A Systematic Review of Extrapleural Pneumonectomy for Malignant Pleural Mesothelioma

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Introduction: The primary objective of the present systematic review was to evaluate the safety and efficacy of extrapleural pneumonectomy (EPP) for patients with malignant pleural mesothelioma.

Methods: A systematic review of relevant studies identified through five online search databases was performed. Two reviewers independently appraised each study.

Results: Thirty-four of 58 relevant studies from 26 institutions containing the most updated data were evaluated for survival and perioperative outcomes after EPP. The median overall survival varied from 9.4 to 27.5 months, and 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 postoperatively. Patients who underwent trimodality therapy involving EPP and adjuvant chemoradiotherapy had a median overall survival of 13 to 23.9 months.

Discussions: The current evidence suggests that selected patients with malignant pleural mesothelioma may benefit from EPP, especially when combined with neoadjuvant or adjuvant chemotherapy and adjuvant radiotherapy.

Key Words: Malignant pleural mesothelioma, Extrapleural pneumonectomy, Systematic review.

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Malignant pleural mesothelioma (MPM) is a rare and aggressive disease arising from the pleural mesothelium, with a reported survival of less than 12 months.[1] Despite advances in modern systemic chemotherapy, long-term survival in patients with MPM remains limited.[2] Because of the lag time between asbestos exposure and disease manifestation, the peak incidence of MPM in the United States is projected to be between 2010 and 2020. Other developed countries show similar epidemiological trends, and the health, medicolegal, and industrial implications of this disease will continue to intensify in the years to come.[3–5]

The standard of care for patients with MPM has not been established. Extrapleural pneumonectomy (EPP) has been performed as a treatment option.[6–63] This procedure involves en bloc resection of the parietal pleurae, lung, ipsilateral hemidiaphragm, and ipsilateral pericardium. A number of studies have demonstrated encouraging results for selected patients with MPM who underwent EPP. However, because of the relentless nature of the disease, treatment failure after EPP alone remains high.[48] Since then, a number of institutions have combined EPP with adjuvant chemotherapy and/or radiotherapy. In comparison with procedures such as pleurectomy and decortication, EPP aims to achieve radical cytoreduction and facilitate maximal delivery of postoperative radiotherapy.

Despite a heightened interest in EPP over the past decade, concerns about the morbidity and mortality of this surgical procedure, and its efficacy, have delayed a consensus in its practice. In addition, there is a lack of robust clinical data on prognostic factors for overall survival and quality of life evaluation. To date, no randomized controlled trials (RCTs) have been conducted to examine the potential benefits of EPP. The most recent systematic review conducted by Maziak et al.[64] provided an informative summary of existing literature up to February 2004. However, significant changes have taken place since that time. More recently, innovative multimodalities such as neoadjuvant chemotherapy and hyperthermic intraoperative chemotherapy (HIOC) have been evaluated.[6–8] The current systematic review aims to determine the efficacy of EPP either alone or as part of a multimodality therapy in the current medical setting, with a primary focus on survival and perioperative outcomes. In addition, quality of life assessments were also systematically examined.

METHODS

Literature Search Strategy

Electronic searches were performed using Ovid Medline, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Database of Abstracts of Review of Effectiveness from January 1985 to January 2010. To achieve the maximum sensitivity of

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the search strategy and identify all studies, we combined "mesothelioma" as a Medical Subject Headings (MeSH) term or a keyword and "pneumonectomy" as a MeSH term or keyword. The reference lists of all retrieved articles were reviewed for further identification of potentially relevant studies. All relevant articles identified were assessed with application of inclusion and exclusion criteria.

Selection Criteria

Eligible studies for the present systematic review included those in which patients with histologically proven MPM were treated by EPP. Adjuvant therapy included chemotherapy, radiotherapy, photodynamic therapy, and hyperthermic or normothermic intrapleural chemotherapy. Neoadjuvant therapy included systemic chemotherapy. For studies that included patients who underwent EPP as a subset of patients who had other treatments, results for patients who underwent EPP were extracted when possible. When centers have published duplicate trials with accumulating numbers of patients or increased lengths of follow-up, only the most complete reports were included for qualitative appraisal. It is acknowledged that criteria for patient selection for EPP varied among institutions and sometimes within an institution in different time periods. All publications were limited to human subjects and in English language.

Abstracts, case reports, conference presentations, editorials, and expert opinions were excluded. Review articles are omitted due to potential publication bias and possible duplication of results. Studies published before 1990 and those that included 10 or fewer patients who underwent EPP were also excluded.

Data Extraction and Critical Appraisal

Findings from initial scoping searches were used to decide outcomes for the present review. The primary outcomes included overall survival, 30-day mortality and morbidity, and quality of life assessments. The secondary outcomes included disease-free survival, recurrence rates, prognostic factors on overall survival, intraoperative blood loss, length of hospitalization, and operation time. All data were extracted from article texts, tables, and figures. Two investigators (C.Q.C. and T.D.Y.) independently reviewed each retrieved article. Discrepancies between the two reviewers were resolved by discussion and consensus. The final results were reviewed by the senior investigators (P.G.B. and B.C.M.).

RESULTS

Quantity of Trials

A total of 428 references were identified through the five electronic database searches. After exclusion of duplicate or irrelevant references, 121 potentially relevant articles were retrieved for more detailed evaluation. After applying the selection criteria, 58 remained for assessment (Table 1). A number of centers published studies with duplicating patients at different follow-up periods or different primary objectives. Thirty-four of 58 studies from 26 institutions containing the most complete or updated data were included in the final analysis on survival and perioperative outcomes (Table 2). Overall, a total of 3749 patients who underwent EPP for MPM were identified from the 58 selected studies, with 2462 patients included in the final evaluation.

Assessment of Survival

A summary of survival outcomes for patients undergoing EPP for MPM is presented in Table 2. The median overall survival ranged from 9.4 to 27.5 months.[6–63] However, it should be noted that a number of studies calculated survival from the date of diagnosis or commencement of chemotherapy rather than the date of surgery.[17,35,43,48–50,56] The 1-, 2-, 3-, and 5-year survival rates varied from 36 to 83%, 5 to 59%, 0 to 41%, and 0 to 24%, respectively. Median disease-free survival ranged from 7 to 19 months, and an additional study reported 20 months for distant recurrence and 26 months for local recurrence.[6–63] When the middle two quartiles of the included studies are analyzed, median overall survival ranged from 12 to 20 months, and the 1-, 2-, 3-, and 5-year survival rates varied from 50 to 68%, 26.5 to 40.5%, 19 to 30%, and 10 to 19%, respectively.[6–63]

Assessment of Perioperative Outcomes

The perioperative outcomes are presented in Table 2. The overall perioperative mortality rates ranged from 0 to 11.8%, with the middle two quartiles falling between 3.7% and 7.6%. Overall perioperative morbidity rates ranged from 22 to 82%, and major morbidity rates ranged from 12.5 to 48%.[6–63] A number of studies reported the number of events rather than the number of patients with postoperative complications and were excluded from the analysis as it was not possible to determine how many patients had multiple complications.[14,15,19,49,52] Intraoperative blood loss ranged from 500 to 2314 ml. Operative time ranged from 3.25 to 6.5 hours. Hospitalization duration ranged from 8 to 43 days.[6–63]

Assessment of Quality of Life

Three studies reported quality of life assessments using a variety of questionnaires. Ribi et al.[53] and Weder et al.[35] assessed 45 patients who underwent EPP and evaluated their quality of life using the Rotterdam Symptom Checklist (RSCL) and Schedule for the Evaluation of Quality of Life-Direct Weighting (SEIQoL-DW) before surgery, on day 1 of cycle 3, and at 1 month, 3 months, and 6 months postoperatively. Results indicated that both RSCL and SEIQoL-DW scores remained stable during chemotherapy, followed by a significant deterioration 1 month postoperatively. RSCL overall scores improved at 3 months but remained beneath baseline levels until 6 months after surgery. SEIQoL scores improved to baseline levels at 3 months but deteriorated at 6 months. Ambrogi et al.[39] used the Short-Form-36 (SF-36) item and St. George's Respiratory Questionnaire to assess 16 patients who underwent EPP preoperatively and at 3, 6, 12, and 24 months postoperatively. Comparable with the Swiss reports, this study found improvements in nearly all the SF-36 domains at 3 months. After 12 months, only physical domains remained significantly above the baseline levels, followed by deterioration in all domains at 24 months. Similarly, the St. George's Respiratory Questionnaire results

