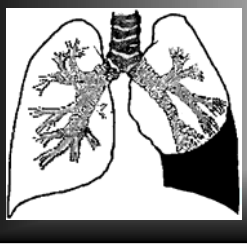
International Pleural Newsletter



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Radical Surgery for Mesothelioma

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Diffuse malignant pleural mesothelioma is a remorseless cancer which is steadily increasing in frequency[1]. Chest wall pain and breathlessness are common presenting symptoms and patients often present for repeated aspiration or drainage of their pleural effusion and it may be months before a diagnosis is finally made. Once made, many if not all patients are already in advanced stages of the disease. The cancer often progresses quickly, surrounds the lung, invades and restricts it, and patients usually face death within a year of diagnosis[2]. For the majority, palliation of symptoms is all that is offered.

Faced with increasing numbers and desperation, many patients and their doctors hold out the hope of cure achieved by radical surgery. The aim of surgery is to eradicate all the tissues that might be involved ideally with good clearance margins. This very radical surgery, commonly known as extra-pleural pneumonectomy (EPP), involves the removal of the whole lung, all the parietal pleura, the diaphragm, and the pericardium. Not only must the patient be fit enough to undergo this procedure with operative risks of up to 9%[3], the cancer must be in an early enough stage to make this technically feasible. Due to the nature of mesothelioma, its extent and pattern of growth, and proximity to major organs, this is not always possible.

To date, the benefits of radical surgery have not been proven in randomized trials. The best evidence we have at hand comes from case series, many reporting improved outcomes, but selecting the fittest patients with early stage disease who are most likely to do well[4,5]. Nearly all these claims follow this five point illogical sequence:

1 Statistically define features predicting longer survival
2 Operate on those with favorable features
3 Do not operate on those with unfavorable features
4 Compare those chosen for surgery *vs* those not operated on
5 Operated patients do better - QED!

Radical surgery as a single modality has not been associated with any demonstrable survival benefit[6]. Comparing the results with historical controls or a reference population is completely invalid. We have studied the survival of patients with mesothelioma in two tertiary centers. Both groups were managed similarly with best supportive care, but survival varied widely, far greater than any difference claim in trials of therapy[2]. This may well be due to lead time bias or a difference in diagnostic threshold, but whatever this explanation might be, it illustrates the need for a contemporaneous control group, and the case for a randomized controlled trial.

The benefits of EPP can only be proved if the best available combination is used[7]. At present the best results are with tri-modality therapy: chemotherapy for three cycles; radical surgery as described (removing the parietal pleura, mediastinal pleura, pericardium and diaphragm, en bloc with the lung); and radical radiotherapy. The tri-modality treatment plan set out above is so demanding and must be administered so selectively that it cannot possibly be evaluated other than within a randomized controlled trial against the best alternative active treatment.

The MARS (Mesothelioma And Radical Surgery) trial is now launched in the British Isles. This is a pilot study of 50 patients aimed at determining the feasibility and acceptability of performing an adequately powered randomized trial comparing EPP against no EPP surgery within the context of trimodality therapy. If successful, it will lead to a main trial, the aim of which is to determine if surgery is beneficial in terms of survival and quality of life. The target is to recruit 700 patients over three years into a worldwide trial.

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Radiotherapy for Mesothelioma

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Mesothelioma cells are relatively sensitive to radiotherapy, but the large target volume of the affected pleural surface, as well as toxicity to adjacent lung, heart, mediastinum, spinal cord and liver, limit the radiotherapy dose that can be given to attempt disease control or cure. Therefore, the effects of radiotherapy alone on prolonging survival in mesothelioma are minimal, with response rates as low as 3%, with significant mortality and morbidity.

***Prophylaxis against needle tract metastases*:** Prophylactic radiotherapy has been found to prevent malignant seeding at sites of diagnostic or therapeutic intervention in two studies, including a randomized controlled trial, where a 40% control group tumor rate was reduced to zero in the radiotherapy group (21Gy in three fractions over 48 hours, 10-12 days post-procedures)[1,2]. A delay in radiotherapy of more than two months was found to be associated with increased chest wall recurrence in a non-randomized study[3]. A recent study randomized patients to no radiotherapy or low dose single fraction radiotherapy (10Gy, within 15 days of the procedure) and found no significant difference in the incidence of tract metastases between the two groups, indicating single fraction lower dose radiotherapy is not effective[4].

Our center recommends that prophylactic radiotherapy is given to all patients with mesothelioma following any chest procedure, at a dose of 21Gy in three fractions. Radiotherapy is performed with electrons (10MeV), but if electrons are not available, 6MV photons with a 1cm chest wall bolus are used, or alternatively 200kV photons without a chest wall bolus. A field size of at least 4x4cm^2 per procedure site is used, with larger field sizes if there are adjacent biopsy or aspiration sites, all of which need encompassing within the treatment field. All biopsy and aspiration sites in potential mesothelioma cases are marked with Indian ink, so that radiotherapy fields can be adjusted to reliably incorporate all these sites. Further chest interventions outside the radiotherapy field are followed with further radiotherapy. We do not routinely treat patients with indwelling pleural catheters with prophylactic radiotherapy, although this was successfully done with no adverse catheter effects in one patient who developed tumor around the catheter insertion point. Prophylactic radiotherapy is well tolerated, with few adverse effects, although most patients describe mild tiredness and may experience mild skin irritation.

***Symptom palliation*:** Radiotherapy has an established role in symptom palliation, particularly for pain, but also

dyspnea, dysphagia, superior vena cava obstruction and brain metastases[5]. The newer technique of inverse planned stereotactic intensity modulated radiotherapy (IMRT) allows a homogeneous dose distribution in the target volume, with more accurate protection of the normal surrounding tissue, by dividing the treatment field of any beam direction into subfields with different intensity levels. No lung toxicity has been reported with this technique and the one year overall survival after radiotherapy was 18%. This approach may have a palliative role in patients, particularly those with a small tumor burden[6].

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The Etiology of Mesothelioma
Is there a Role for Simian Virus 40 (SV40)?

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Prior to Wagner et al's report of 33 mesotheliomas occurring among crocidolite asbestos exposed individuals in South Africa, many pathologists questioned if such a malignancy actually existed[1]. This arose since mesothelioma is an uncommon tumor that can occur with variable histological presentations making the malignancy difficult to recognize in the absence of a case cluster. It is perhaps the most important (and only) thoracic tumor whose identity and etiology was defined in the 20th century. A similar mesothelioma cluster was identified in Turkey caused by exposure to erionite, a fibrous zeolite.

The theory of a SV40 etiology for mesothelioma

A role for SV40 in human mesothelioma etiology was not suggested by a case cluster; but rather from the observation that injected SV40 caused pericardial mesotheliomas in hamsters[2]. Polymerase chain reaction (PCR) was then used to connect SV40 to human mesothelioma by amplifying small segments of the virus DNA (mainly 105 base-pair units) in a significant percentage of human mesotheliomas.

One explanation offered for the presence of the virus in these mesothelioma cases was that SV40 was a contaminant of the polio vaccine (raised in SV40-infected monkey kidney cells) and other vaccines used from the mid-1950 into the 1960s. Individuals with SV40-containing mesothelioma might have been exposed to the early vaccines or became infected from others who were exposed to SV40 tainted vaccine. The lack of SV40 in the mesotheliomas from countries not using the contaminated vaccine lent credibility to the vaccine theory.

What are the limitations of claiming an SV40 etiology for mesothelioma?

The most significant limitation is the lack of epidemiological evidence of an increasing age incidence of mesothelioma among the vaccinated population and the flat age incidence trend in women. In the United States, Price and Ware[3] estimated a total of 2,550 mesothelioma cases (2,000 males and 550 females) occurred in 2000. The mesothelioma incidence (not adjusted for age) was about 0.92 cases of mesothelioma (pleural plus peritoneal) per 100,000 population. For males, the mesothelioma rate was 1.4 per 100,000; for females the rate was 0.4 per 100,000. The background incidence of mesothelioma is so low, and the increase caused by asbestos exposure so large, that the asbestos-related incidence in males can be tracked in the general population. Males dominate the group occupationally exposed to asbestos, due to the trades in which such exposures occur. The trend among women is flat and there is no trend in the mesothelioma incidence which might suggest a role for SV40.

Arguments have been presented claiming Hill's criteria for association and causation have been met for SV40. But the most important aspect - an increase in mesothelioma incidence from SV40 - has not been met and therefore the causation argument is not convincing.

The experimental animals result and the SV40 sequences amplified from human mesothelioma tumors initially presented a compelling story. However, recent well controlled PCR experiments amplifying the regions

of SV40 important in transformation found them not to be present in a large series of mesothelioma cases from many regions of the world. Nor was the SV40 large T antigen expression, required for malignant transformation, found using immunostaining with highly specific SV40 antibody[4]. Lopez-Rios et al[5] reported that the high risks of false-positive is due to the presence of SV40 sequences in common laboratory plasmids.

SV40 may well rarely be a human carcinogen and there is interesting information to support this claim. While there were possibly exposures to SV40, from polio vaccine or other sources, these were insufficient to cause a detectable increase in mesothelioma. Thus the only well-established etiology of mesothelioma in USA and Europe remains the exposure to amphibole asbestos minerals (crocidolite, amosite, tremolite-actinolite asbestos and perhaps anthophyllite asbestos). There remain also the background cases of unknown etiology as described by Price and Ware[3].

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Gene Therapy for Mesothelioma

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Gene therapy involves the transfer of genetic material (cDNA, full length genes, RNA, or oligonucleotides) into somatic or germ line cells. The most common clinical application of gene therapy is for cancer treatment. Technology at present can only support local, but not systemic, delivery of gene therapy. A number of modalities have been explored, among which 'Suicide gene' therapy appears an attractive approach.

The most widely studied suicide gene is the herpes virus thymidine kinase enzyme (HSVtk). This enzyme converts the non-toxic nucleoside analogue ganciclovir into a phosphorylated form (GCV-P), and then to the highly toxic tri-phosphorylated (GCV-PPP) analogue by mammalian kinases. GCV-PPP passes to adjacent *untransfected* cells via gap junctions or via uptake by apoptotic bodies creating a bystander effect. In addition, the dying cells created an inflammatory environment that can stimulate anti-tumor immune responses.

Malignant pleural mesothelioma (MPM) is an especially good target for gene therapy because: 1) it is primarily a local tumor with metastases occurring very late, 2) no effective treatment exists, and 3) access to the pleural space can be gained easily. We choose to deliver the HSVtk suicide gene with an adenoviral vector delivery system. Adenovirus is a double stranded DNA virus that does not integrate into chromosomal DNA, causes mild human disease (colds) and has been used in vaccine trials. Adenoviral vectors can be produced in high titer for use in clinical trials, have a wide host range, do not require dividing cells, and are safe from the risk of chromosomal integration. Major disadvantages include transient gene expression and strong vector-induced inflammatory responses.

In 1995, our group conducted a series of dose-escalation phase I gene therapy trials using Ad.HSV.tk/GCV in 34 previously untreated MPM patients. All patients had post-therapy biopsies to document gene transfer. These trials demonstrated: 1) clear evidence of intratumoral adenoviral gene transfer; 2) no maximally-tolerated dose; 3) minimal, well-tolerated, toxicities, including transitory hypotension/hypoxemia post-vector delivery at highest dose. Radiographic tumor regression was noted in four patients. Two patients had near complete response and survived almost seven years with minimal residual disease and no additional anti-neoplastic therapy.

Due to limited transgene expression, production of anti-tumor antibodies in some patients, and the long duration of regression, we believe our results were probably due to immunological responses induced by Ad.HSV*tk* therapy, rather than direct tumor eradication via suicide gene. We therefore adopted a strategy of trying to elicit an anti-tumor immune response directly utilizing an adenovirus expressing an anti-tumor cytokine. We chose interferon (IFN)-ß for a variety of reasons. Type 1 interferons have been used for anti-tumor therapy and can activate the immune system against tumor cells: via NK cell and macrophage activation, T cell proliferation, and up-regulation of MHC Class I mediated tumor associated antigen expression. In preclinical studies, a single dose of Ad.muINF-ß to animals with established tumors (AB12) led to 100% survival.

In 2003, we initiated a Phase I dose-escalation trial of a single intrapleural instillation of Ad.IFN-ß into patients with mesothelioma or metastatic pleural disease. Ten patients (seven had mesothelioma) received a single dose of Ad.IFN-β at two dose levels after pre-treatment leukopheresis. The first three patients received ($9x10^{11}$ viral particles) of Ad.IFN-β, which were well tolerated: two patients developed lymphopenia. Two of three patients in this cohort are still alive 23 and 28 months after treatment. Four mesothelioma patients received a higher dose ($3x10^{12}$ viral particles): One experienced transient hypoxia (grade 3) but has survived 18 months since without complications. Three additional patients have been dosed at $9x10^{11}$ viral particles without evidence of serious adverse events.

We plan to begin a second phase I trial to deliver two doses of Ad.IFN-β vector seven days apart in patients with MPM and malignant pleural effusions. We will analyze this trial by assessment of 1) the overall toxicity; 2) the immune response of the tumor to the adenoviral vector; 3) efficacy of gene transfer; and 4) tumor response via CT and PET scanning.

Currently, progresses in gene therapy are limited by availability of effective and specific vectors. A feasible short term goal of pleural immunogene therapy is to maximize "bystander" effects while also taking advantage of the inflammatory effects induced by intrapleural vector injection. The long-term goals of the field include development of more efficient gene transfer technique and better understanding of tumor biology.

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IMAGES OF THE PLEURA

Renal Cell Cancer Metastasis to the Pleural Surface

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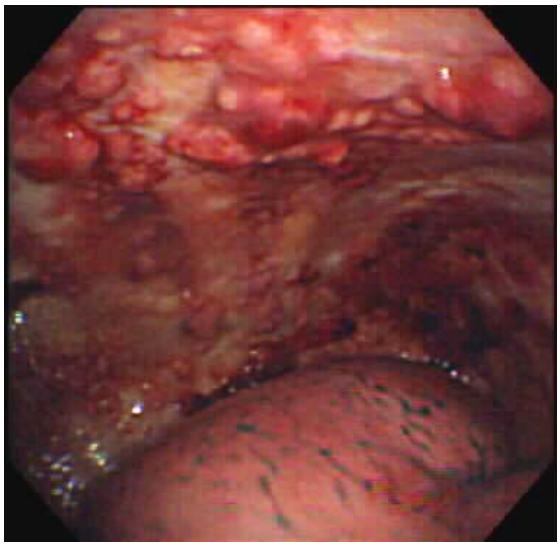

This image shows dense conglomerates of tumor mainly at the parietal pleural surface with the surface of the lung being relatively unaffected. The diagnosis in this 65 year old male with a recurrent effusion was metastatic renal cell carcinoma. The primary cancer was resected two years prior and the patient was symptom and disease free until dyspnea due to the effusion occurred.

Amongst malignant pleural effusions, renal cell carcinoma accounts for only a small proportion. A preponderancy of papillary tumor subtypes has been reported in small case series. The prognosis for these patients is poor and treatment is aimed at palliation mainly through pleurodesis.

If biological agents are considered in the treatment of metastatic disease in the patients with effusions, pleurodesis may best be performed before initiation of therapy. This can prevent worsening shortness of breath due to increased pleural fluid accumulation secondary to capillary leaks.

If you have any comment on the Newsletter or any interesting cases of pleural disease, contact:

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