Novel Induction Therapies for Pleural Mesothelioma

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Malignant mesothelioma is becoming increasingly common, and rates of diagnosis are expected to continue to increase in the coming years because of the extensive use of asbestos in industrialized countries and the long time interval between exposure and onset of disease. Although much research has been done on the optimal treatment for this disease, the overall prognosis remains grim. The main components of therapy are surgery, chemotherapy, and radiation therapy, but there is controversy in the literature about the optimal inclusion and sequencing of these treatments, as each has unique risk profiles. We have developed a new Surgery for Mesothelioma After Radiation Therapy protocol consisting of induction-accelerated hemithoracic radiation followed by extrapleural pneumonectomy. The rationale behind this protocol is to maximize both the tumoricidal and immunogenic potential of the radiotherapy while minimizing the radiation toxicity to the ipsilateral lung. Our initial trial demonstrated the feasibility of this approach and has shown encouraging results in patients with epithelial histology. In this article, we reviewed the current literature on induction chemotherapy for mesothelioma as well as described the Surgery for Mesothelioma After Radiation Therapy protocol and upcoming studies of novel induction therapies for mesothelioma.

Semin Thoracic Surg 26:192–200

Keywords: mesothelioma, surgery, pleuropneumonectomy, hemithoracic radiation, neoadjuvant therapy, extrapleural pneumonectomy

INTRODUCTION

Mesothelioma has been a malignancy that is difficult to both diagnose and treat successfully. Recognized to be related to asbestos exposure by Wagner in 1960, pleural tumors, and specifically mesothelioma, have been a known entity for centuries, yet the optimal treatment of pleural mesothelioma is unknown.[1] The first description of a pleural malignancy was in 1767 by Lieutaud, followed by identification of the epithelial nature of the tumor by Eberth in 1870.[2] Mason is credited with performing the first pleuropneumonectomy in 1949, and the procedure was advocated by a number of surgeons in the following decades, yet it fell out of favor because of the very high morbidity and mortality rates.[3] In the 1970s, Wanebo reviewed the cases of mesothelioma at Memorial Hospital from 1939-1972. The findings of the study were that epithelial histology afforded improved survival when compared with that in fibrosarcomatous histology, and the average overall survival for resected epithelial mesothelioma treated with postoperative radiotherapy was 28 months. Despite the poor prognosis for all patients diagnosed with epithelial mesothelioma, "[s]omewhat better survival is obtained in this group of patients if pleurectomy with resection of most of the tumor mass is combined with external irradiation and systemic chemotherapy."[2] Although this article was written almost 40 years ago, the similarity of the results to modern studies is striking and highlights the fact that mesothelioma remains a very difficult disease to treat. Focus must therefore be placed on discovering innovative treatment protocols in an effort to improve survival.

Currently, the 3 main modalities used in mesothelioma treatment are surgery, radiotherapy, and chemotherapy, but there is much debate in the literature about both the necessity and the timing of each treatment option. Improving outcome for this disease is becoming increasingly important, as

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1043-0679/$-see front matter
http://dx.doi.org/10.1053/j.semtcvs.2014.08.003

the number of cases of mesothelioma is expected to continue to increase rapidly in the coming years. Without any treatment, the median overall survival is less than 12 months.[4] Poor prognostic factors include performance status (European Organization for Research and Treatment of Cancer classification score), histology, sex, and positive lymph nodes.[5-15]

SURGERY FOR MESOTHELIOMA

There is still much debate in the literature about which surgical technique is appropriate for the management of mesothelioma and, in some cases, whether surgery should be included in the treatment algorithm at all. The main surgical options, from least extensive to most extensive, include talc poudrage, pleurectomy decortication (PD), extended (radical) PD (EPD), and extrapleural pneumonectomy (EPP).

In recent years, the focus of studies has been either on EPP or on PD or EPD. In 2004, Maziak et al[16] performed a systematic review of studies on surgical resection for mesothelioma. After reviewing the current literature, the authors concluded that there was insufficient evidence to be able to make any conclusions regarding the role of surgery in the management of mesothelioma. Only one randomized controlled trial (RCT) has been performed investigating surgery for mesothelioma, comparing EPP with no surgery. In this RCT, the mesothelioma and radical surgery trial, the authors concluded that there was no evidence to support the use of EPP in the treatment of mesothelioma.[17] However, this study has been widely criticized because of the small sample size and the unusually high operative mortality.[18] In addition, up to 20% of the patients in the nonsurgical arm underwent surgery, while 34% of the patients in the surgical arm did not undergo EPP. Overall, the trial demonstrated the difficulty to randomize patients with mesothelioma to surgery, as the participating centers required 3 years to enroll 50 patients instead of the predefined target of 1 year.[18,19] In a subsequent mesothelioma and radical surgery 2 trial, the authors are planning to assess the feasibility to randomize 50 patients to PD vs no surgery after induction chemotherapy in a 2-year period.

In planning curative surgery, as with any malignancy, the goal is a microscopic clear (R0) resection. Mesothelioma makes the goal of an R0 resection uniquely challenging because of the extensive and widespread nature of the disease. Therefore, the surgical focus has been macroscopic complete resection with the plan of incorporating other therapeutic modalities to treat residual microscopic disease.[19-21] This need for multimodality therapy also highlights the importance of timing and order of therapy, as survival benefit may be dependent on the completion of all prescribed treatments.

As mentioned earlier, EPP was first described as a treatment for mesothelioma in the 1940s but did not regain popularity until many years later owing to the high rate of associated morbidity and mortality. Typically, the surgery involves en bloc resection of the pleura, lung, pericardium, and diaphragm. The pericardium and diaphragm are then reconstructed with a prosthetic mesh.[22] The mortality rate has declined as experience with this surgery has improved from 31% reported by Butchart in the 1970s to less than 5% in many centers currently.[5,9,15,23-28] The morbidity rate remains high, ranging between 35% and 80%.[11] The most common complications encountered after EPP is atrial fibrillation accounting for up to half of the complications. Other complications include respiratory failure, empyema, bronchopleural fistula, vocal cord paralysis, venous thromboembolic complications, chylothorax, and technical failure (eg, patch dehiscence). The improvement in mortality rates at specialized centers has presented EPP as a relevant therapeutic option, and proponents of EPP feel that it provides the patient with the most radical surgery. Conversely, opponents of EPP feel that it subjects the patient to undue morbidity and mortality risk with little purported survival benefit over more conservative surgery, such as PD.[29]

A review by Flores et al[13] of 663 patients from 3 centers who were undergoing surgery for mesothelioma showed improved survival for patients who had undergone PD (hazard ratio = 1.4 in favor of PD), yet concluded that choice of surgery should be tailored to patient characteristics because of the multifactorial reasons contributing to the marginal survival benefit for PD. More recently, Rusch et al[30] collected the largest international database with 3101 cases from 15 centers as part of the revision process for the TNM staging system. Among 1494 patients undergoing surgery with curative intent, the best outcome was achieved in patients with stage I disease who were undergoing EPP. Other trials have compared PD and EPP, but none of them has compared PD and EPP in a prospective predefined group of patients.[31] At a recent meeting of the International Mesothelioma Interest Group in 2012, international experts concluded that macroscopic complete reduction should be the goal of cytoreductive surgery, and the type of surgery chosen should depend on "individual surgical judgement and expertise."[19]

Studies have found that the pattern of disease recurrence differs based on the surgery performed,