Trimodality therapy for mesothelioma

Debating the benefits of surgery alongside radiation and chemotherapy

by Marc de Perrot, MD, MSc, FRCSC and Christopher Lee, MD, FRCPC

ABSTRACT

There are limited treatment options for malignant pleural mesothelioma. Cisplatin-based chemotherapy has shown some survival benefit, but results remain discouraging. Radiation has been used as a palliative measure. Recent attempts to improve the effect of radiation with surgical resection have shown some promise.

At the 8th annual Ontario Thoracic Cancer Conference, Dr. Marc de Perrot presented a promising view of trimodality therapy with the evolution of mesothelioma surgery, while Dr. Christopher Lee pointed to shortcomings in the evidence supporting surgery in all but a very select patient group. In this article, Drs. Lee and de Perrot provide the key points of their debate.

Dr. Marc de Perrot describes vastly improved outcomes with the SMART approach to trimodality therapy

Malignant pleural mesothelioma (MPM) remains a dreadful cancer with limited therapeutic options and extremely poor survival. Most patients die from local progression and cachexia associated with unremitting pain from the invasion of the intercostal nerves, ribs, spine and brachial plexus. Despite the fact that the use of asbestos was banned in most Western countries in the 1970s and early 1980s, the incidence of MPM is still rapidly rising, with almost 500 new cases per year in Canada. Whether this epidemic will plateau in the next decade remains speculative.

MPM can be differentiated into 3 subtypes based on their histology: epithelial, biphasic and sarcomatoid. The epithelial subtype is the most common, affecting about 70% of patients. Median survival ranges between 6 and 12 months depending on the histologic subtype, performance status, gender and presence of an abnormal blood count such as anemia, elevated white cell count, elevated platelets and/or elevated neutrophil-to-lymphocyte ratio. The clinical staging system is often not a reliable prognostic factor since many patients with apparently early-stage disease are up-staged on final pathologic staging.

STANDARD OF CARE

Currently, the only recognized standard of care for MPM is cisplatin combined with an antifolate agent such as pemetrexed or raltitrexed. This combination was shown to improve median survival by about 3 months, from 9 to 12 months, in 2 large randomized controlled trials (RCTs). In patients with good prognostic factors (such as epithelial subtype, good performance status and minimal chest pain) treated with chemotherapy alone, median survival is approximately 18 months and the chance of 3-year survival is 15%. Hence, although chemotherapy with cisplatin-pemetrexed or cisplatin-raltitrexed provides some survival benefit, the results remain very discouraging and other strategies need to be explored.

The alternatives to chemotherapy are surgery and radiation. Surgery includes pleurectomy-decortication (PD), extended pleurectomy-decortication (EPD) and extrapleural pneumonectomy (EPP). The term EPD was recently proposed to encompass the group of patients undergoing PD with resection-reconstruction of the diaphragm to achieve an R1 resection. EPD differs from PD, which would not necessarily require resection of the diaphragm and would often be associated with residual macroscopic disease after surgery. Indications for surgery vary by centres and expertise. However, most investigators currently agree that surgical macroscopic complete resection and control of micrometastatic disease play a vital role in the multimodality treatment of MPM, as in the treatment of other solid malignancies. All patients with a diagnosis of MPM should be evaluated in a multidisciplinary setting with medical oncology, radiation oncology and surgery. Surgery should be offered if an R0 (complete resection with no microscopic residual tumour) or R1 (surgical margins show microscopic evidence of tumour cells) resection is deemed safely achievable. The type of surgery depends on clinical factors and on individual surgical judgment and expertise.

Marc de Perrot, MD, MSc, FRCSC is a surgeon in the Division of Thoracic Surgery, Toronto General Hospital and Princess Margaret Cancer Centre, and Head of the Toronto Mesothelioma Research Program. Christopher Lee, MD, FRCPC is a medical oncologist with the British Columbia Cancer Agency Fraser Valley Cancer Centre.
FEATURE

PROGRESS IN SURGERY
Since the first surgical series for MPM were reported in the 1970s, considerable progress has been made in quality and safety. Most series now describe an operative mortality of 5% or less after EPP or EPD. Despite progress, the long-term results of surgery alone have been discouraging and emphasis has turned to combination therapy to see further improvements in outcome.

SURGERY FOLLOWING CHEMOTHERAPY AND RADIATION
Following the demonstration by Weder et al. that induction chemotherapy followed by EPP was safe, and the study by Rusch et al. showing that high-dose hemithoracic radiation provided excellent local control, several groups adopted a trimodality approach with induction chemotherapy followed by EPP and adjuvant hemithoracic radiation. In our experience at the Princess Margaret Cancer Centre, this approach led to excellent local control with only 25% of patients experiencing local recurrence and a 3-year survival of 53% in patients who completed the radiation and did not present mediastinal node involvement. Radiation was safely delivered using intensity-modulated radiation therapy (IMRT).

Based on this experience, we developed the SMART (Surgery for Mesothelioma After Radiation Therapy) concept to optimize the quality of radiation. This approach offers the advantage of short accelerated radiation treatment with an hypofractionated regimen delivering 25 Gy in 5 daily fractions over 1 week to the entire ipsilateral hemithorax by IMRT, with a concomitant boost of 5 Gy to volumes at high risk based on computed tomography (CT) and positron emission tomography (PET) scan findings. EPP is performed within 1 week after the end of radiation to prevent the development of pneumonitis.

IMPLEMENTING THE SMART PROTOCOL
This protocol was implemented at Princess Margaret Cancer Centre in November 2008 for patients with histologically proven, previously untreated, resectable cT1-3N0M0 MPM. It includes the possibility of adjuvant chemotherapy after surgery with cisplatin-pemetrexed or cisplatin-raltitrexed for patients with ypN2 disease on final pathology. The results have been extremely encouraging since the first time, we are reaching a 3-year survival rate of about 80% in patients with epithelial subtype. Hence, this protocol has now become our treatment of choice for patients with resectable epithelial disease. Current research in our laboratory has shown that the benefit obtained with high-dose hypofractionated radiation followed by extended surgery is likely related to the net positive effect on cancer immunity. In future, this protocol could potentially be refined through the use of new immunomodulating compounds entering the clinical arena.

The difficulty with surgery and radiation is that, in contrast to chemotherapy, both techniques are extremely difficult to standardize and results are highly dependent on the expertise of individuals providing care. Hence, the performance of a RCT to demonstrate the benefit of surgery and/or radiation will very likely be impossible in MPM. The MARS trial was an attempt to perform a large RCT to compare EPP and radiation to no surgery. Considering that an estimated 670 patients would have been required to demonstrate a difference between the surgical and nonsurgical arms, the investigators started with a feasibility trial to see if 50 patients could be randomized in 1 year. This was not achieved as it took 3 years to randomize 50 patients. In addition, a third of the patients scheduled for surgery did not undergo EPP and 20% of the patients in the control arm eventually underwent surgery. This trial demonstrates the difficulty of randomizing patients to surgery vs no surgery in MPM and highlights high variability in the delivery of surgery, since the authors observed an operative mortality of 18% after EPP in the study.

Thus, surgery and high-dose hemithoracic radiation for MPM should only be done in centres with the required expertise to limit risk and obtain the greatest benefit. Denying patients access to such treatment due to the lack of a RCT, however, could be detrimental for them and to efforts to refine therapeutic strategies in mesothelioma.

In conclusion, while cisplatin-based chemotherapy with pemetrexed or raltitrexed is the only standard of care for patients with MPM, the results remain very disappointing even in the best group of patients. Additional strategies such as surgery and radiation must be considered. Currently, the SMART approach with a short course of high-dose hypofractionated hemithoracic radiation followed by surgery provides the best outcome, with a 3-year survival of approximately 80% in patients with epithelial subtypes. Ongoing research in our laboratory suggests that this approach could potentially be optimized with the use of immunomodulating compounds to target the immune system at the time of radiation or following radiation. Patients with mesothelioma should be strongly encouraged to participate in clinical trials for their own potential benefit and to further refine the therapeutic armamentarium against this challenging disease.

Dr. Christopher Lee regards patient selection, not trimodality therapy, as the key determinant of outcome
Routine management of malignant pleural mesothelioma (MPM) includes assessing the suitability of the patient for systemic therapy while ensuring adequate symptom control with other palliative measures. Radical surgery with the goal of improving long-term survival outcomes is an option in only a select subset of patients.

RESULTS WITH EXTRAPLEURAL PNEUMONECTOMY
The first report of extrapleural pneumonectomy (EPP) for pleural mesothelioma was a small series published in 1976. Since that time, a number of institutions have established expertise in performing the procedure, with contemporary perioperative morbidity and mortality rates between 2% and 5%.

Current treatment programs based on EPP incorporate postoperative hemithorax radiotherapy plus neoadjuvant or

References on page 45
adjuvant chemotherapy: trimodality therapy. Removal of the pleura, pericardium, diaphragm and lung by EPP used to be performed to accomplish en bloc resection of the tumour. However, it was soon recognized that R0 resection was rarely achieved, prompting the addition of hemithorax radiotherapy to improve local disease control. Chemotherapy was then added to try to reduce distant as well as local recurrence rates.

Institutional case series of EPP have been published and updated over the years, with a detailed review of these data in 2008 by Flores and colleagues. Among 385 patients treated with EPP, the 1- and 2-year survival rates were 50% and 25%, respectively. However, the degree to which the long-term survival outcomes seen with trimodality therapy represent a real benefit is uncertain.

CHEMOTHERAPY
In the last decade, chemotherapy has been accepted as a standard treatment option in the management of MPM, with evidence that it is associated with a modest survival benefit. Typical 1- and 2-year survival rates for treated patients are around 40% and 20%, respectively. Based on population data from British Columbia and Ontario, 40% to 50% of individuals with MPM are not suitable candidates for chemotherapy or decline treatment. Among those who receive chemotherapy, only 15% to 20% are reasonable candidates for radical surgery. This represents no more than 10% of all patients with MPM.

The process of determining the most suitable candidates for trimodality therapy necessarily focuses on younger patients with good performance status and less comorbidity. Another factor is the selection of patients with epithelial mesothelioma, which is associated with a better prognosis compared to those with sarcomatoid or mixed histology. As well, institutions that employ neoadjuvant chemotherapy require response after several cycles of treatment before scheduling surgery.

The effect of selection is seen in Figure 1, which shows the survival of patients treated with platinum-based combination chemotherapy in British Columbia from 1999 to 2005 (only one of whom was referred for EPP). For all patients, the 1- and 2-year survival rates are 42% and 21%, respectively. Selecting a subgroup of patients under age 70 years with good performance status, epithelial histology, and who survived 100 days after the start of chemotherapy (equivalent to completion of a neoadjuvant course), the 1- and 2-year survival rates improve to 56% and 40%.

The best level of evidence supporting a role for EPP in managing MPM comes from institutional case series, summarized in the review by Flores and colleagues. However, a case-control study from Western Australia raises concerns about selection bias accounting for any apparent survival benefit of EPP. The study looked at 36 patients who were referred for trimodality therapy; only half agreed to surgery or were deemed suitable candidates after further workup. Prognostic factors such as histology favoured the EPP group, but overall survival was the same for those who ended up not undergoing trimodality therapy. The 1- and 2-year survival rates for groups with and without EPP were around 75% and 40%, respectively.

Supporting the argument against EPP as part of trimodality therapy are the results of the MARS trial, a feasibility study to assess enrolment in a randomized controlled trial (RCT) comparing EPP to less aggressive management. The basic trial design and survival analysis have been criticized for being underpowered. Nevertheless, the MARS trial is the only RCT of EPP vs no EPP, and 1-year survival was inferior in the EPP arm: 52% vs 73% with no EPP.

Long-term survival outcomes reported for trimodality therapy may be primarily a function of selection bias. The benefit of EPP in the management of MPM is uncertain, and the evolution to trimodality therapy has been driven both by the limited ability of radical surgery to achieve local disease control and persistent concerns regarding distant relapse.

References
References from Dr. Marc de Perrot, page 22


