival: 1yr – 50%, 2yr – 22% ▪ EBRT median dose: 41.4Gy (range 30.1-48.8Gy) ▪ CT was given 1-2m post RT for 2 to 3 cycles
Phillips, 2003 (40) Case series	15pts - Group I ^e 40pts – Group II ^e 15pts – Group III ^e 70 patients	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	<u>Median/ 1yr/ 2yr/ 5yr</u> <u>Group I – 6m/ 20%/7%/0%</u> <u>Group II – 6m/ 18%/10%/0%</u> <u>Group III – 14m/ 54%/40%/27%</u>	<ul style="list-style-type: none"> ▪ Single centre with data from 1989 – 1999 ▪ 2pts from group III thoracotomy could not diagnosis; 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)

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

Protocol ID	Title and details of trial
RPCI-RP-9812	Phase II pilot study of surgery and adjuvant intracavitary photodynamic therapy with large diffuser fibers in patients with malignant mesothelioma. Projected accrual: 20 patients within 3 years. Status: open as of February 2003.

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

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For a complete list of the Lung Cancer Disease Site Group members and the Practice Guidelines Coordinating Committee members, please visit the Cancer Care Ontario Web site at: http://www.cancercare.on.ca/access_PEBC.htm.

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Evidence-based Series #7-14-2: Section 3

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

Report 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.

<p>BOX 1: DRAFT RECOMMENDATIONS (approved for external review June 6 2003.)</p>
<p><i>Target Population</i></p> <ul style="list-style-type: none"> • This evidence summary applies to adult patients with diffuse or localized malignant pleural mesothelioma.
<p><i>Recommendations</i></p> <ul style="list-style-type: none"> • 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.

Item	Number (%)		
	Strongly agree or agree	Neither agree nor disagree	Strongly disagree or disagree
The rationale for developing a clinical practice guideline, as stated in the "Choice of Topic" section of the report, is clear.	40 (89%)	4 (9%)	1 (2%)
There is a need for an evidence summary on this topic.	37 (82%)	7 (16%)	1 (2%)
The literature search is relevant and complete in this evidence summary. ¹	36 (82%)	8 (18%)	0
I agree with the methodology used to summarize the evidence. ¹	40 (91%)	4 (9%)	0
I agree with the overall interpretation of the evidence in the evidence summary.	41 (91%)	4 (9%)	0
The Opinions of the Disease Site Group section of this evidence summary is useful. ^a	33 (75%)	8 (18%)	3 (7%)
An evidence summary of this type will be useful for clinical decision making.	31 (69%)	10 (22%)	4 (9%)
At present, there is insufficient evidence to develop a practice guideline on this topic.	36 (80%)	2 (4%)	7 (16%)
There is a need to develop an evidence-based practice guideline on this topic when sufficient evidence becomes available. ^b	38 (88%)	1 (2%)	4 (9%)
How likely would you be to consider surgery as a treatment option for patients with malignant pleural mesothelioma in your practice? ¹	Very likely or likely	Unsure	Not at all likely or unlikely
	18 (41%)	8 (18%)	18 (41%)

^a 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 co-morbidities, 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

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2. Browman GP, Newman TE, Mohide EA, Graham ID, Levine MN, Pritchard KI, et al. Progress of clinical oncology guidelines development using the practice guidelines development cycle: the role of practitioner feedback. *J Clin Oncol.* 1998;16(3):1226-31.