

Contemporary Management of Malignant Pleural Mesothelioma

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ABSTRACT

The rapidly increasing incidence of malignant pleural mesothelioma underlines the urgency to achieve a consensus in the management of this tumor, which is biologically distinct from most other tumors. For patients with stage I tumors of epithelial type and good performance status, pleuropneumectomy combined with chemotherapy and radiotherapy provides the best chance of prolonged survival, but further investigation is required to determine the optimum combination of adjuvant therapy. Debulking pleurectomy/decortication combined with adjuvant therapy is a worthwhile alternative for patients with more advanced disease, impaired performance status or tumors of less favorable histology (sarcomatous or biphasic). More clinical trials are urgently required to identify better adjuvant therapy for tumors containing sarcomatous elements. On currently available evidence, neither radiotherapy

nor chemotherapy offer worthwhile prolonged disease control when used in isolation, although both have an important role as part of multimodality therapy. Hyperthermia may enhance the effect of both radiotherapy and chemotherapy, and newer radiosensitizing agents also need evaluating. Research into immunotherapy and gene therapy suggests that these newer approaches may have a place if tumor volume is small. In practice they will probably need to be combined with other therapeutic modalities, and further clinical trials are required. Consensus in mesothelioma management currently remains elusive but it seems clear that the way forward will involve striving for much earlier diagnosis, the use of multimodality therapy and collaboration between centers with special expertise in mesothelioma treatment to organize multicenter trials. *The Oncologist* 1999;4:488-500

There is no clear consensus on the treatment of malignant pleural mesothelioma, in contrast to the treatment of most other tumors. This is particularly unfortunate as the natural history of the tumor is one of rapid progression towards death within 12-15 months of first symptoms if untreated [1, 2]. The need to find effective treatment is given added urgency by the dramatically increasing incidence of mesothelioma in most western countries, and this is expected to peak around the year 2020 [3]. It is estimated that mesothelioma deaths in men will double over the next 20 years [3].

The reasons for a lack of consensus in the management of mesothelioma are partly historical, partly related to the unique biology of the tumor and partly due to failure so far to find any single treatment or treatment combination which offers more than short-term tumor suppression in most patients. Historically, the very existence of a primary tumor

of the pleura was disputed in the first half of this century [4] and, even when it became accepted as a distinct entity with a clear relationship to asbestos exposure in many patients [5], difficulties were still encountered in distinguishing the tumor from adenocarcinoma in many instances [6]. Until more sophisticated immunocytochemical techniques were developed to distinguish between epithelial mesothelioma and adenocarcinoma, there is no doubt that many cases treated as mesothelioma were, in fact, cases of secondary adenocarcinoma. This added to the confusion in the interpretation of the results of treatment.

The biological behavior of mesothelioma is distinct from that of other solid tumors in that mesothelioma tends to grow in a sheet-like fashion, covering the surface of the parietal and then the visceral pleura; it shows little tendency to invade structures deep into the pleura in the early course of the disease, unless the pleura is breached by needles or

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tubes, when it will spread readily along needle or tube tracks [7]. Part of the explanation for this unusual behavior appears to lie in the relative lack of proteases in comparison to other solid tumors [8]. In many instances the tumor appears to begin in a multifocal fashion resulting in scattered deposits of tumor with normal pleura intervening, suggesting either that a field change has occurred throughout the pleura, or that the tumor has metastasized locally within the pleural cavity [9]. Because the tumor is either broadly extensive on the pleural surface or multifocal at the time of detection, it does not lend itself to localized surgical excision. Surgical treatment aimed at complete resection therefore has to be much more extensive and is only suitable for a minority of patients (vide infra).

Although much research work is in progress, more innovative approaches to treatment using immunotherapy or gene therapy have yet to make an impact [10]. Preliminary results suggest that they are unlikely to be effective alone and will probably need to be combined with conventional treatment. Further advances will only come from a better understanding of tumor biology [11, 12]. Meanwhile, the poor response to a wide variety of surgical approaches and conventional radiotherapy and chemotherapy, with a large number of different agents, continues to foster a rather nihilistic attitude toward the management of mesothelioma, and many chest physicians and oncologists recommend only palliative treatment to control recurrent pleural effusion [13].

Logically, selection of treatment should, as with other tumors, depend on histological type, tumor stage at the time of presentation and on the patient's performance status, particularly in relation to cardiac and respiratory function.

HISTOLOGICAL TYPE

Diffuse malignant pleural mesothelioma is classified by three histological types: pure epithelial (tubopapillary), pure mesenchymal (sarcomatous) or a mixture of the two (biphasic). Several series have demonstrated that pure epithelial mesothelioma is associated with a better prognosis [14-16] and that it responds better to radical surgery [14, 17]. Fortunately, epithelial mesothelioma is the most common histological type in most series. As with lung cancer treatment, it is likely that different approaches will be required for tumors of different histological type.

TUMOR STAGING

Several different staging classifications have been proposed for mesothelioma, the most recent and comprehensive being that proposed by the International Mesothelioma Interest Group (IMIG) based on the tumor/node/metastasis (TNM) system [18]. The IMIG staging system has been validated by *Rusch* and found to correlate well with prognosis

Table 1. Butchart staging system [14]

Stage I	Tumor confined within the capsule of the parietal pleura, i.e. involving only ipsilateral pleura, lung, diaphragm, and external surface of pericardium within the pleural reflection.
Stage II	Tumor invading chest wall or mediastinal tissues or structures, e.g., esophagus, trachea, great vessels. <ul style="list-style-type: none"> • Lymph node involvement within the chest.
Stage III	Tumor penetrating diaphragmatic muscle to involve peritoneum or the retroperitoneal space. Tumor penetrating pericardium to involve its internal surface or the heart. <ul style="list-style-type: none"> • Involvement of the opposite pleura. • Lymph node involvement outside the chest.
Stage IV	Distant blood-borne metastases.

[16]. The first staging system, which the current author proposed in 1976 [14] (referred to subsequently in the literature as the Butchart staging system), still has the advantage of simplicity and relevance to prognosis and therapeutic options (Table 1); whereas the IMIG staging system (Table 2) may only be applied postoperatively or at autopsy, as it relies on histological criteria to differentiate one stage from another. It is therefore impossible to implement accurately in nonsurgical treatment regimes.

In the Butchart staging system, stage I disease is tumor which has not invaded structures beyond the parietal pleura and has not metastasized to regional lymph nodes or beyond. Its relationship to prognosis, demonstrated first in 1976 on a relatively small number of patients undergoing radical surgery [14], has been confirmed most recently in a large series of 183 patients treated by pleuropneumectomy and adjuvant therapy. In this series patients with negative resection margins and negative lymph nodes (Butchart stage I) had significantly better survival [17].

There is very little difference between the Butchart staging system and the IMIG system in the designation of stage I, except that in the IMIG system confluent visceral pleural tumor or extension of tumor into the paraenchanyma of the lung places the tumor in stage II. However, in practice, scattered foci of visceral pleural tumor (IMIG stage I) very quickly coalesce to form confluent tumor, and in early disease it is very common to encounter a mixture of scattered foci in some areas and early confluence of some foci in others. Furthermore, once the visceral pleura is involved by tumor, parenchymal lung involvement is inevitable, as microscopic tumor spreads into the lung along the fibrous septa of the pulmonary lobules. More importantly, from a practical point of view, neither confluent visceral tumor nor parenchymal pulmonary invasion prejudice complete removal of tumor by pleuropneumectomy.

Table 2. IMIG staging system [18]

T1	<p>T1a Tumor limited to the ipsilateral parietal pleura, including mediastinal and diaphragmatic pleura No involvement of the visceral pleura</p> <p>T1b Tumor involving the ipsilateral parietal pleura, including mediastinal and diaphragmatic pleura Scattered foci of tumor also involving the visceral pleura</p>
T2	<p>Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features:</p> <ul style="list-style-type: none"> ▲ involvement of diaphragmatic muscle ▲ confluent visceral pleural tumor (including the fissures) or extension of tumor from visceral pleural into the underlying pulmonary parenchyma
T3	<p>Describes locally advanced but potentially resectable tumor Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleural) with at least one of the following features:</p> <ul style="list-style-type: none"> ▲ involvement of the endothoracic fascia ▲ extension into the mediastinal fat ▲ solitary, completely resectable focus of tumor extending into the soft tissues of the chest wall ▲ nontransmural involvement of the pericardium
T4	<p>Describes locally advanced technically unresectable tumor Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral) with at least one of the following features:</p> <ul style="list-style-type: none"> ▲ diffuse extension or multifocal masses of tumor in the chest wall with or without associated rib destruction ▲ direct transdiaphragmatic extension of tumor to the peritoneum ▲ direct extension of tumor to the contralateral pleura ▲ direct extension of tumor to one or more mediastinal organs ▲ direct extension of tumor into the spine ▲ tumor extending through to the internal surface of the pericardium with or without a pericardial effusion; or tumor involving the myocardium

N—Lymph nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases in the ipsilateral bronchopulmonary or hilar lymph nodes
N2	Metastases in the subcarinal or the ipsilateral mediastinal lymph nodes, including the ipsilateral internal mammary nodes
N3	Metastases in the contralateral mediastinal, contralateral internal mammary, ipsilateral, or contralateral supraclavicular lymph nodes

M—Metastases

MX	Presence of distant metastases cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present

Stage	Description	Stage	Description
Stage Ia	T1a N0 M0	Stage III	Any T3 M0 Any N1 M0 Any N2 M0
Stage Ib	T1b N0 M0	Stage IV	Any T4 Any N3 Any M1
Stage II	T2 N0 M0		

More significant differences exist between the Butchart and the IMIG staging systems in the more advanced stages.

In the IMIG system, any lymph node involvement places the tumor at least in stage III, whereas in the Butchart system,

ipsilateral or mediastinal intrathoracic lymph node involvement is stage II. In the author's experience, truly contralateral intrathoracic nodal involvement is very unusual. The IMIG system adopts the same nomenclature for node status as the TNM classification for lung cancer, with hilar nodes being classified as N1 and mediastinal or internal mammary nodes classified as N2. With a tumor which begins in the parietal pleura, this is illogical, as internal mammary nodes are often involved before hilar nodes. Only mediastinal nodes may be sampled by mediastinoscopy and it is therefore not possible to accurately assess nodal status fully with this procedure prior to beginning treatment. It is possible, however, to sample all nodes using frozen section histology at the time of surgical exploration.

In the Butchart staging system tumor is resectable, although with reduced prognosis, up to stage II, whereas in the IMIG system, tumor is deemed resectable up to stage III, while stage IV contains inoperable tumor, contralateral and extrathoracic nodal involvement and metastatic disease. Both staging systems have advantages and disadvantages. To avoid confusion, all further references to stage in this review article use the Butchart staging system. Readers may "convert" to the IMIG system if they wish by using Tables 1 and 2.

The problem with all staging systems is that currently available imaging techniques do not reliably identify tumor stage, especially in early disease when tumor volume is relatively small. Because of potential staging inaccuracies, therapeutic regimes which do not involve surgical treatment are more difficult to evaluate. Gross chest wall involvement with rib destruction is easily identified on computerized tomography (CT) scan; but, at the other end of the spectrum, early chest wall involvement associated with minimal pleural thickening is sometimes impossible to detect with any imaging technique and can only be identified with certainty at operation, when the parietal pleura is stripped off the chest wall by blunt dissection. As with other tumors, the larger the tumor the more likely it is to have metastasized or invaded neighboring structures. Not surprisingly therefore, total tumor volume, as measured by three-dimensional CT, correlates with nodal status, overall staging, and survival [19]. However, autopsies on individual patients with tumors of epithelial type reveal that occasional patients die from extensive tumor bulk within the hemithorax, causing respiratory failure without any spread of tumor outside the confines of the parietal pleura or lymph node involvement [14]. Despite the effect of overall tumor bulk on prognosis in most patients, locally bulky disease does not necessarily predict local invasion at that site, in the author's experience. Hence local tumor thickness per se should not be taken as evidence of inoperability. Loss of fat planes between thickened pleura and underlying structures and tumor surrounding more than

50% of a mediastinal structure do, however, raise likelihood of involvement [20]. Thoracoscopy can provide information on the degree of parietal and visceral pleural involvement, but can provide no information on invasion of underlying structures. It therefore cannot reliably predict stage Ia or Ib according to the IMIG system. Diaphragmatic muscle involvement and eventual penetration to involve the peritoneal surface is particularly difficult to detect unless it is gross in extent. Magnetic resonance imaging (MRI) provides coronal and sagittal images in addition to axial images and hence offers slightly better assessment of diaphragmatic involvement than CT [20]. Laparoscopy has proved useful in detecting diaphragmatic penetration in equivocal cases [21]. Coronal MRI images provide better assessment of apical disease [22] spread into the fissures and bone invasion [23] than CT. MRI is also useful in distinguishing between benign and malignant pleural thickening [24].

PERFORMANCE STATUS

A detailed assessment of performance status is an essential precursor to treatment planning, particularly if radical surgical treatment is contemplated. Pleuropneumectomy is a major surgical procedure which is suitable only for very fit patients. Once the disease is established, lung function tests unfortunately provide little guidance on pulmonary reserve, as they are dominated by the effects of the pleural effusion and pulmonary restriction caused by tumor on the lung surface. Much better information is provided by a detailed history of premorbid exercise capacity and respiratory symptoms, coupled with CT assessment of the contralateral lung. Patients being considered for radical surgery should have a history of good exercise tolerance without dyspnea prior to developing mesothelioma and should be free of chronic bronchitis or asthma. The contralateral lung should be normal on CT; evidence of emphysema or asbestosis for example should preclude radical surgery.

Cardiac assessment involves a detailed history and examination supplemented by exercise electrocardiogram and echocardiography. Radical surgery should only be contemplated in patients with normal cardiac function. Nutritional status is also important. Neither cachectic patients nor very obese patients are suitable for radical surgery. Renal function should be normal to reduce the risk of renal failure both post-operatively and following subsequent chemotherapy. Few patients over the age of 70 will be suitable for radical surgery unless exceptionally fit.

CHOICE OF TREATMENT

Given that no form of treatment currently available can reliably eradicate mesothelioma, it is important to have a full and open discussion with the patient and his or her family

regarding treatment options. For patients who are very elderly, frail or compromised by other medical conditions or whose disease is at an advanced stage, there is little controversy: only palliative treatment or supportive care should be advised. However, for younger, fitter patients and particularly those with early disease, the choice of treatment is more controversial. Many patients will have difficulty accepting that the disease is “incurable” or that “nothing can be done” and will wish to explore all possible therapeutic options. Nowadays many patients access the medical literature via the internet and are already well informed at the first consultation. Ethical issues in relation to clinical trials also need to be taken into consideration given that the literature contains numerous phase II trials of various chemotherapeutic agents, either alone or in combination, which produce only short-term tumor regression in a minority of patients. Hopes should therefore not be falsely raised that a “new drug” in a forthcoming trial may cure or even control the disease.

SURGICAL TREATMENT

Surgery in mesothelioma can be radical, debulking or palliative. Radical surgery (pleuropneumonectomy) aims to eradicate all macroscopic disease and is therefore feasible only in stage I or early stage II disease (involved nodes or early localized chest wall invasion). All of the ipsilateral pleura, lung and pericardium are removed and, because diaphragmatic pleura cannot be separated from the diaphragmatic muscle for embryological reasons, it is necessary to remove the hemidiaphragm also as part of the procedure. Visualization of the diaphragm is facilitated by two levels of access to the chest through the same skin incision (Fig. 1) [7], although some surgeons use a single

thoracotomy incision [17]. Debulking surgery involves parietal pleurectomy (leaving diaphragmatic pleura in place) and decortication of the lung (inevitably leaving some tumor on or in the lung in most cases) and is usually combined with other treatment modalities. Pleuropneumonectomy is a very major operation and in the author’s view has no place as a debulking procedure, for example leaving the diaphragm in place with tumor covering it in the so-called “modified” pleuropneumonectomy procedure. Palliative surgery ranges from thoracoscopy and talc pleurodesis to more limited pleurectomy to achieve pleural symphysis [7].

Margin of clearance is an issue which continues to cause controversy. If pleuropneumonectomy has been used as a debulking procedure only, margins will clearly be positive. Even if it is used radically with “curative intent” in early disease, performing an “extracapsular” excision by staying outside the parietal pleura and resecting the diaphragm (Fig. 1), margins of clearance will be very small. The definition of “negative resection margins” depends on the criteria used by each pathologist and on the number and location of sites sampled on each specimen.

Radical surgery is a major operation, suitable only for fit patients with normal cardiopulmonary function. In the past, pleuropneumonectomy has been condemned on the grounds of high mortality and morbidity and failure to achieve more than short to medium-term palliation. However, the results of pleuropneumonectomy in the literature need to be interpreted with caution. Many of the early reports in the literature were anecdotal accounts of two or three cases. Some authors summarized the anecdotal reports of others and attempted to draw conclusions about the efficacy of the operation. In addition,

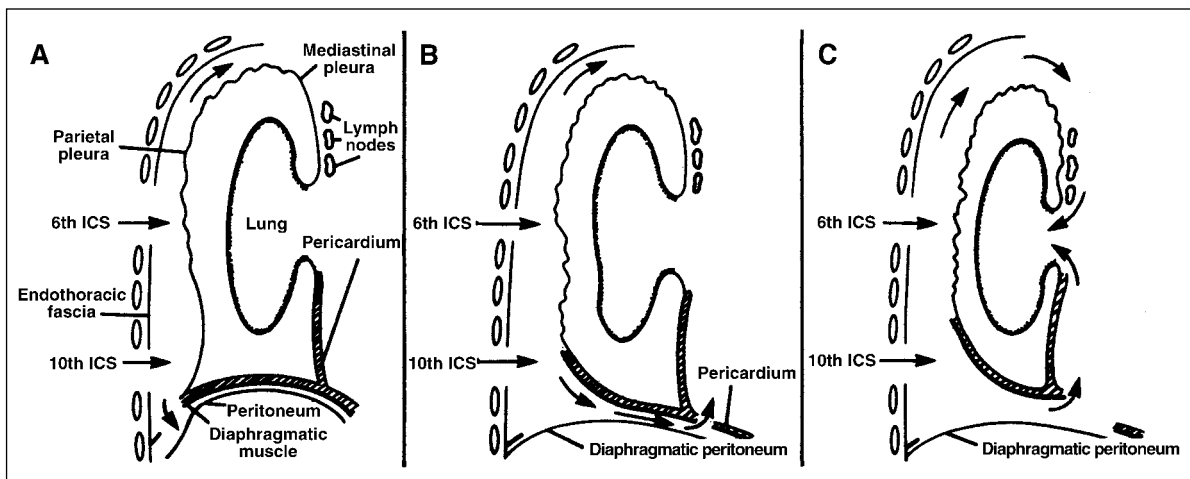


Figure 1. Technique of pleuropneumonectomy. The diagram on the left shows the division of the diaphragm outside the pleural reflection, preserving the peritoneum. The middle diagram represents the division of the pericardium outside the pleural reflection. The diagram on the right shows the completion of the pneumonectomy intrapericardially and en bloc excision of mediastinal lymph nodes. ICS = intercostal space. The firm attachment of the parietal pleura to the diaphragm and pericardium is shown by the hatched lines. Reproduced with permission from [7].

interpretation of almost all series is hindered by one or more of the following factors:

- ▲ Lack of information on preoperative performance status.
- ▲ Lack of staging information, making it likely that some unsuitable tumors of advanced stage were submitted to surgery.
- ▲ Selection bias, with only more advanced disease being submitted to pleuropneumonectomy, early disease being treated with pleurectomy/decortication.
- ▲ Lack of precise histological typing and even confusion with secondary adenocarcinoma.
- ▲ Lack of detail about preoperative interventions such as tube drainage of effusion, thoracoscopy or open pleural biopsy, which could have seeded tumor into the chest wall.
- ▲ Varied surgical technique, with some techniques certain to leave residual tumor, e.g. failure to resect the affected hemidiaphragm.
- ▲ Lack of information about adjuvant therapy or varied adjuvant therapy.

In recent years surgical mortality has fallen to a level similar to that of pneumonectomy for lung cancer in centers with a large experience of pleuropneumonectomy, and it has become apparent that pleuropneumonectomy combined with chemotherapy and radiotherapy extends survival in some categories of patients, particularly those with pure epithelial histological type and no lymph node involvement [17].

Sugarbaker and colleagues in Boston have done much to revive interest in radical surgery for mesothelioma in recent years [17]. For many years it has been apparent that pleuropneumonectomy alone could not eradicate the tumor, even in stage I, because of small margins of clearance and the risk of tumor seeding, and that it would be necessary to combine the operation with other treatment modalities [6]. The Boston group has used both chemotherapy and radiotherapy after pleuropneumonectomy. Unfortunately, because their protocol has changed at various times over the years and they have not disaggregated the data, it is impossible to determine which combination, if any, has been most successful. Prior to 1985, a combination of doxorubicin and cyclophosphamide was used; between 1985 and 1994 cisplatin was added to this regime; between 1995 and 1997 the regime was changed to carboplatin and paclitaxel. Throughout the period of analysis external radiation therapy was used in all patients to treat the hemithorax, mediastinum and areas of residual tumor or localized positive resection margins, but the radiation dose to the mediastinum in particular appears to have been higher in recent years [17]. A

further change in protocol has now been made with the use of hyperthermic intrapleural cisplatin postoperatively [25].

In recent years the results achieved by *Sugarbaker* and colleagues have been better than those previously reported for any treatment combination in mesothelioma (particularly in certain subsets of patients) [17]. Despite their rather surprising previous finding that positive resection margins or residual local disease did not influence survival [26], in their most recently published results on a larger series of patients, they draw attention to positive resection margins, lymph node (N2) involvement and nonepithelial histology as adverse predictors of survival [17]. Patients with epithelial histology, negative resection margins and negative lymph nodes achieved 68% two-year and 46% five-year survival [17]. These results are extremely encouraging and, if confirmed by other investigators in well-designed trials, offer considerable promise for younger, fitter patients presenting with stage I epithelial histology. They also provide scope to combine trimodality therapy with other innovative forms of treatment in the hope of improving results still further. Intrapleural interleukin 2 (IL-2) for example is reported to have a 55% response rate in early disease [27]. Pretreatment with IL-2 would thus be an approach worth evaluating. Gene therapy, which is also discussed below, may similarly have a role either pre- or postoperatively.

Based on currently available evidence, fit patients with stage I epithelial mesothelioma should be offered pleuropneumonectomy followed by chemotherapy and radiotherapy. But at present, it would appear that patients with sarcomatous histology or involved intrathoracic nodes will derive little benefit from trimodality therapy according to the protocols used by *Sugarbaker* and colleagues [17]. However until further trials have explored other chemotherapy regimes more targeted to sarcomatous tumors rather than epithelial tumors, it is probably too early to rule out this approach altogether in these patients.

Debulking surgery (pleurectomy and decortication) in combination with radiation therapy, using intraoperative brachytherapy and postoperative external beam radiation, has been reported to extend survival [28]. The place of pleurectomy/decortication has been reviewed by *Rusch* [16, 29] contrasting the results to pleuropneumonectomy in a personal series [16]. Median survival was greater in the pleurectomy/decortication group, but patients undergoing pleuropneumonectomy had more advanced disease and in many cases did not receive any adjuvant therapy, unlike the pleurectomy/decortication group, rendering the comparison invalid. The pattern of recurrent disease differed between the two groups of patients, with local recurrence tending to occur after pleurectomy/decortication and distant metastases after pleuropneumonectomy [16]. The risk of local recurrence after

debulking surgery was not diminished by adjuvant therapy [29]. Nevertheless it was concluded that this combination of therapy remained a useful form of treatment for patients whose medical condition precluded pleuropneumectomy [29].

Although unlikely to eradicate the disease, debulking surgery has a place in abolishing pleural effusion, controlling symptoms such as chest wall pain and extending survival when combined with other treatment modalities. It can also be used as a surgical alternative in the patient who is found at operation for planned pleuropneumectomy to be unsuitable for this procedure because of unexpected local invasion. Thus, in otherwise fit patients, a thoracotomy is rarely a "wasted" or "unnecessary" operation in early mesothelioma, at least in cases of epithelial type. Although the data in favor of pleuropneumectomy are persuasive, at least for epithelial mesothelioma, the choice between pleuropneumectomy and pleurectomy/decortication in stage I disease in patients fit enough for either procedure will only be put on a scientific basis by randomized trials of one surgical procedure or the other in combination with the same adjuvant therapy. Such trials have never been performed.

Limited palliative surgery in the form of thoracoscopy and talc pleurodesis to eradicate effusion is useful in patients who cannot tolerate more extensive surgery. However, adhesion between visceral and parietal pleura can only be achieved if the underlying lung will expand sufficiently to meet the chest wall. Often a rind of tumor on the lung surface will prevent this from occurring. If this is the case, a limited thoracotomy and decortication of the affected area of lung may be successful [7]. An alternative approach would be the use of intrapleural chemotherapy or immunotherapy in an attempt to reduce the bulk of tumor on the lung surface.

RADIOTHERAPY

Radiotherapy as a primary isolated treatment for mesothelioma has so far been unsuccessful in extending survival [30], although it appears to confer benefit when combined with other forms of treatment [17]. In general, mesothelioma is regarded as relatively radioresistant, although mesothelioma cells grown in tissue culture from different patients have shown marked variation in their response to radiation, and it has been suggested that each patient's mesothelioma cells should be assessed for radiation sensitivity before beginning a course of radiotherapy [31]. The technique of external beam radiation is important in order to achieve good pleural dose distribution while sparing the underlying lung as much as possible and shielding the liver and stomach [32]. Different methods of fractionation of radiation treatment have been evaluated following previous surgery and chemotherapy in small numbers of patients with no one particular method found to have any advantage [33].

Radiotherapy is more effective if combined with radiosensitizing agents. Paclitaxel and carboplatin both have this property and may partly account for the improved results of trimodality therapy reported by *Sugarbaker* and colleagues referred to above [17]. Recently it has been reported that the angiogenesis inhibitor, angiostatin, a cleavage fragment of plasminogen, interacts with radiotherapy to create a synergistic effect in some tumors [34]. There are no reports of its use in mesothelioma yet, but it would appear to merit research in this tumor also. Hyperthermia is reported to enhance the effect of radiotherapy in mesothelioma, with higher response rates and fewer in-field recurrences [35].

Radiotherapy is useful in treating localized pain due to chest wall invasion [30, 36] although pain relief is often short-lived [37] with pain recurring after a median time interval of 69 days (range 32-363 days) in one large series [35]. Radiotherapy is more effective in preventing seeding into the chest wall following thoracoscopy, needle aspiration and chest tube placement [38, 39]. Patients being considered for radical surgery should therefore undergo local radiotherapy to needle, tube or thoracoscopy tracks prior to definitive treatment, delaying at least one week before surgery to allow the full cytotoxic effect of the radiotherapy to occur.

CHEMOTHERAPY

The literature contains numerous reports of the use of various cytotoxic drugs as primary treatment for mesothelioma, given both systemically and intrapleurally. Although many produce a response in some patients, complete response is very unusual, and partial responses occur in less than one-third of patients in most series [40]. Recently somewhat higher response rates have been reported using a combination of methotrexate and vinblastine together with cisplatin in those patients able to tolerate the latter drug (53% response rate) [41] and using paclitaxel in combination with a platinum compound. In a small series paclitaxel and carboplatin produced a 57% response rate [42]. Experimentally in mice with mesothelioma, the combination of paclitaxel and cisplatin has been shown to be synergistic, producing higher response rates than either drug singly [43]. Similar synergism has been reported between paclitaxel and arginine butyrate on mesothelioma cells in tissue culture [44]. Continuous paclitaxel infusion during radiotherapy acts as a radiation sensitizer and is reported to be well tolerated [45].

An improved response occurs in many tumors using hyperthermic chemotherapy, as malignant cells are more susceptible to the cytotoxic effect of drugs at a higher temperature [46, 47]. Optimum enhancement occurs when heat and chemotherapy are given simultaneously [48]. Some drugs only exhibit an enhanced effect when the temperature reaches 42°-43°C (e.g., doxorubicin and bleomycin) but in others,

such as cisplatin, the enhanced response is linear at temperatures from 39°-43°C. Good tolerance and improved pharmacokinetics have been reported in a small phase I study in pleural mesothelioma using intrapleural perfusion with cisplatin at 41.5°C in combination with pleurectomy/decortication or pleuropneumectomy [49]. No phase II studies have been reported in pleural mesothelioma but encouraging short-term results have been reported using hyperthermic cisplatin in peritoneal mesothelioma, with no short-term recurrence of disease in "optimally debulked" patients [50]. *Sugarbaker* and colleagues are now evaluating hyperthermic cisplatin both intrapleurally and intraperitoneally following pleuropneumectomy in a phase I trial, using sodium thiosulphate to reduce systemic toxicity (personal communication). It is hoped that intraperitoneal hyperthermic cisplatin will reduce the risk of recurrent tumor in the peritoneal cavity. The chemotherapy is followed by radiation therapy, as in their previous protocol. So far the treatment combination has been well tolerated in more than 30 patients. Full results will be reported when the trial is complete.

Many oncologists take the view that as chemotherapy alone produces little more than short-term tumor regression or stabilization with no prospect of cure, it is not justified to submit patients to the unpleasant side effects of these drugs for such a brief response. Certainly the ethical issues of entering patients into clinical trials to test new cytotoxic drugs or drug combinations need to be taken into consideration before patients are invited to participate. At present it appears that the most useful role of chemotherapy in mesothelioma is as part of bimodality or trimodality therapy in patients with early epithelial tumors (stage I or very limited stage II), perhaps in association with induced local hyperthermia. Unless more effective drugs can be found, it probably cannot be justified as isolated therapy in advanced disease (stage III or IV).

IMMUNOTHERAPY

The positive correlation between tumor infiltrating lymphocyte numbers and better prognosis in mesothelioma [51] underlines the importance of an immunological response to the tumor, and much research has been conducted into the basic immunology of mesothelioma in recent years in the hope that this would lead to new approaches to treatment [12, 52, 53]. One of the most important cytokines involved in determining tumor growth in mesothelioma is transforming growth factor-beta (TGF- β), a potent immunosuppressant, which inhibits the immune response to the tumor and which is produced in large quantities by many mesotheliomas [52]. This makes it an obvious target for therapy, but research work in this area has yet to translate into clinical success. Experimentally in mice, interferon-alpha (IFN- α) has been shown to suppress TGF- β mRNA in mesothelioma cells but a significant therapeutic

effect only occurred if treatment was commenced very early in the course of the disease, equivalent to "mesothelioma in situ" [54]. This accords with the poor response to IFN- α reported clinically in established disease [55, 56], even when combined with cytotoxic drug regimes [57-59].

Other immunological approaches to enhance the immune response to mesothelioma have been evaluated, involving either IL-2 or gamma-IFN. Neither systemic IL-2 nor direct intratumor injection of IL-2 (using a recombinant vaccinia virus expressing human IL-2) have been effective [60, 61]. In contrast, intrapleural IL-2 seems well tolerated and a 55% response rate has been reported in patients who were predominantly in stage I or II and predominantly of epithelial type. The median survival of responders and nonresponders was 28 months and 8 months, respectively ($p < 0.01$) and responders had 58% two-year survival and 41% three-year survival [27]. The same group also evaluated intrapleural gamma-IFN and found it less effective with an overall response rate of only 20%, although in stage I disease, the response rate was 45% [62]. Despite the low clinical response rate, intrapleural gamma-IFN has been shown to decrease intrapleural IL-6 concentrations produced by malignant cells and to cause activation of macrophages and cytotoxic T-lymphocytes [63].

GENE THERAPY

Experimental studies in rodents have demonstrated that it is possible to transfer the herpes simplex thymidine kinase (HSVtk) gene to mesothelioma cells using an adenovirus vector, and subsequently treat with the antiviral drug ganciclovir to kill the mesothelioma cells, thereby eliminating tumor nodules [64]. This form of treatment is effective experimentally even when only a small percentage of mesothelioma cells is transduced, suggesting that there is an important "bystander effect" also [64, 65]. However, currently available viral vectors are less efficient at delivering genes to tumor cells interspersed in a dense, fibrous stroma, as in mesenchymal (sarcomatous) or mixed histology mesotheliomas [66]. Because of this problem and poor penetration of bulky tumor, it is likely that this type of gene therapy will need to be combined with either debulking or radical surgery.

Following the experimental work in animals, trials have begun to evaluate gene therapy clinically [66]. A phase I clinical trial of recombinant adenovirus containing HSVtk gene injected intrapleurally followed by systemic treatment with ganciclovir for 14 days has revealed good tolerance of therapy but some side effects. These included fever, anemia, transient liver enzyme elevations and bullous skin eruptions in some patients. Gene transfer was documented in 11 out of 20 patients [67]. Since this initial report, a new adenoviral vector has been developed which appears to be as effective with less toxicity [68]. Phase II trials have yet to be reported. Studies of

gene transfer in malignant pleural effusions have revealed that chondroitin sulphates markedly inhibit gene transfer by interacting with the vector in solution. The authors suggest that drainage of the pleural effusion prior to treatment should allow more efficient gene transfer [69].

Another approach in gene therapy involves restoration of a gene product usually absent in mesothelioma cells. The gene product p16INK4a can be re-expressed in mesothelioma cells following transfer with an adenovirus. Experimentally this has been shown to inhibit tumor formation, arrest tumor growth and diminish tumor size and spread [70]. Several other chromosomal losses have been identified in mesothelioma, suggesting that some may contain putative tumor suppressor genes [71-73]. The therapeutic possibilities of gene restoration therapy clearly need to be explored also.

PHOTODYNAMIC THERAPY

Photodynamic therapy involves administration of a tumor-localizing photosensitizing agent followed by activation of the agent by light of a wavelength specific to its absorption spectrum. The most commonly used photosensitizers are porphyrin-related compounds which bind to various cytoplasmic membranes within the cell. Light activation in the presence of molecular oxygen causes oxidative damage at the subcellular level, leading to cell death [74]. Cytotoxicity also occurs as the result of vascular damage, impaired blood supply and local hypoxia [75]. It is thought that a heightened immune response to the tumor may also be induced [76]. Experimental work with nude mice bearing human mesothelioma tumors has shown that mesothelioma is locally sensitive to photodynamic therapy. Various photosensitizing agents and light dosing regimes have been investigated [77-80], together with studies to define the optimum time interval between sensitizer administration and light activation [81]. Currently available technology limits effective light treatment penetration to about 1 cm [82], which means that intrapleural photodynamic therapy must be combined with debulking or radical surgery in most cases.

The literature contains several anecdotal reports of small numbers of mesothelioma patients treated with photodynamic therapy in combination with various types of debulking surgery, and there are two reports from one center of a phase II study which yielded results inferior to other published surgical series in the literature [83, 84]. Only one phase III study has been reported [85]. This also showed no benefit for photodynamic therapy in terms of survival or local disease control in patients also treated with a combination of debulking surgery, cisplatin, IFN- α and tamoxifen [85].

Not only has photodynamic therapy proved to be ineffective clinically in trials reported to date, but there is also concern about its damaging effect on normal and healing tissues.

Concern has been raised particularly about the risk of bronchopleural [84, 86] and esophagopleural [86-88] fistula, and in one series the combination of pleuropneumectomy and intracavitary photodynamic therapy was associated with a mortality of 28.6% [84].

A small number of enthusiastic scientists and physicians continue to investigate photodynamic therapy in mesothelioma using newer technology and different photosensitizing agents in combination with various additional treatment modalities. Further trials are awaited with interest. However, on currently available evidence, it seems unlikely that this type of therapy will become part of the standard treatment for mesothelioma in the near future.

PALLIATIVE THERAPY

In patients whose performance status is poor or whose tumor has reached an advanced stage (III or IV), palliative therapy may have a role in helping to relieve the pain of chest wall involvement or the dyspnea due to recurrent pleural effusion. Radiotherapy has already been mentioned as a means of controlling chest wall pain. Strong opiates will almost certainly be required also, and in patients with intolerable pain, cordotomy may need to be considered. In patients with recurrent pleural effusion, thoracoscopy and instillation of talc can be useful to induce pleural adhesion [89], but only if the underlying lung is not so restricted by tumor on its surface that it will not expand sufficiently to reach the chest wall. If the lung has little or no tumor on its surface, outpatient management may be possible, using a small-bore catheter and a drainage bag in conjunction with sclerotherapy [90]. Pleuroperitoneal shunts are inadvisable as they risk seeding tumor into the peritoneal cavity. If the lung is restricted by tumor and recurrent effusions are troublesome, local treatment with chemotherapy, radiotherapy or immunotherapy may be worthwhile as a means of shrinking tumor on the lung surface sufficiently to allow re-expansion. However the natural history of advanced disease is that eventually the lung becomes fixed in a position midway between full expansion and complete collapse by contiguous tumor and progressive fluid formation ceases.

It has been suggested on theoretical grounds that cytokine inhibitors may have a role in palliative therapy by helping to control pain and cytokine-mediated paraneoplastic effects such as cachexia, fever and the thrombophilia associated with thrombocytosis [52]. No clinical studies have been reported.

FUTURE PROSPECTS

In the past there has been a tendency to think of diffuse malignant pleural mesothelioma as one disease in therapeutic terms, irrespective of histological type and tumor stage. This does not happen with other tumors and is equally illogical and

inappropriate in mesothelioma. As with other tumors, early diagnosis while the disease is still in stage I or even at an "in situ" stage must be the goal in order to maximize therapeutic options, particularly if immunotherapy or gene therapy is to be used. Patients with pure epithelial mesothelioma have a better prognosis and respond better to trimodality therapy. Stage I patients with epithelial mesothelioma who meet the fitness criteria described above should therefore be offered the option of radical surgery in combination with chemotherapy and radiotherapy. Further research is required to determine the optimum combination of these modalities in terms of timing of adjuvant therapy, individual drugs, use of hyperthermia and route of administration. The place of immunotherapy and gene therapy as adjunctive treatments also remains to be defined. For example, it may be possible to reduce tumor bulk and perhaps downstage the disease with immunotherapy prior to radical surgery, if treatment is started early enough. Gene therapy may have a role either preoperatively or in destroying the microscopic disease that remains after radical surgery. These and other combinations of treatment need to be tested in well-designed clinical trials, probably on a multicenter basis in order to enroll sufficient numbers of patients.

Finding means to improve treatment for sarcomatous and mixed histology mesothelioma remains an even greater challenge. At present radical surgery does not seem worthwhile for these patients when combined with currently employed chemotherapy and radiotherapy. However, chemotherapy combinations used for treating other sarcomas need to be

evaluated as adjunctive therapy before radical surgery is abandoned altogether as a treatment modality.

Much remains to be learned about tumor biology and immunology and specifically why some tumors of apparently identical histology respond better to therapy than others. Ultimately the hope must be that development of tumor markers capable of identifying very early asymptomatic malignant change in patients at risk, coupled with the discovery of the fundamental cause of malignant transformation in mesothelial cells at the genetic level, will lead to gene therapy given early enough to restore "normality" to these cells. Diffuse malignant mesothelioma of the pleura should not be labeled as "incurable" until all possible treatment combinations have been properly evaluated in well-designed clinical trials. A collaborative approach involving basic scientists and oncologists, thoracic surgeons and physicians with experience in treating mesothelioma is essential. Because mesothelioma is still a relatively rare tumor despite its increasing frequency, treatment should ideally be concentrated in relatively few supraregional centers in order to maximize expertise, and allow innovative treatment combinations to be implemented with the greatest chance of success. Evaluation of new therapeutic approaches will be achieved more rapidly if these supraregional centers collaborate in multicenter trials. The nihilistic approach of simply waiting until the mesothelioma epidemic eventually begins to decline spontaneously in 20 or 30 years is untenable, in view of the hundreds of thousands of deaths which will result if no effective treatment is found [3].

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