Trimodality Therapy (Chemotherapy, Surgery, and Radiation) for Malignant Mesothelioma: Can Some Patients actually be Cured?

Malignant mesothelioma is a relatively rare but particularly deadly malignancy that arises from the lining of the pleural (chest) cavity or peritoneal (abdominal) cavity. About 70% of cases of mesothelioma are directly related to asbestos exposure, usually with about 30 or 40 years between exposure and diagnosis. While there are only about 2200 cases per year in the USA, this number is expected to increase over the next decade, as workers exposed to asbestos earlier in their lives eventually begin to manifest symptoms of the malignancy. After 2015 or so, this may begin to decline due to laws regulating exposure to asbestos in recent decades, but these laws don’t exist in the developing world, so mesothelioma is likely to be a worldwide problem for the foreseeable future.

The usual patient with mesothelioma presents with chest pain and/or shortness of breath, with x-rays showing thickening of the pleural lining with associated pleural effusion. Many times the fluid around the lung contains no cancer cells, so a biopsy of the pleura is necessary to make the diagnosis. It usually occurs only on one side; distant spread is unusual. So if it is technically “localized”, why is it so hard to cure? The main problem with mesothelioma is that most patients present with advanced disease that has no chance of curative treatment with surgery. In fact, mesothelioma is a malignancy that classically is not thought to be really “curable” at all. Surgery is usually used for palliation, to drain the fluid and peel the malignant rind away from the lung so that the patient can breathe easier and with less pain. Of course there are case reports or case series of patients with limited disease who can be aggressively treated with surgery and have lived >5 years (most oncologists’ definition of cure), but the reality is that these patients are few and far between. To date, studies of patients treated with surgery have shown about the same average overall survival as patients treated palliatively with chemotherapy alone (about 9-12 months).

This brings us to the study published this week in the Journal of Clinical Oncology by Dr. de Perrot and colleagues (abstract here). Since 2001, select patients with mesothelioma at Prince Margaret Hospital and Toronto General Hospital in Toronto, Canada, have been treated with an aggressive regimen that begins with 3 cycles of cisplatin-based chemotherapy followed by staging to see if they were still possibly resectable. If so, they underwent a surgery called extrapleural pneumonectomy (EPP), which is a huge surgery that removes an entire lung with the surrounding pleural cavity, pericardium, and hemidiaphragm as a single piece. After the surgery, patients were then given fairly high doses of radiation (50-60 Gy) to the entire half of their chest where the lung used to be. You can imagine that you would have to be pretty healthy to be considered for this treatment. In addition to having no metastatic disease and being healthy enough for surgery, all patients had to have what is considered to be favorable histology (epithelioid or mixed) with no sarcomatoid histology, which has a dismal prognosis.

All in all, 60 patients since 2001 were found to be eligible for this regimen. We don’t know how many patients with mesothelioma were seen in Toronto to get down to these 60 patients, but
my guess is that this was less than half of all comers. 53 of them made it through three cycles of chemotherapy, 45 patients made it to surgery, and 41 were able have all visible tumor removed. Only three patients died from the surgery, which is actually pretty impressive, although 1/3 of patients had major complications. 30 patients (down to 50% already) underwent the post-operative radiation course.

The median overall survival for this group was 14 months. To compare, the median survival in the only phase III randomized trial of chemotherapy alone (cisplatin and Alimta) in mesothelioma was 12.1 months. Let’s look at the curves from the 2 trials (trimodality on the left, chemo alone on the right), highlighting only the first 2 years.

![Graph showing survival curves](Click to enlarge)

If you’re saying “Gee, those look pretty similar”, you would be correct. The difference is in the tail of the curve (red box). Essentially no patients treated with chemotherapy survive even to 2 years, much less 5 years, whereas in the de Perrot paper 10% of patients were still alive at 5 years! By looking even closer at the patients in the study, they were able to piece out which patients had a better chance of long-term survival with trimodality treatment. Turns out it is the patients who had no involvement of the mediastinal lymph nodes (N2 nodes) who did well (see below), with a median survival of 59 months with trimodality treatment versus 8 months if they were unable to complete the treatment.
They also found that less invasive tumors (T1-2) did better than more invasive tumors (T3-4), and that epithelioid histology did better than mixed histology. So what can we take away from this? It would appear that it is possible for some patients, specifically those with no mediastinal nodal involvement, to be cured of malignant mesothelioma with aggressive trimodality therapy. But I think it is important to emphasize that this is a tiny proportion of the mesothelioma patients who walk in the door who would be eligible for this treatment. Only 50% of this highly selected population made it through all of the treatment, and if they couldn’t complete the regimen they had an identical survival to patients who had chemotherapy alone. In conclusion, I do think there is a role for surgery in mesothelioma and any advancement that leads to cures in this terrible disease is fantastic, but until this can be applied to a larger percentage of the patients I think it will remain out of reach for most patients.