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Short Review

A Struggle against Mesothelioma: Mini Review on the Current Role of Surgery in the Management of Mesothelioma

Tanya Sinha*, Azar Hussain, Mahmoud Loubani, Michael Cowen and Syed Qadri

Hull York Medical School, UK

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Corresponding author:
Tanya Sinha,
Hull York Medical School, UK,
Email: tanyasinha@hotmail.co.uk

ABSTRACT

Malignant Pleural Mesothelioma (MPM) is a rare cancer of the pleural surface usually associated with previous asbestos exposure. It often presents with shortness of breath, pleural effusion, weight loss and progressive chest pain. There exists a long latency period between the exposure of asbestos and the development of the pleural mesothelioma, which frequently leads to metastases of the cancer by the time of diagnosis. This poses several difficulties in the management of this disease. Options for management include chemotherapy, radiotherapy, immunotherapy and surgery. Surgery for mesothelioma can be classified as diagnostic, palliative and therapeutic. Surgical intervention as a part of multimodality treatment is highly controversial and is usually limited to patients fitting certain criteria. It includes Extended Pleurectomy/Decortication (EPD) and Extrapleural Pneumonectomy (EPP). EPD involves the removal of the parietal and visceral pleura, pericardium and diaphragm, whereas EPP involves the resection of the entire lung, pleura, pericardium and diaphragm. At present, these interventions are only used to reduce the initial tumour burden as cyto reduction and are often followed by chemotherapy and/or radiotherapy to treat remaining microscopic and/or macroscopic disease. The metastatic disease and recurrence are normally treated with chemotherapy or/and radiotherapy as part of palliative therapy. The superiority of either surgical technique is unclear due to the absence of randomised controlled trials. So far, the biggest trial to study the use of surgical intervention in MPM is the MARS study. This study reported that EPP has a higher mortality than chemotherapy in the treatment of MPM. There are studies currently underway that may shed more light upon the effectiveness of surgical intervention. This mini review provides a bird's eye view of current literature surrounding the use, benefits and risks of EPD and EPP for MPM.

EPIDEMIOLOGY

Mesothelioma is a rare malignancy originating in the pleura, peritoneum, pericardium and tunica vaginalis. It arises from the mesothelial surface of these areas with most of the cases arising from the pleura. Majority of the MPM cases (over 75%) are associated with asbestos exposure. Radiation therapy for non-Hodgkin lymphoma, simian virus 40 and germline mutations in the BRCA1 gene associated protein -1 (BAP1) have also been linked to the development of pulmonary mesothelioma [1-3]. MPM is known to cause 1% of all cancer deaths in the UK and the number of people dying as a result of mesothelioma in the UK is expected to peak in 2020 [4,5].

Mesothelioma has caused 2526 deaths in 2017 in the UK with 2087 male and 439 female deaths [6]. Highest rates of mesothelioma are seen in developed industrialized countries (Northern and Western Europe and Australia) [7].International Agency for Research on Cancer indicates 30443 cases of malignant mesothelioma and 25576 deaths worldwide [8]. The overall incidence of MPM varies over time and geographic locations. Incidence of asbestos related MPM development was shown to decline from 2.4-2.6 cases per 10,000 person years in 1980-2000, to 1.1 cases per 10,000 per years in 2001-2010 in Greece [9]. This decline was attributed to a change in the asbestos type used in households. Furthermore epidemiological studies found an increase in incidence of MPM from 24 cases in 1998 to 82 cases in 2005, followed by a decline in 2006 to 68 cases in Egypt [9]. Malesindicate a higher incidence of mesothelioma - whether thisis due to genetic susceptibility or whether it is a reflection upon occupational exposure to asbestos is unclear, though the latter is more likely [5,6].

PATHOGENESIS

As mentioned, asbestos exposure is the most common (94%) cause of MPM [5]. Asbestos are a group of mineral fibres that are classified into two groups: amphibole and serpentine. Amphibole fibres (in specific, crocidolite) are typically known to be the highly carcinogenic type of asbestos and are implicated in the formation of MPM [1,10]. It is thought that these inhaled fibres can penetrate into the pleural space where they interact with mesothelial cells leading to repeated cycles of scarring, damage and chronic inflammation, resulting in carcinogenesis [10]. Four main processes have been proposed to explain carcinogenesis resulting from asbestos inhalation. Firstly, the presence of asbestos in the pleural space can attract immune cells including macrophages to the site, which phagocytose the asbestos fibres and produce abundant amounts of reactive oxygen species [10]. These reactive oxygen species can cause intracellular DNA damage and hence, lead to the development of cancerous cells. Secondly, it is thought that the asbestos fibres can themselves penetrate the mesothelial cells where they damage chromosomes, interfere with mitotic spindles (and hence mitosis) and affect repair of abnormal DNA. Thirdly, studies show that asbestos exposed mesothelial cells create a favourable environment for tumour growth through the release of inflammatory cytokines such as interleukin-1β, tumour growth factor-β, platelet-derived growth factor and vascular endothelial growth factor. Fourthly, asbestos can promote the expression of proto-oncogenes and increase abnormal cellular proliferation through the phosphorylation of several protein kinases [10,11]. Simian virus 40 (SV40) has also been implicated in the development of MPM either by inactivating the p53 and pRb or by activating various protein kinases resulting in uncontrollable cell growth [12].

PRESENTATION AND INVESTIGATIONS

At presentation, patients with MPM commonly exhibit shortness of breath, pleural effusion, weight loss and dull, progressive chest pain. Some other symptoms and signs include fatigue, night sweats, fever and finger clubbing. Non-specific findings including anaemia, eosinophilia, hypergammaglobulinemia and thrombocytosis have been found in 60% to 90% of patients. Metastasis of the tumour may present with bone tenderness and pain, abdominal pain, hepatomegaly and gastrointestinal obstruction [1,4]. Recommendations for investigations include an initial thoracentesis with a pleural cytologic examination and a thoracoscopic biopsy or open pleural biopsy for histological confirmation of diagnosis [13]. Differentiating between MPM and metastatic pleural malignancy may be challenging. Guidelines suggest that metastatic pleural malignancy commonly involves the lung parenchyma and/or mediastinal/hilar lymph node enlargement, whereas asbestos exposure (and hence, MPM) can sometimes present as pleural plaques [14]. Upon CT imaging, one may find a unilateral pleural effusion which affects the right hemithorax 60% of the time [1,4]. MRI scans may aid in showing the extent of the metastasis, though it is not commonly used. Most commonly, integrated PET-CT scan is used to define the extent of the cancer and visualise the response to treatment. However, without histology via biopsy, a definitive diagnosis is difficult to reach A pleural biopsy and thoracoscopy is commonly used for diagnostic and staging purposes [1,15]. Biopsies can indicate the histologic appearance of the tumour cells. Three cellular types of mesothelioma exist: epithelioid, sarcomatous and biphasic mesothelioma. Epithelioid tumours are the most common types. Histology of the tumour cells can aid in reaching a definitive diagnosis. Furthermore, the management of this

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disease requires an understanding of the type of cells that the tumour consists of as studies show that epithelial cells, in particular, respond better to chemotherapy in comparison to sarcomatoid and biphasic mesothelioma [1,15-17].

According to American Society of Clinical Oncology Clinical Practice Guidelines in 2018, recommendations for diagnosis are as below [13].

1.1: Clinicians should perform an initial thoracentes is when patients present with symptomatic pleural effusions and send pleural fluid for cytologic examination for initial assessment for possible mesothelioma (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

1.2: In patients for whom antineoplastic treatment is planned, it is strongly recommended that a thoracoscopic biopsy should be performed. This will: (a) enhance the information available for clinical staging; (b) allow for histologic confirmation of diagnosis; (c) enable more accurate determination of the pathologic subtype of mesothelioma (epithelial, sarcomatoid, biphasic); and (d) make material available for additional studies (eg, molecular profiling) (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong).

MANAGEMENT

Management of MPM consists of chemotherapy alone or in combination with surgery, radiotherapy and immunotherapy. Currently, pleural aspiration can be conducted as part of an initial diagnostic workup for patients presenting with pleural effusion [18]. Soluble Mesothel in-Related Peptides (SMRPs) and glycoprotein fibulin-3 are two biomarkers that are being investigated for early detection and progression of mesothelioma- it has been suggested that these markers are over expressed in mesothelioma [1,20,21]. Once detected, the tumour is categorised into four stages (I, II, III, IV) with stage IV being the most severe, through the tumour (T), node (N), metastasis (M) system [1]. Management options include radiotherapy, chemotherapy, immunotherapy, some targeted therapies and surgery. Radiotherapy has shown to have some beneficial results in mesothelioma. However, its use is limited by the need to treat large portions of the hemi thorax due to the nature of the disease. This disorder can affect the entire pleura and therefore radiotherapy of the hemi thorax can affect structures such as the heart, oesophagus and spinal cord- all which are sensitive to radiation. Radiotherapy can also be used postoperatively as an adjuvant to surgery, though it is recommended that this be provided in centres with experience in radiotherapy for mesothelioma [1,13,15]. A study by Valerie Rusch et al., states that higher doses of radiation administered after certain forms of surgery for mesothelioma is associated with low risk of local reoccurrence of the cancer in the chest wall; however, mesothelioma often has an insidious onset of symptoms which almost always leads to a delay in diagnosis and hence the development of metastasis. This study suggests that adjuvant radiotherapy does not provide much benefit in preventing the development of new metastasis and therefore its use in the management of mesothelioma can be limited [20]. Radiation associated problems such as radiation pneumonitis, myelitis and hepatitis limits its use. On contrary, chemotherapy has shown good survival benefit. The combination of platinum and pemetrexed (with folic acid and vitamin b12 supplementation) is often the gold standard first-line therapy for this disease [13]. The phase III EMPHACIS trial, phase III EORTC trial and the International Expanded Access Program has shown that this regime shows improvement in survival rate by about 3 months giving a median overall survival of around 12 months [21]. Carboplatin can be substituted for cisplatin to decrease toxicity [1,21]. A study by Laura V Klotz et al indicated that chemo-perfusion with platinum-based chemotherapeutic agents such as cisplatin in combination with surgical intervention (in specific, EPD) is a safe approach for selected patients with epithelial MPM [22]. Hyperthermia in addition to chemotherapy agents has also been used in some studies. Hyperthermia (to 40°) is shown to increase the effects of intracavitary therapies by increasing penetration in the tissues and enhancing their cytotoxic effects through modification of cell membrane permeability [23]. Some targeted therapies are also currently in clinical trials. Drugs including bortezomib (a proteasome inhibitor) are being analysed for their use in mesothelioma, especially for patients who do not respond well to the first line treatment [24]. Immunotherapy for cancer is relatively a novel concept in the management of neoplasms. Several studies have assessed the use of cytokine therapy in the management of MPM. Administration of IL-2 has shown some success in tumour

regression in some patients. Recently, a treatment therapy consisting of adenovirus containing human IFN-α-2b combined with systemic chemotherapy has shown to have a median increase in overall survival of 21.5 months. However, further trials need to be conducted in order to understand the true efficacy of this management regime [25,26].

Various forms of adjuvant radiotherapy aim to target any local recurrence post-surgery and hence improve overall survival rate. Studies and guidelines often recommend adjuvant therapy alongside cytoreduction through surgery [13].A certain type of radiotherapy, known as Intensity Modulated Radiation Therapy (IMRT), has shown great promise in targeting the tumour whilst minimising side effects through delivering lower doses to nearby structures [27,28]. There is still some debate in the literature regarding whether adjuvant radiotherapy can bring significant results to overall survival rate of people with MPM. As cited earlier, due to the nature of this disease, radiotherapy can cause significant damage to nearby body structures and hence mortality remains high.

Surgical intervention for the management of MPM is controversial. If the tumour has been found to be resectable, four types of surgery can be performed as treatment- EPD, EPP, limited pleurectomy and thoracoscopy with pleurodesis.The aim of surgical intervention is often to reduce the initial tumour burden through macroscopic disease clearance and is often followed by chemotherapy or radiotherapy (or both) to manage microscopic disease and any remaining macroscopic disease. The histology of the tumour also plays a part in surgical intervention – epitheloid mesothelioma is the only type of mesothelioma where surgery has been offered for curative-intent [1,15].

SURGICAL CYTOREDUCTION

Surgery for mesothelioma can be offered for diagnosis (pleural biopsy), staging, symptomatic control (TALC pleurodesis), curative intent (EPP and EPD) and palliative surgery (partial pleurectomy and parenchyma-sparing debulking (P/D)).The two most commonly discussed forms of surgery for curative-intent for MPM are EPD and EPP.EPD involves the resection of the visceral and parietal pleura, the pericardium and hemi-diaphragm. EPP, on the other hand involves removal of all the parietal and visceral pleura, pericardium, diaphragm and the lung [29,30]. Surgical resection is only offered to those patients who are deemed fit enough to undergo radical surgery (i.e. adequate pulmonary function in the non-affected lung, no significant renal, liver or cardiac comorbidities and who's tumour has shown to be resectable (often stage I or II and rarely, stage III)). Studies indicate that stage I tumours resected by EPP showed a median survival of 40 months whereas those who received EPD showed a median survival of 23 months [15]. Patients presenting with significant cardiac comorbidities, sarcomatous tumour histology and poor performance status typically have a worse prognosis and hence, are not usually considered for surgical resection [13,15,20]. EPD is often considered the less aggressive surgical procedure in comparison to EPP. The benefits of EPD are that it poses less physiologic stress to the patient as the lung is not removed, which may lower operative mortality. Furthermore, it may be offered to older patients and those who have limited cardio respiratory reserve. However, leaving the lung intact may also bring several disadvantages. Some of the common disadvantages include prolonged air leak, empyema and the inability to remove the entire tumour [31]. The use of postoperative radiotherapy in this instance is also limited as the lung is still present and hence, the likelihood of radiation damage to the lung is very high. Several studies also indicate that the local re-occurrence rate is also very high (64%-80%). In comparison to the EPP, the local recurrence rate for EPD is shown to be 1.5 to 2 times higher due to the lung being left in situ [17]. Therefore, though EPD can offer some symptomatic relief and palliation, it is not usually considered as a first-line management option for MPM [20,32]. A review by Raphael Bueno et al suggests the use of EPD for a large majority of cases should be a part of multimodality treatment rather than for palliation alone [33]. That review indicates a beneficial decrease in operative mortality for EPD from <10% to 0%-2% through better patient selection- in particular, those with early-stage disease. Additionally, the 90 day mortality for EPD is quoted to be from 0.0%-9.2% [33].

EPP, on the other hand, is thought to be a more aggressive surgical procedure as it involves the removal of the affected lung. This surgical procedure tries to ensure complete macroscopic removal of the disease; therefore, theoretically EPP ensures long-term survival of patients. Several studies have shown that this procedure, though it does not offer curative

treatment for MPM, can increase the survival rate. Since the entire lung is removed, the local recurrence rate is also shown to be lower than with EPD (33% in EPP group compared with around 65% in the EPD group) [34]. The most common complications noted after EPP was the development of reversible atrial fibrillation, Acute Respiratory Distress Syndrome (ARDS) and pulmonary embolism. Haemodynamic monitoring, however, can be used to assess the degree of ARDS and can aid in guiding management [33]. However, EPP is still associated with an operative mortality of 4-9% and high morbidity (postoperative complications occur in over 60% of patients) and the overall survival benefit that it brings remains debatable amongst studies [24,29]. The 90-day mortality has shown to be 8.0%- 13.5% for EPP in the UK depending on different centres [33]. Our previous study of 30 patients who underwent EPP has shown 0% operative mortality, and overall median survival of 20±24 months, 3 year survival of 35% and a 4 year survival of 31% while 2 patients were alive after 7 years at the time of study [15]. More recent studies are reporting a significant reduction in operative mortality to 3.4% [35]. These surgical techniques are often coupled with preoperative and/or postoperative chemotherapy. Surgery often aims to target the original tumour and its partial or complete macroscopic resection from the hemi thorax to attain R0 or R1 resection [34]. Trials such as the MesoTRAP study looking at video-assisted thoracoscopic partial EPD in patients that have a trapped lung due to malignant pleural mesothelioma, and EORTC 1205, a randomized multi-centre trial comparing the use of EPP and EPD in terms of effectiveness and safety are currently underway [31,35-37]. Furthermore, following on from the MARS trial, a MARS 2 study is currently comparing surgery (EPD) with no surgery in respect to overall survival, quality of life and cost-effectiveness for mesothelioma [38]. These trials may help in providing more information regarding the efficacy of surgical intervention in MPM.

According to American Society of Clinical Oncology Clinical Practice Guideline in 2018, recommendations for surgical cytoreduction are as below [13]

1.1: In selected patients with early-stage disease, it is strongly recommended that a maximal surgical cytoreduction should be performed (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

1.2: Maximal surgical cytoreduction as a single modality treatment is generally insufficient; additional antineoplastic treatment (chemotherapy and/or radiation therapy) should be administered. It is recommended that this treatment decision should be made with multidisciplinary input involving thoracic surgeons, pulmonologists, medical and radiation oncologists (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

2.2: Patients with ipsilateral histologically confirmed mediastinal lymph node involvement should only undergo maximal surgical cytoreduction in the context of multimodality therapy (neoadjuvant or adjuvant chemotherapy). Optimally, these patients should be enrolled in clinical trials. (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

3.0: Maximal surgical cytoreduction involves Either Extrapleural Pneumonectomy (EPP) or lung-sparing options (Pleurectomy/Decortication [P/D], extended P/D). When offering maximal surgical cytoreduction, lung-sparing options should be the first choice, due to decreased operative and long-term risk. EPP may be offered in highly selected patients when performed in centers of excellence (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

A maximal cytoreduction (either lung sparing or non–lung sparing) should only be considered in patients who meet specific preoperative cardiopulmonary functional criteria, have no evidence of extra thoracic disease, and are able to receive multimodality treatment (adjuvant or neoadjuvant) (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Adjuvant therapy

Use of adjuvant platinum-based chemotherapy and hemi thoracic radiotherapy alongside surgical treatments is often practiced.This regime, known as tri modal therapy, has had inconsistent results, possibly due to the lack of research into surgical treatment of MPM and the aggressive nature of the disease [39]. The MARS trial indicated that EPP as part of tri modal therapy has shown to offer no benefit to the patient [30]. More recent studies, have however, shown an increase in

the overall median survival to 45.5 ± 24 months in patients who received tri modal treatment with surgical intervention, with 31% of patients surviving 4 or more years [15,34,40]. Studies indicate a 3-year survival rate of 50% of patients who undergo tri modal treatment and a 5 year survival rate of 30% compared to a 20% 3 year survival rate in patients who do not undergo tri modal treatment [15]. Laura V Klotz et al has shown that tri modality therapy is a safe approach for selected patients with epithetlioid MPM [22]. A multicentre retrospective analysis of patients with MPM from 1982 to 2012 reported significantly improved survival with adjuvant therapy than chemotherapy alone (19.8 vs 11.7 months, p value: 0.001) [41]. American Society of Clinical Oncology Clinical Practice Guideline recommends adjuvant or neo adjuvant treatment as part of tri modality treatment with strong evidence [13].

CONCLUSION

MPM has a very poor prognosis with life expectancy being less than 18 months for most patients. Surgical intervention can be quite intensive and is not often practiced. Studies have indicated inconsistent results regarding the efficacy of surgical intervention. Analysing the most suitable and effective surgical option of MPM can be difficult as it has many limitations. Firstly, surgical options are only available to those who fit set criteria; finding patients who do fit into this criterion and who give consent to the procedure, can limit the amount of data available to study [42]. There is also a latency period between the exposure to asbestos and the development of mesothelioma which often means that people who develop mesothelioma are over the age of 75 (the peak age of mesothelioma in 2013-2015 in the UK is 80-84) [5,43]. This often means that these patients are more likely to have several other co-morbidities. This further limits the amount of data available for analysis as a lot of these patients may not fit the criteria for, or be fit enough for, surgical intervention. Furthermore, as pleural mesothelioma can be aggressive, the time between detection and surgical intervention can lead to the tumour becoming more invasive and hence, inoperable. There continues to be a lack of randomized trials that compare EPP and EPD and therefore the most effective surgical treatment still remains clouded. EPD is more favoured as it is noted to be considerably less radical than EPP, and several recent studies encourage the use of this technique over EPP because of its lower mortality and morbidity rate, higher 30-day mortality and lower complication rate [17,19,29,31,34,44]. Studies also indicate a worse post-operative quality of life with EPP compared with EPD [45,46]. Patients with epithelioid mesothelioma and negative nodal metastasis seem to benefit more from cytoreductive surgery as part of a multimodality treatment, compared to chemotherapy alone [15,34]. Recent clinical practice guidelines for mesothelioma management from American Society of Clinical Oncology recommends the surgical cytoreduction as an important part of treatment in early stage disease for better survival. Surgeons should be proactive in MDT for the management of mesothelioma. Surgical cytoreduction should be offered according to patients' age, stage of disease, co-morbidities, surgeon's experience and performed in high-volume centres within multimodality protocols.

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