Should Lawyers Advise their Meso Clients on Treatment Options?

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Manning the Oars

A mesothelioma client[1] is on a ship whose hull has been breached. His first instinct is to rush for the nearest medical "lifeboat" that promises to extend his life. Do lawyers have a duty to advise their meso clients about the best available medical treatment "lifeboat?"

Every lawyer who represents mesothelioma clients knows that the patient and his family are in the throes of crisis. We know that eventually the tumor will take our client's life. We also know that the tort system puts a premium on a longer "damaged" life. The longer a terminal patient lives, the greater the damages, and the greater chance the case will be resolved at, or near, trial, where settlement values usually peak.

The "longevity" premium is especially high in California, where the law allows an *in extremis* plaintiff to get to trial within four months, but then penalizes his estate if the cancer kills him before the jury renders a verdict.[2] The legislature has exacted a "penalty" of sorts by stripping the family of any right to recover damages for the pain, suffering, disfigurement, and anguish that their mortally wounded loved one endured while alive.

Regardless of intent, the California legislature has rewarded tortfeasors whose bad conduct kills instead of maims — (hence, the sick joke here: "If you run your car over a guy, check the rear view mirror. If he's still moving, shove it in reverse.") In the litigation world of winners and losers, if the measure is strictly money, the defendants enjoy an economic windfall when their victim perishes. The victim earns a chance at a full recovery only if he survives, and thus lawyers clearly have a pecuniary interest in their client's longevity.

To Live and Die in Los Angeles: A Premium on Life

From July 2000 to September 2007, our firm represented 37 living mesothelioma clients whose personal injury cases were filed in Los Angeles. Of those, 40.5 percent died before their case was resolved. *See Charts A1-A3, "To live and die in Los Angeles Superior Court" on page 5.* Some died before their depositions while others died right before trial, just as we began to seriously engage in settlement negotiations. When our clients died, the defendants either took their settlement offers off the table or slashed them to the bone. Clearly, in California and in Oregon[3], which limits the recovery in a death case, plaintiffs' lawyers again have an interest in their client's longevity.

It's intuitive that the longer a meso patient lives, the more therapies he will pursue, and the more medical costs he will incur. As lawyers, we need to know about the various therapies and their respective costs, if only so that we can present the jury with future medical costs, which can be enormous. An *ad hoc* body of meso medical experts in 2006 presented Congress with anecdotal data to defend the common sense supposition that for meso patients to get more life, it takes more money. The group argued against the proposed $1.1 million one-size-fits-all matrix award to mesos irrespective of age, wage loss, and dependents, because in select cases this would not even cover the patient's medical bills. The group cited instances in which "long term" survivors had medical bills for multi-modal therapies ranging from $201,000 to $1.4 million. *See Chart B, "Longer life, bigger bills: medical costs for 14 meso victims" on page 6.*

Our experience with medical bills for long-term survivors is even more dramatic. The average past and present medical bills for the

Charts A1-A3: To Live and Die in Los Angeles Superior Court

The Law Offices of Roger G. Worthington, P.C., has filed 37 living mesothelioma cases in Los Angeles, California from July 19, 2000, to September 21, 2007. See Chart A1 below.

- Of those 37 cases, 15 clients, or 40.5 percent, died before or during trial, showing the desperate need for a speedy trial setting* and resolution of the patient's claim because the victim earns a chance at a full recovery only if he survives. For these patients, justice delayed is literally justice denied.
- Of the 15 clients, 11 clients died before or during trial. See Chart A2 on page 6.
- Of the 15 clients who died before trial, 4 clients died before they were even able to secure a trial date. See Chart A3 on page 6.

*Under California law, the courts are required to set cases for trial if the plaintiff is over the age of 70 or the plaintiff produces a declaration in which a medical doctor opines that there is substantial medical doubt that the plaintiff will survive six months [C.C.P. §34 (d)]. Typically, the motion for preference is filed after the defendant appears in the case, which usually takes six weeks.

last 10 meso cases set for trial in Los Angeles was $308,000. The low was $216,000 and the high was a whopping $2.4 million for a 72 year-old, three-year survivor who pursued multiple therapies. *See Chart C, "Verified medical bills for nine RGW, PC living meso clients, 2007" on page 6.*

Lawyers can present the jury with reasonable and medically necessary bills for *past* medical services. It's more difficult to present evidence of *future* costs. If our client belongs to a defined treatment protocol, and is somewhere in the middle of it, it's easier to assess the future costs on a case-by-case basis, if you have a knowledgeable treater. The problem is that in the real world, meso patients must be opportunistic and "light on their feet," swiftly and smartly shifting from one regimen to a newer and more promising one. If medical experts could agree on a standard of care that utilizes a uniform treatment protocol we conceivably could put on credible evidence of future medical costs in *every* case.

Lawyers have stronger cases with longer-living meso clients, and we should therefore deeply care about the treating physicians and the treatment options the client pursues. That said, how do we go about learning what the best options are?

I Want More Life

For meso patients, the crux of the crisis is how to buy more time. How can we as lawyers help, if at all? Medical, logistical, and philosophical questions abound: how bad is the tumor? What treatment options are there? Are they any good? How much do they cost? Is one form of surgery better than another? Is surgery even necessary? If my client gets radical treatments, can he still endure a grueling two-week deposition? Can he make it to trial? Can he still play golf, hike, bike, or putter with his grandkids? What's his quality of life going to be? How long has he got?

Where does the patient or the lawyer look for answers when the data are confusing, when there are no clear answers, and when there is no

Chart A1: 37 Living Meso Cases filed in Los Angeles Super. Ct., 7/2000-9/2007

Client	Date Filed	Trial Date	DOD	DOB
TH	07/19/2000	12/18/2000	12/23/2000	02/17/1942
SS	06/13/2001	01/07/2002	11/29/2001	01/01/1927
SM	01/03/2002	07/29/2002		12/05/1938
ES	02/07/2003	08/27/2003	08/22/2003	07/23/1939
EE	10/09/2003	05/11/2004		10/20/1938
BT	12/03/2003	09/08/2004		07/19/1944
DM	03/23/2004	08/23/2004	09/18/2004	07/27/1927
LV	09/28/2004	03/15/2005	04/14/2005	02/21/1943
MM	04/21/2005	11/01/2005	10/15/2005	12/09/1926
RW	07/08/2005	08/09/2006	06/11/2006	01/06/1946
HH	09/27/2005	04/27/2006		01/03/1931
VL	11/01/2005	07/05/2006		08/12/1925
WS	11/01/2005		02/09/2006	07/31/1937
JM	11/09/2005	06/26/2006	10/07/2007	04/27/1946
SB	11/15/2005	04/27/2006		01/12/1935
GK	02/01/2006	08/21/2006	01/08/2007	11/04/1934
AB	02/17/2006	08/30/2006		08/04/1931
NL	04/27/2006	10/04/2006	07/17/2006	11/30/1943
DH	05/26/2006	12/19/2006		04/04/1954
JB	07/20/2006		11/25/2006	04/28/1943
EH	08/04/2006	03/26/2007	12/18/2006	06/03/1940
BH	08/25/2006	03/26/2007		11/15/1927
RL	10/11/2006	10/10/2007		09/22/1938
AC	11/17/2006	07/23/2007		11/24/1938
GP	12/06/2006	04/30/2007	02/02/2007	09/27/1938
LG	01/16/2007	08/11/2008	02/05/2007	04/04/1932
EG	01/25/2007	01/07/2008		12/17/1956
FC	01/31/2007	09/17/2007		02/12/1944
EB	03/12/2007	10/22/2007		09/10/1932
FM	03/16/2007	10/15/2007		12/03/1926
JG	04/09/2007	04/14/2008		11/08/1958
JO	06/19/2007	01/02/2008		09/14/1927
OB	06/21/2007	02/13/2008	11/01/2007	10/20/1933
BS	07/10/2007			09/20/1950
CR	07/11/2007	03/17/2008		07/27/1937
KK	09/04/2007			10/11/1938
AT	09/21/2007		10/02/2007	07/08/1934

Chart A2: 29.7 percent died before or during trial

Client	Age	Filing Date	Trial Date	DOD
TH	58	07/19/2000	01/24/2001	12/23/2000
SS	74	6/13/2001	01/07/2002	11/29/2001
ES	64	02/07/2003	08/27/2003	08/22/2003
DM	77	03/23/2004	08/23/2004	09/18/2004
LV	62	09/28/2004	03/15/2005	04/14/2005
MM	78	04/21/2005	11/01/2005	10/15/2005
RW	60	07/08/2005	08/09/2006	06/11/2006
NL	62	04/27/2006	10/04/2006	07/17/2006
EH	66	08/04/2006	03/26/2007	12/18/2006
GP	68	12/06/2006	04/30/2007	02/02/2007
OB	74	06/21/2007	02/13/2008	11/01/2007

Chart A3: 10.8 percent died before even obtaining a date for trial

Client	Age	Filing Date	DOD
WS	68	11/01/2005	02/09/2006
JB	63	07/20/2006	11/25/2006
LG	74	01/16/2007	02/05/2007
AT	73	09/21/2007	10/02/2007

Chart B: Longer Life, Bigger Bills — Medical Costs for 14 Meso Victims

Name	Gender	Diagnosis Age	Status	Age at Death	Medical Costs	Diagnosed
E.B.	MALE	44	Deceased	45	$201,626.77	12/08/99
J.D.	MALE	34	Living	N/A	$238,557.90	11/22/99
T.L.	MALE	46	Deceased	48	$258,078.11	06/05/03
C.R.	FEMALE	49	Deceased	53	$260,238.55	11/15/01
R.P.	MALE	44	Deceased	46	$261,891.19	03/17/00
J.P	MALE	51	Deceased	53	$292,254.78	01/26/00
R.T.	MALE	59	Living	N/A	$414,409.57	10/01/03
K.W.	FEMALE	54	Living	N/A	$450,740.11	02/17/99
B.W.	MALE	52	Living	N/A	$555,000.00	04/02/03
R.O.	MALE	32	Deceased	33	$576,124.90	11/12/00
P.B.	MALE	57	Deceased	59	$731,854.12	03/13/02
K.A.B.	MALE	51	Living	N/A	$1,243,237.00	06/08/01
D.C.	MALE	15	Deceased	19	$1,249,649.42	04/04/99
K.H.	MALE	56	Deceased	57	$1,439,696.61	01/11/02

As reported by the Doctor-Patient Alliance in their report to Congress of June 30, 2005, above is a list of actual medical costs for 14 mesothelioma patients. These figures do not include out of pocket costs, travel and lodging, or other incidentals such as OTC drugs. The complete letter can be found at www.mesothel.com/pages/alliance_policy_paper.htm.

Chart C: Verified Medical Bills for Nine RGW, PC Living Meso Clients, 2007

Name	Age	Venue	Treatment Costs	Trial date
NL	62	Los Angeles Cty., Calif.	$576,367.00	10/04/06
TR	57	Pierce Cty., Wash.	$278,953.00	Died before trial setting
GD*	73	Multnomah Cty., Ore.	$216,479.77	10/24/07
RS	57	Los Angeles Cty., Calif.	$252,753.00	07/02/07
MS	73	Multnomah Cty., Ore.	$275,181.02	12/07/07
EB	75	Los Angeles Cty., Calif.	$265,512.00	10/22/07
SB**	72	Los Angeles Cty., Calif.	$2,400,000.00	04/27/06
FM	80	Los Angeles Cty., Calif.	$256,336.00	10/15/07
AC	69	Los Angeles Cty., Calif.	$315,786.00	07/23/07

* Died during trial. Under Oregon law, the decedent's estate's recovery is limited to $500,000 for non-economic damages. O.R.S. § 31.710
** Medicare lifetime healthcare reimbursement of $2.1 million was surpassed. The jury awarded $12 million for pain and suffering and $600,000 for past medical expenses.

The number is Chart C were actual medical costs compiled while the client was alive at a time near trial, and do not include anticipated future medical costs.

standard of care? Where do you look for answers when the doctors may not even know?[4]

Let's step into the breached hull of a meso patient and try to pick the best lifeboat. He's just been diagnosed. Water is pouring in. Now what?

Searching for a Lifeboat on a Sinking Ship

If the ship is going down, your first instinct is to grab for the nearest lifeboat. If you had time to reflect, though, you might ask: how bad is the breach? How much water have we taken on? Can it be repaired? How fast? Are the bilge pumps working? And what about the lifeboat itself? Is it stocked with provisions? Is it seaworthy? As with the sinking ship, with asbestos cancer you need to assess or *stage* the damage at the same time that the damage is escalating out of control.

Staging a tumor is complex. Meso doesn't thrive as a solitary ball-type nodule. It's diffuse. It spreads, usually within the confines of the pleural space – if the patient is "lucky" – otherwise, by itself or during surgery (including needle biopsy) it can spread like wildfire. Oftentimes we won't truly know the proper stage until after radical surgery, when lymph nodes are dissected, as few doctors require mediastinoscopy before surgery, and PET scans, though helpful, are not reliably diagnostic of nodal invasion. There are at least five different types of meso, some more amenable to treatment than others, and there are at least six different tumor-staging systems with no uniform use among doctors. It's like trying to get the same answer from six different people, none of whom speaks the other's language.

Regardless of the staging system, common sense teaches that the earlier the stage, the higher the survival on average.

Let's say we have an accurate fix on the size, type, and extent of the pleural cancer: an early stage epithelial tumor that hasn't invaded any surrounding organs or any lymph nodes, and the patient is a male in his early 60s. Let's assume further that the patient is aware of multiple options such as chemotherapy and radiation, but at the outset wants desperately to rid his chest of the beast.

Our patient's threshold decision is whether to hook up to chemotherapy or jump right into radical surgery. He must make this decision while his ship is taking on prodigious quantities of water. Amidst the mayhem, he must get to, and choose, a lifeboat. Even if the waters were calm and he had the luxury of time, 19 years of watching how these decisions are made make it clear that the client's decision still involves a throw of the dice when compared to decision-making in other cancers.

The problem is a lack of reliable data. Few surgeons are at the forefront of mesothelioma treatment and they often have little incentive to publish the results of their work. Since mesothelioma is an uncommon cancer, research money is scarce. Everybody talks about the merits of randomized clinical trials, but few treatment centers have the funds to finance them, and fewer still have been willing to set aside ethical concerns and design and recruit for one.

Another theory is that some centers or doctors may worry that their "treatment program," if subjected to rigorous outside scrutiny, could be shown to be ineffective. Those who do publish are always at risk of criticism for "cherry picking" because the pool of patients is so small, the outcomes so often fatal, and because a patient – if he's lucky – may over a 3-4 year survival period seek different treatments from different hospitals. Very few surgeons or oncologists "quarterback" their patient from start to finish. If it's a daunting obstacle for doctors, it's even more daunting for lawyers.

A common approach is to look at the work of leading surgeons and pick the surgery that advertises the longest survival time. Unfortunately, surgical studies are typically retrospective rather than prospective and lack a non-surgically treated comparison group,[5] so it's impossible to say whether surgery actually helped. The advent of chemotherapy, used alone and used in combination with surgery, opens other vistas…and new horizons of uncertainty.

Deciding which lifeboat to take isn't just hard for the patient, it's hard for the doctor as well. Treatment ranges from doing everything to doing nothing. If the doctors are divided, how can a lawyer possibly give sound advice? And if the doctor and lawyer are confounded, how can a patient ever hope to get through the maze?

iMedicine: The Quest for Good, Solid Data

The meso client's first step is to hop on the Internet, where his beleaguered boat is quite often capsized by a monster wave of information, pseudo-information, and misinformation. His first task is to begin ruling out bad options like the unregulated nostrums in the Bahamas and Tijuana.

However much time this takes, the client finally concludes that although there is no single option, surgery is most often the bedrock of a successful meso treatment *plan*. The most recent study examining mesothelioma survival reviewed 939 cases and showed that surgery plus other treatments is associated with a median survival of 20 months.[6] And although there is no consensus on the best way to treat mesothelioma, the International Association for the Study of Lung Cancer makes clear that the goal is maximal tumor debulking in patients who are candidates for surgery.[7] That is, leave no *visible* chunks of tumor behind. There was *no* agreement among the experts, however, about the optimal type of surgery, the need for radiation therapy, or the need for combined modality treatment incorporating chemotherapy.[8]

So the one thing we think we know—that surgery extends survival—we don't really know. Flaws in past data and the development of new techniques mean that the intuitive choice of surgery—cut the tumor out—won't be validated until a true randomized prospective trial has been done. Just such a trial is underway in the United Kingdom, although even this groundbreaking study will only test the extra-pleural pneumonectomy (EPP) and not the lung-sparing pleurectomy/decortication(PD).[9]

Until those results, how is a patient to decide, as the clock ticks and water fills the engine room?

Choices: The Good, the Bad, And the Ugly

Mesothelioma defies quick fixes. It has a long incubation period, its symptoms are often interpreted as pneumonia, it's a soft and diffuse tissue, the diagnosis is not easy, the time from diagnosis to treatment is harrowingly short, it commonly afflicts elderly patients in their 70s and 80s, and it is associated with co-morbidity factors such as heart and lung disease that make aggressive treatment risky at best.

The medical seascape reflects this violent storm of circumstances, as doctors vacillate between two extremes. Some surrender to nihilism and counsel that the ship is quite literally sunk. Others subscribe to the radical interventions of slash, burn, and poison, otherwise known as surgery, radiation, and chemotherapy. Most agree that, left untreated, the patient will almost certainly die in a median of nine months.[10]

On top of that, for many patients, the first concern is insurance. Will their HMO or Medicare cover a non-standardized series of treatment by out-of-plan doctors? Most won't. Many doctors will tell a patient that they don't need to go to UCLA or Brigham and Women's Hospital in Boston because they have a perfectly good thoracic surgeon in the neighborhood who, by the way, has only done one or two, if any, radical surgeries in his entire career.

Chemotherapy: The Standard of Care?

In 2004, the FDA approved Alimta for the treatment of mesothelioma. Before that, there was no drug that had been approved specifically for meso, and most patients were steered to multi-modal therapy protocols that included radical surgery. Oncologists and Eli Lilly touted Alimta/Cisplatin as the new "standard of care." A large randomized trial showed that the Alimta/Cisplatin regimen offered about 12.1 months of life while Cisplatin alone offered about nine. Since then, many surgeons have commented that they are seeing fewer patients, as primary care doctors have begun to bypass surgeons and refer their patients directly to the town oncologist.

Experts in the field continue to differ, and most, like thoracic surgeon Dr. Raja Flores, agree that "controversy still exists with regard to standard care."[11] The reason that experts disagree is that promising results and longer lives seem to result from multi-modal therapy, which uses chemotherapy in conjunction with some form of surgery. *See Chart D, "Cocktails and Single Shots: Measuring Drugs by the Numbers," on page 8, which provides an overview of available drugs and median survival times.* Critics note that the University of Chicago Alimta/Cisplatin study that led to FDA approval barely reached levels of statistical significance,[12] prompting some to conclude that if Alimta/Cisplatin is the standard of care, it's not by much.

Clinical Trials: More Drug Cocktails

Bewildering, experimental, little accountability, less data, and fraught with complex rules for eligibility, clinical trials are sometimes the only hope a meso patient has. Most involve combinations of drugs. By definition, as "experimental," there is little, if any, data about survival times or recurrence rates. On the other hand, cost is rarely a factor, as the sponsor of the trial normally supplies the drugs and the attendant medical care.

A full listing and description is available in Chart E, "Best web resources for clinical trials" on page 8. There are about nine trials in the U.S. still

recruiting patients. Your client and his doctor should look at each one carefully.

Multimodal Therapy: The Kitchen Sink Approach

Since there is no silver bullet, doctors have combined different treatments, hoping that the mixture of therapies will provide a lifeboat. Multimodal therapy, which uses surgery as the bedrock and adds chemotherapy or immunotherapy with radiation, is associated with longer survival in younger, early stage mesothelioma patients.[13]

Multimodal therapy based on surgery appeals to common sense and to the approach with other cancers: extract the monster from the chest, and then blast all remaining traces with radiation or drugs. It also appeals to thoracic surgeons, who make their living cutting. Just when it seems like the lifeboat choice is getting clearer, though—at least we know we need surgery—new issues arise, buffeting the boat harder than ever.

The three surgical options are talc pleurodesis (TP), pleurectomy/decortication (PD), and extrapleural pneumonectomy (EPP). That much is easy. But here's the kicker: "There are no randomized studies comparing these techniques [TP, PD, EPP] and results are generally found in retrospective series that often used different staging systems, further confounding comparisons."[14] The effect of surgery on mesothelioma is unclear because there has never been a randomized, controlled clinical trial to determine whether PD or EPP improves the survival of patients or even effectively palliates the symptoms of the disease.[15] To compare techniques and decide which one is better, there must be a trial that randomly assigns some patients to a treatment group, and others to a nontreatment group. This is the only way to answer the question, "How much better is this than that?"

It's important to understand what these experts are saying — because you can't reliably compare patients, and you can't reliably compare treatments versus non-treatments, you therefore can't reliably compare outcomes. *An educated guess at best, a roll of the dice at worst.*

But which guess is best? Multimodal therapy is associated with increased survival, and most patients with early stage, lymph node negative tumors will seriously consider surgery. At this point, the lawyer *as patient-advocate* can help.

Talc Pleurodesis (TP): Stem the Effusions

Though talc pleurodesis is not always recognized as a "treatment" for malignant mesothelioma, some researchers have shown that unselected survival data is comparable to highly selected surgical series of combined pneumonectomy, radiation, and chemotherapy.[16] *Chart F, "Talc Pleurodesis," located on page 9, provides an overview of this treatment option.* Most agree that the TP is very effective in retarding recurrent pleural effusions. Myths abound about whether a meso patient post-TP is eligible for a pleurectomy/decortication, but the truth is a careful surgeon won't be deterred, unless perhaps the TP included a lung biopsy or other procedure that opened up the lung or chest wall to deep tumor invasion.

Chart D: Cocktails and Single Shots — Measuring Drugs by the Numbers

Cytotoxic Agent	Median survival
Methotrexate-alpha interferon-gamma interferon	17[1]
Interleukin-2	15.8[2]
Cisplatin-epirubicin	13.3[3]
Cisplatin-pemetrexed (Alimta)	12.1[4]
Cisplatin-raltitrexed	11.2[5]
Ranpirnase	11[6]
Methotrexate	11[7]
Vinflunine	10.8[8]
Vinorelbine	10.6[9]
Doxorubicin	7.3[10]
Gemcitabine	9.5[11]
Cisplatin	9.3[4]
Oxaliplatin-raltitrexed	9.3[12]
No surgery or chemotherapy	7[13]

We were able to find treatment costs for Alimta/Cisplatin only, which is as follows: Every course consists of six cycles. A patient may receive up to three courses, for a total of 18 cycles. The estimated cost for one course is between $60,000 and $80,000.

Chart D Footnotes

[1] Halme et al, Br J Cancer. 1999 Aug; 80(11):1781-5. Study included 26 patients.
[2] Castegneto B et al, Lung Cancer. 2001 Feb-Mar;31(2-3):303-10
[3] Berghmans et al, Lung Cancer. 2005 Oct;50(1):75-82. 69 patients in this study.
[4] Vogelzang et al, J Clin Oncol. 2003 Jul 15;21(14):2636-44. The only FDA-approved treatment for malignant pleural mesothelioma is a chemotherapeutic doublet of cisplatin and pemetrexed (Alimta). Addition of folic acid and vitamin B12 in the Vogelzang study cited here significantly reduced toxicity without adversely affecting survival time. In the study, 2/3 of patients were epithelial type, and 78% were stage III or stage IV. Only patients ineligible for surgery were used. Results were not based on a full intention-to-treat analysis, and were reported as being only fractionally inside the range of statistical significance.
[5] van Meerbeeck et al, Proceedings of the American Society of Clinical Oncology, 2004. Abstract 7021.
[6] Vogelzang et al, Program and abstracts of the American Society of Clinical Oncology 36th Annual Meeting; May 20-23, 2000; New Orleans, Louisiana. Abstract 2274. Pemetrexed is approved for use in the United Kingdom by the National Institute for Health and Clinical Excellence, Reuters, July 9, 2007. Pemetrexed with cisplatin is the standard of care for mesothelioma in Australia, www.ohsrep.org.au.
[7] Solheim et al, Br J Cancer. 1992 Jun;65(6):956-60. Study included 60 patients.
[8] Talbot et al, J Clin Oncol. 2007 Oct 20;25(30):4751-6.
[9] Steele et al, J Clin Oncol. 2000 Dec 1;18(23):3912-7. Study included 29 patients.
[10] Lerner et al, Cancer. 1983 Dec 1;52(11):1981-5.
[11] Byrne et al, J Clin Oncol. 1999 Jan;17(1):25-30.
[12] Fizazi et al, J Clin Oncol. 2003 Jan 15;21(2):349-54.
[13] Herndon et al, Chest. 1998 Mar;113(3):723-31.

Radical Surgery: Keep the Lung? Or let it go?

Several studies have examined the issues associated with mesothelioma treatment and survival. *See Chart G1, "Six recent studies on meso surgery—a toss up?" on page 10.* Take a look, but don't take comfort that the best and brightest are on the case. Few of these trials are available in the U.S., where research money for meso is depressingly tight.

"The mother of all clinical trials?", *Chart G2 on page 11*, lists the only randomized clinical trial ever held to test the efficacy of meso surgery versus non-surgery. Unfortunately, the trial only tests EPP and is only available in the United Kingdom.

Chart E: Best Web Resources for Clinical Trials

◆ NIH Clinical trials ... www.clinicaltrials.gov/
◆ NCI Clinical trials ... www.cancer.gov/clinicaltrials

Chart F: Talc Pleurodesis

Title	Patient Group	Results	Conclusions	Reference
Thoracoscopic Talc Poudrage in Malignant Pleural Effusions: Effective Pleurodesis Despite Low Pleural pH	25 meso patients in a prepaid, closed-panel health maintenance organization	Pleurodesis was successful in 22 of 25 (88 percent). There were no thoracoscopy-related deaths.	TP is an effective technique in malignant pleural effusions. The short hospital stay and high success rate make this approach a good choice in palliating symptomatic malignant pleural effusions.	Aelony et al, Chest. 113:1007, 1998.
Extrapleural Pneumonectomy	A review of several studies, total patient group not specified.	Talc pleurodesis facilitates extrapleural dissection at the time of EPP and may also prevent intraoperative spillage of malignant cells that may increase the risk of local recurrence.	It is best to proceed with the EPP within 2 to 3 weeks after pleurodesis.	Miller D, CTSNet, 2003.
Medical Thoracoscopy (Pleuroscopy)	A review of several studies, total patient group not specified.	Successful prevention of pleural effusions occurs in 90-100 percent after talc pleurodesis. Recurrences of effusions are infrequent. When followed until death, there was no recurrence in 81 percent. Recurrence mean time of 17 months after pleurodesis.	Unselected survival data for TP is comparable to highly selected surgical series of combined pneumonectomy, radiation, and chemotherapy.	Aelony et al, American Thoracic Society, 2005.
Prolonged Survival After Talc Poudrage for Malignant Pleural Mesothelioma	26 meso patients from a database of 228 patients with recurrent pleural effusions.	Mean survival after TTP was 23.8 +/- 16.3 months (median 19.4, range 2.9-68). Pleurodesis alleviated dyspnea in all patients. No perioperative deaths and one postoperative complication (pneumonia) occurred. Mean hospital stay was 3.9 +/- 2.7 days	TP remains a safe, low-morbidity, inexpensive primary palliative treatment option for malignant pleural mesothelioma and a valid control arm option for therapeutic trials. TP is ideal for patients who wish to avoid thoracotomy, long hospital stays and morbidity from multimodality therapy.	Aelony Y, Respirology. 10:649, 2005.

"Keep the lung or lose it? A comparison of the PD and the EPP," Chart G3 on page 12, breaks down the key differences between the two surgeries. Read it closely. Many of us have been taught that PD is "palliative," a word that suggests the operation is hardly worth the effort, like putting a band-aid on a gashed hull. Many of us presumed that the only chance a meso had for a five-year survival was to head to Boston and have his lung amputated. And yet the published data surprisingly shows that in many cases the PD numbers are better than EPP's. In truth, all surgical procedures to date could and should be considered "palliative."

Why surgery? Surgery designed to remove all possible tumor-invaded or contaminated tissue is *radical surgery.* Because meso is a diffuse tumor, and because surgery itself can spread the cancer cells, in order to eradicate all tumor the surgeon would have to cut out the ribs and intercostal muscles, the pleura, lung, trachea, pericardium, diaphragm, esophagus, superior vena cava, aorta, subclavian artery and vein, nerves, and vertebral bodies.[17] Essentially, whack out everything below the neck and above the gut, and you'll be "cancer free." You'll also be dead.

Both PD and EPP are controversial in that no randomized clinical trial validates either over the other, or even over no treatment at all. The medical benefit of EPP over PD has never been shown, although there are good indications that PD is associated with longer survival. Some surgeons perform both the EPP and the PD. Indeed, Boston is regarded as the home of the EPP, but recently Dr. Sugarbaker's team has been offering the PD as well. How does a "switch hitter" surgeon decide which operation is best? Dr. Harvey Pass of NYU has said he can't really tell until he pops the hood and takes a look inside. Apparently, the more "bulky" a tumor is, the less inclined the surgeon is to do the PD. The problem is that there is no standardized "bulk" threshold, i.e., how heavy and how extensive, questions which can probably only truly be answered if the tumor is cut away from the lung, either intraoperatively via the PD or later after the tumor-encrusted lung has been amputated. As with obscenity, for the bulk-sensitive surgeon, you just know it when you see it.

> "If a patient has a big, bulky tumor, you need to use EPP, period."
>
> -Dr. Raja Flores, M.D., thoracic surgeon and surgical oncologist

With the advancement of science, the sun usually sets on ultra-aggressive surgeries. Radical surgery for breast cancer, sarcomas, and colonic cancer have all evolved into narrower, meticulous operations. There is reason to believe that

meso surgery will eventually conform to this approach, favoring the meticulous and careful surgery of the PD.

Even then, it's clear to us that, just as not all EPP's are performed with equal skill, neither are all PD surgeries. At a recent MARF conference in Washington, D.C., an oncologist informed the largely patient audience that the PD was a relatively "quick" procedure.

We've witnessed three PD's performed at UCLA. From opening to close, each took about ten hours of painstaking and meticulous surgery in order to remove all visible tumor from the chest, while sparing the lung, diaphragm, and pericardium.

During one procedure, another surgeon walked in, saw the massive operation, checked his watch, shook his head and half-joked: "I'll bet you could amputate the whole thing and get three of these operations done in the time it takes you to do one." It turns out that this jest hits close to the truth, as Medicare pays a higher reimbursement to the surgeon who does the EPP over the PD. As working people like to say, "The less you work, the more you get paid."

Survival: The Golden Ring

Patients are hesitant to give up a lung, and this ends up being the strongest argument for them to go with PD. The issue of greatest concern to patients, "Will I survive the operation?" falls squarely in the PD camp. The numbers vary between surgeons, but the literature shows that surgical mortality for the PD is substantially less than the EPP (with less physiologic stress as well)[18], while another study of 384 patients showed deaths from PD at 3 percent, as compared to 5 percent for EPP.[19]

In addition, doctors agree that it's only a matter of time before the tumor recurs. Patients tend to like their chances better if they have two lungs instead of just one. And the distinction between whether the tumor recurs "locally" in PD or "distant" with EPP is not terribly important, as the seeding of tumor during surgery makes virtually every body cavity "local." The lawyer should also note that since the asbestos fibers are distributed between the left and right lungs, if the left lung is removed (or vice versa), experience shows that the same

Roger Worthington, far right, witnessing a pleurectomy with decortication as performed by Dr. Robert Cameron

Chart G1: Six Recent Studies on Meso Surgery — A Toss Up?

The following studies attempt to correlate median survival, surgical mortality, and prognostic factors with the PD and EPP.

Objective	Patient Group	Results	Conclusions	Reference
Compare outcomes of PD v. EPP\ Non-randomized study	57 patients. EPP (45); PD (22)	PD patients much older than EPP patients (median age 62 v. 58); Mean survival for PD: 16 mo v. 15 mo for EPP	Sparing lung in older group does not compromise survival. Hospital ceases to do EPP in N2 cases; stages new patients with mediastinoscopy.	Martin-Ucar et al, Europ Jrnl Cardio-Thor Surg. 31:5, 2007.
Compare outcomes of PD v. EPP Non-randomized study	663 patients from 3 large hospitals (1990-2006); avg. patient age 63	Median Survival for EPP: 12 mo (385 pts); PD: 16 mos. (278 pts). EPP patients 20 percent higher risk of death. Both groups similar rate recurrence.	PD better outcomes, but PD patients earlier stage (Flores). Non-epithelioid tumor 50 percent increased mortality; stage 3 & 4 90 percent higher mortality.	Flores et al, Am Assoc Thoracic Surg, annual mtg. Sept. 2007.
Phase II study to investigate four modality treatment late stage MPM Non-randomized study	49 patients, stage 2-3, 1999-2004. Treated with: pre-op interleukin-2, PD, post op epidoxorubicin + interleukin-2 + systemic chemo (gem/cis) + subcutaneous Interleukin-2	Mean age: 61; No surgical morbidity. Median survival after 59 months is 26 months; 13 patients still alive.	Quad-modal therapy feasible, well tolerated, and produced favorable median survival. Most patients able to complete regimen.	Lucchi et al, Jrnl of Thoracic Oncology. 2(3): 237-242, March 2007.
Assess complications and risks of EPP after chemo Non-randomized study	74 patients who got EPP followed over 59 months, mean age: 57 20 percent got induction chemo 85 percent patients stage III-IV	Post-op mortality: 6.7 percent & 67 percent had significant morbidity/complications, e.g. atrial fib, pneumonia, acute lung injury and mediastinal shift w/ tamponade.	EPP associated with high morbidity. EPP after chemo requires extra vigilance to prevent respiratory complications	Stewart et al, Euro Jrnl Cardio-Thoracic Surg. 27(3), Mary 2005.
Retrospective analysis of limited surgical treatment of MPM at UK hospital over 10 years. Non-randomized study	70 patients, 1989-1999, avg age: 66 Divided into 3 groups: 1) Open biopsy only (21 percent) 2) Talc pleurodesis (58 percent) 3) Pleurectomy for stage I MPM, restricted to parietal pleura (21 percent)	Median Survival: Group 1: 6 mos.; Group 2: 6 mos.; Group 3: 14 mos. Low operative mortality for PD patients. EPP avoided b/c of high morbidity (50 percent) and low survival (10-19 mo); Only do PD if tumor confined to parietal pleura (stage 1)	PD cost effective, well tolerated, few complications, minimally invasive, open to adjuvant therapies, and has survival rates similar to more radical EPP	Phillips et al, Interact. Cardiovasc & Thor Surg. 2:30-34, 2003. Comments: Sugarbaker and Rusch claim no proof PD prolongs survival, yet EPP studies have a huge patient selection bias. Why limit PD to parietal pleura?
Identify MPM prognostic factors at large hospital (MSK) Non-randomized study	945 patients, mean age: 66, 1990 to 2005 EPP: 22 percent, PD: 19 percent	Multi-modal therapy: median survival of 20.1 mos.	Predictors of survival: tumor type, staging, gender, asbestos exposure, smoking, symptoms and laterality	Flores et al, Jrnl of Thoracic Onc. 2(10): 957-965, Oct 2007.

Chart G2: The Mother of all Clinical Trials?

Objective	Patient Group	Results	Conclusions	Reference
Randomized trial w/ 2 groups: 1) chemo + EPP + radiation 2) chemo alone All patients surgery eligible	Recruiting 50-670 MPM patients, must be resectable Multiple centers in UK. No U.S. hospitals participating.	To be determined. Compare overall survival. Compare quality of life for both groups.	A pioneering study, but it requires an EPP and does not allow a PD. Will not address whether survival would be better with PD and adjuvant treatment.	Institute of Cancer Research, UK. Info provided by NCI, clinicaltrials.gov Identifier: NCT00253409, Oct. 2007. This trial is not available in the U.S.

pathogenic disease process will often rear its ugly head in the adjoining lung.

Bad data can be easily found in the very places that patients most commonly troll for answers. *See Chart H, "Example of data misrepresentation" on page 13.* Even the Mesothelioma Applied Research Foundation sometimes provides questionable data.

On its website, MARF had posted a table that purported to correlate the median survival with various treatment modes. Without citing any author, it listed the survival for the PD as 13 months, rather than the correct figure, which is between 19 and 22 months depending on the institution or surgeon who does the surgery. That's how hard this is, and that's how difficult it is to come by reliable data.

Buying More Quality Life

Helping a meso client means more than winnowing out the best survival data. Clients want to know about quality of life. If their ship is going down, and their time is sorely limited, few want to spend precious days, let alone months, going through horrendous recoveries. They want treatment that will allow them the quality of life to enjoy the time left with their families and friends. We were unable to find a single study examining quality of life for different meso treatments, and even studies that only look at a single treatment modality rarely address quality of life associated with a given procedure. The upcoming UK trial we discussed previously is groundbreaking because it also considers quality of life issues associated with EPP v. chemotherapy.

Consider doing more for your client than counseling him to leap into the first lifeboat. Helping him ask the tough questions to a doctor pushing a particular treatment benefits everyone. We may want to fixate on statistics and numbers, but clients may rank quality of life "intangibles" as their top priority. It's imperative that the lawyer and the client understand foreseeable complications no matter the therapy, and always have a back-up plan ready.

Alternative Therapies: Keeping the Beast at Bay

A few leading surgeons have taken steps to experiment with new compounds designed to delay tumor recurrence and manage it at tolerable levels. These doctors recognize that eradication may be the ideal, but until then it's best to try to tame the beast. Dr. Robert Cameron at UCLA has achieved promising results by having his patients take a daily injection of low dose interferon-alpha after surgery and radiation. In an unpublished study, he reported median survival of greater than 36 months for this particular multi-modal therapy.

Dr. Harvey Pass is another surgeon at the forefront of finding new and better compounds to delay tumor recurrence. As an example, Dr. Pass performed a clinical trial in which he had his post-surgery patients, either PD or EPP, take tetrathiomolybdate in pill form, an anti-angiogenic copper chelate compound that he describes as "maintenance" therapy. For state 1 or 2 patients he has reported a time to progression of 18.5 months, which is encouraging but requires validation in a larger trial.

Although promising, neither study has been tested in a randomized clinical trial due to lack of funding. *For more information on novel treatments, see Chart I, "Alternative therapies: Interleukin, interferon, and gene therapy" on page 14.*

Do Surgeons Rate?

Even with decent data, many patients will still base their treatment decisions on intangibles, such as the doctor's bedside manner, the doctor's enthusiasm, location of the hospital, the hospital's reputation, and scuttlebutt found on Internet chat rooms. "*Harry saw Dr. X and he's been alive now going on 5 years,*" may be more convincing to a patient than a stack of peer-reviewed randomized clinical trials.

Consumer Reports hasn't yet rated meso surgeons, but getting specific information about surgeons is crucial to choosing the best lifeboat. We faxed, emailed, and made follow-up phone calls to the top meso surgeons in the country, and we applaud those who participated in our survey. We laud doctors who disclose that surgery alone doesn't result in a cure, who freely share their data with their patients and the medical community, and who advocate for more research to buy meso patients more time.

The nonresponse rates of the doctors to whom we sent surveys also illustrate the problem: if we can't get complete surgical data leveraging a career and extensive contacts in meso law and science, how much harder is it for patients to self-educate?

"The bulk of the tumor doesn't matter in selecting the type of surgery, but rather the invasiveness of the tumor is the key. In general, non-invasive tumors can be removed equally well by either surgical technique, if performed by an adequately-trained, meticulous surgeon. By the same token, if the tumors are invasive, then they cannot be removed adequately regardless of the surgical technique."

- Dr. Robert Cameron, M.D., thoracic surgeon and surgical oncologist

We also used Medline to research the published results of the surgeons we surveyed who did not respond, and contacted a total of about 15 meso surgeons. In *Chart J1, "Surgeons who responded to Worthington survey,"* we list as much baseline data as we could get from thoracic surgeons who treat meso. We also included a column to find out which surgeons testify for their meso clients. A patient should know whether their doctor feels comfortable sharing with a jury their expertise in treating the disease *and* assessing the damages.

No Quick Fixes

> "MPM does not have one widely accepted treatment modality since none reliably results in cure."[20]

This is the bottom line for mesothelioma science today: no cure. At the same time, there are certainly some slow fixes. Since few doctors have experience with the disease, one five-year survivor summed up the first step in a sound treatment plan as, "Get thee to an expert. And when you're done with him, get thee to another."

Lawyers can ask some simple, critical questions about survival rates, and encourage their meso clients to do the same:

- What was the staging of the patients for whom the rate is claimed?
- How was staging decided (PET scan, mediastinoscopy, open lung biopsy)?
- How selective was the group for whom the rate is claimed?
- Are these your rates, or someone else's?
- For PD, what kind of PD do you do and is your goal a R1 resection?
- How many mesos do you see each year? In your career?
- How many mesos do you treat each year? In your career?

And even as they try to help clients guide their way through the roughest of waters, lawyers can get on the boat, help read the navigation charts, and even man the oars. Most lawyers who have been "in the business" for a decade or more have working relationships with meso doctors. It's important for lawyers to not only fund research, but also to drive it, by taking an interest in the research objectives of the doctor or institution they financially support.

Chart G3: Keep the lung or lose it? A comparison of the PD and the EPP

	EPP	P/D
Resection Margins	Best result is R1 margin, or removal of all gross/visible tumor	Same
Surgical Tumor Spread	Surgical wound expanded into pericardium and peritoneum. May spread cancer to other areas.	Surgical wound limited. Diaphragm and pericardium spared if at all possible (>80 percent)
Post Op Radiation Therapy	Clear field available, but adjacent liver, stomach, heart at risk for radiation toxicity. IMRT of questionable benefit.	Detailed techniques with lung blocking can deliver radiotherapy w/ lung intact and minimal toxicity
Patient Selection	No co-morbidity, adequate lung reserve, younger (mean age < 60 years)	Older patients, 60-70+ y/o, later stage disease, lower performance status okay
Operative Procedure	More uniform: removal of parietal and mediastinal pleura, diaphragm, pericardium and lung	More variable: at UCLA, complete removal of visceral pleura, all gross tumor removed, regardless of "extent" or "bulk" of tumor, including removal from pulmonary fissures. Lung, pericardium (most often), and most of diaphragm spared.
Adjuvant Therapies	Chemo applied before, during or after. Radiation post-operatively.	Same. At UCLA, PD considered equivalent or superior to EPP and part of aggressive multimodality therapy
Recurrence	Because surgical wound extends into pericardium and diaphragm, tumor recurs in "distant" location but this is really "local" extension. New cancer in remaining lung may occur because asbestos exposure creates a field defect. High rate of recurrence in short time.	9 months median recurrence in one PD study at Brigham and Women's of 44 PD with intraoperative chemo lavage.
Survival	17-22 months median survival (Maziak 2005). Higher survival may reflect creative patient selection (Meerbeeck, 2005).	17-22 months median survival (Maziak, 2005).
Operative mortality	5.9 – 14 percent (Maziak, 2005)	0 percent to 5.4 percent (Maziak, 2005)
Physician Benefits	Shorter operative time (3-5 hours); higher reimbursement ($1,380-1,848) (Cameron 2006); easier radiation therapy planning.	Longer operation (4-12 hours; lower surgical fee ($1,207 to 1,703) (Cameron 2006); comfort of doing less harm.
Expertise	Experienced cancer centers, preferably as part of prospective randomized clinical trials (none currently active or even planned in the U.S.)	Same. Surgeon must be meticulous and perseverant, removing all gross tumor from chest wall, lung, and surrounding areas. Shouldn't be done as "fall back" procedure for those patients who cannot have EPP due to extensive disease

Hope and Heartbreak: Oregon Case Study

I recently had a 72 year-old, stage 2, lymph node negative union pipefitter client with high performance status who was extremely intelligent. I told him about the PD and the EPP, and he flew from his home in Portland, Oregon to UCLA to learn more. In the end, he wanted to be close to home, so he picked the local thoracic surgeon who promised a good result with the EPP, an operation the surgeon had performed only a few times. The surgeon amputated the lung and most of the diaphragm, and in the process probably seeded the abdomen with cancer cells. Within a few months, the tumors swelled within Greg's gut. He died savagely, painfully, and tragically on the second day of trial in Oregon, where the law caps the widow's recovery at $500,000, a number that had already been greatly sur-

passed in settlements. Prior to Greg's death, the local surgeon adamantly refused to testify live or by deposition, even when Greg's son, a medical doctor, asked him to. The surgeon did offer up a letter in which he stated that Greg had bad "recurrent" disease in his abdomen after he had performed "a large surgical resection in *attempt for cure*" – but, alas, *"this cure* has not been realized…"

I personally reviewed with Greg the risks of both procedures and emphasized the dangers of having an EPP performed by a thoracic surgeon with little mesothelioma experience. He never questioned the reliability of the data, nor did he express any regret about his decision. Would Greg have chosen differently—and be alive today—if he'd had access to a simple chart laying out the relative risks?

It's impossible to say. He may have been set against any surgery far from his home, and who can blame him? Quality of life means something different to everyone.

At the same time, I've always felt it was my obligation to inform my client about specific doctors and the data underlying their regimen. Unfortunately, there is no master document to which anyone can refer. We're often left with suggesting a clinical trial, or a doctor, or a hospital, with little more than anecdotal evidence. Institutions jealously guard their data, and few report in published journals. Even those who do find the time to write up their results do not always have their work accepted for publication. The small number of people who choose a given treatment under the same conditions (tumor staging, cell-type, and lymph node involvement, to name only three crucial parameters) make larger, randomized trials unlikely to happen any time soon. The more we try to make a good recommendation, the harder it gets, and the more we tend to shrink behind the vague generalizations of "mesothelioma help" web sites.

Helping clients live longer and better lives is the right thing to do. But for those who simply shrug at the moral imperatives, there's a bottom-line factor as well: a longer life means the ability to withstand grueling depositions, appear at trial, and have a shot at getting a full and fair recovery. We should help our clients get more life, just as we are duty-bound to present evidence of all past, present and future damages.

This burden is one that many lawyers are unwilling to pick up because medicine evolves. Fifteen years ago there was no standard of care. Ten years ago EPP was the whisper choice. Three years ago Eli Lilly and a cadre of oncologists touted Alimta/Cisplatin as the standard of care without any serious objection from the medical community. Now, patients are asking hard questions about the EPP, and surgeons are looking more closely at the razor-thin margin of statistical significance that pushed Alimta into the anointed role of "FDA-approved treatment." Trial lawyers have an interest in critically examining which option makes the most sense. Does this mean that we don the doctor's white coat? No. But if we're advertising ourselves as guides, we'd better be able to offer the best roadmap we can lay hands on, and let the chips fall where they may.

If we as lawyers make the affirmative choice to market to patients in their time of crisis, and to hold ourselves out as experts with inside information and connections to the medical world, if we speak to clients in tones of concern about their medical condition and suggest that we can guide them, then we must make good on the implied promise: we must be able to discuss chemotherapy, radiation, talc pleurodesis, palliation, and surgery, and make recommendations to doctors who we think can help, after we've done our "due diligence" on them. We must amass the data, analyze it, and we must share it. If we truly believe in it, we must be willing to put our money where our mouth is, and help fund good research by good doctors who truly care. And part of truly caring is being willing to testify for their patients in lawsuits for compensation.

Anything less is bad business, bad lawyering and bad judgment.

Mesothelioma tumor removed by Dr. Cameron during pleurectomy/decortication surgery, 2005

Chart H: Example of data confusion

The chart below was once on the Mesothelioma Applied Research Foundation's website. A copy of this article was sent to MARF by a patient, and MARF corrected the problem by removing the data. This is an example of how difficult it is even for experts and institutions dedicated to curing mesothelioma to provide 100 percent reliable data about the ever-changing landscape of this disease.

Treatment	Median Survival (months)
Supportive Care	6 to 9
Thoracic Pleurodesis	7 to 9
P/D	13**
EPP	30**
Pleurectomy/Brachytherapy	11
Multimodal EPP	13 to 19
Surgery/Photodynamic Therapy	14
Radiotherapy alone	8 to 15
Single Agent Chemotherapy	6 to 9
Combination Chemotherapy	6 to 16

**The MARF table had no citations and *incorrectly listed PD survival as 13 months*, rather than the correct number of 22 as cited by Flores, Maziak, Martin-Ucar, Cameron, and other studies. There was no citation for a 30-month median survival for EPP or for any other data in the table. Former URL: www.marf.org/Resources/Treatment/Treatment.html#Primary_Treatments

Footnotes

[1] This article focuses on treatment for malignant pleural mesothelioma. Peritoneal mesothelioma cases face many of the same problems, but its treatment is beyond the scope of this article. Yan T et al, Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for diffuse malignant peritoneal mesothelioma, ANZ J Surg. 2007 May;77 Suppl 1:A88-9. Analysis of 100 patients showed a median survival of 52 months for patients who received debulking surgery and intra-peritoneal chemotherapy.

[2] CCP §377.34

[3] O.R.S. § 31.710, formerly cited as OR ST § 18.560, Awards for noneconomic damages. (1)

Except for claims subject to ORS 30.260 to 30.300 and ORS chapter 656, in any civil action seeking damages arising out of bodily injury, including emotional injury or distress, death or property damage of any one person including claims for loss of care, comfort, companionship and society and loss of consortium, the amount awarded for noneconomic damages shall not exceed $500,000.

[4] An oncologist who spoke at the 2007 Mesothelioma Applied Research Foundation's annual symposium described pleurectomy/decortication as "quick and easy, but unwarranted." A client of mine in Iowa said that his treating physician described the PD as "completely useless." Others call PD "palliative only," or slightly better than doing nothing. No randomized, controlled clinical trial has ever been conducted on *any* surgical option for malignant mesothelioma, much less reached any of the above conclusions specific to PD.

[5] Flores R, Zakowski M et. al., Prognostic factors in the treatment of malignant pleural mesothelioma at a large tertiary referral center, J Thorac Oncol., Oct 2007.

[6] Id.

[7] van Meerbeck J, Boyer M, Consensus report: Pretreatment minimal staging and treatment of potentially respectable malignant pleural mesothelioma, Lung Cancer, 2005 Jul supplement

[8] Id.

[9] United Kingdom randomized trial with two groups: chemo + EPP + radiation v. chemo alone. All patients are surgery eligible. The trial is recruiting 50-670 MPM patients, must be resectable. Trial will be conducted at multiple centers in the UK. No US hospitals participating. The study will compare overall survival and quality of life for both groups. This will be a pioneering study, but it will be examining the EPP, not the PD, and will not address whether EPP is superior to PD. Institute of Cancer Research, UK. Info provided by NCI, clinicaltrials.gov Identifier: NCT00253409 (Oct. 2007)

[10] van Ruth S, Baas P, Surgical treatment of malignant pleural mesothelioma, a review, Chest, Feb. 2003

[11] Flores and Zakowski, Id.

[12] Steele and Klabatsa, Chemotherapy options and new advances in malignant mesothelioma, Annals of Oncology, Jan. 2005

[13] Flores and Zakowski, Id.

[14] Ismail-Khan R, Robinson L, et. al.: Malignant pleural mesothelioma: a comprehensive review, Cancer Control, 2006 Oct;13(4):255-63

[15] Maziak D, Gagliardi A, et. al., Surgical management of malignant pleural mesothelioma: a systematic review and evidence summary, Lung Cancer, 2005, 48:157-169

[16] Aelony Y, Thoracoscopic talc poudrage in malignant pleural effusions: effective pleurodesis despite low pleural pH, Chest, 1998

[17] Cameron R, Extrapleural pneumonectomy is the preferred surgical management in the multimodality therapy of pleural mesothelioma: con argument, Annals of Surgical Oncology, 2006

[18] Ismail-Khan R, Robinson L, Id.

[19] Flores and Zakowski, Id.

[20] Ismail-Khan R, Robinson L, Id.

Chart 1: Alternative Therapies: Interleukin, Interferon, and Gene Therapy

Title	Patient Group	Results	Conclusions	Reference
Improved Survival with interferon alpha maintenance therapy following pleurectomy/decortication and radiation for malignant pleural mesothelioma	139 patients with malignant pleural mesothelioma were evaluated. 65 patients were eligible and underwent surgery.	The median overall survival from the time of the operation was 13.2 months (entire group), 17.7 mo (group completing surgery and radiation), and a remarkable and highly statistically significant >>37months for the group receiving interferon maintenance therapy	Complete pleurectomy/decortication and postoperative radiation therapy may provide similar survival to the more radical procedure of extrapleural pneumonectomy particularly in advanced stage disease. In addition, interferon alpha maintenance therapy may provide substantial improvement in survival over existing therapies. Further studies are warranted, and mechanisms of this effect are being investigated. PD + IMRT + Interferon = >37 months median survival	Cameron et al, presentation to the Society of Thoracic Surgeons. Jan 2006.
A phase II trial of Tetrathiomolybdate [TM] after cytoreductive surgery for malignant pleural mesothelioma (MPM)	34 cytoreduced malignant mesothelioma patients	24 month overall survival, 24 month progression free survival Stage I/II (n=13) 60 percent 69 percent Stage III (n=17) 23 percent 0 percent	TM has antiangiogenic effects in postoperative MPM patients and the VEGF serum level is a robust biomarker in this therapy. TM has minimal toxicity and is at least comparable in efficacy to previous multimodality trials of cytotoxic agents for MPM. TM should be evaluated for use with standard MPM regimens, as well as for post surgical maintenance monotherapy.	Pass et al, American Society of Clinical Oncologists' annual meeting. 2004.
Interleukin-4 Receptor Cytotoxin as Therapy for Human Malignant Mesothelioma Xenografts	13 mesothelioma patients	PE38KDEL mediated a dose-dependent decrease in tumor volume and a dose-dependent increase in survival.	The chimeric protein, IL-4(38-37)-PE38KDEL, has potent anti-tumor effects against MPM both in vitro and in vivo.	Cameron et al, Ann Thorac Surg. 2004 Aug; 78(2):436-43.
Combined Epirubicin and Interleukin-2 Regimen in the Treatment of MM: A Multicenter Phase II Study of the Italian Group on Rare Tumors	21 chemotherapy naïve malignant mesothelioma patients	Only one patient achieved a partial response, resulting in an overall response rate of 5 percent (1/21) with a median progression-free and overall survival of 5 and 10 months.	These results do not support the use of such a combination in the management of malignant mesothelioma.	Bretti et al, Tumori. 1998 Sep-Oct;84 (5):558-61.
Interleukin-2 in combination with tamoxifen in malignant pleural mesothelioma	25 mesothelioma patients	Of 25 patients treated in this investigation, a promising median survival of 15.1 months was observed for the whole group.	The overall toxicity of the combination of IL-2 and tamoxifen was found to be acceptable, consisting predominantly of skin rashes and mild flu-like symptoms.	Ulsperger et al, Eur J Cancer. 2001; 37(suppl 6):45. Abstract 154.
Cytokine gene therapy of mesothelioma. Immune and anti-tumor effects of transfected interleukin-12	Mice	AB1-IL-12 induced systemic immunity that was effective at reducing the incidence of parental AB1 tumor at a distal site, but its effects were dose-dependent.	Paracrine secretion of IL-12, generated by gene transfer, can induce immunity against MM that can act locally and also at a distant site. In addition, there was no evidence of toxicity, which has been associated with the systemic administration of IL-12.	Caminschi et al, American Journal of Respiratory Cell and Molecular Biology. 1999 Sep; 21:347-356.

Chart J1: Surgeons Who Responded to Worthington Survey

	# Meso Consults Per/Yr	# Mesos Treated Per/Yr	Est.# of Mesos Treated Career	EPP	P/D	TP	Surg. Morality	Pre-Op Chemo	Post-Op Chemo/Rad	Median Survival Months	Est.# of Depos For Mesos 2006
Robert Cameron[a]	75	40	300	N	Y	Y	<1 percent	N	Y	18-36	6
Raja Flores[b]	60	50	450	Y	Y	Y	1 percent	Not always	Not always	20	0
David Harpole[c]	40-50	40-50	250+	Y	Y	Y	5 percent	Y	Preferred	20-22 w/trimodality	1*
Harvey Pass[d]	60	35-45	400-500	150	100	N	5 percent [EPP]; 1 percent [PD]; 2 percent [All meso patients]	Y	Y	Stage dependent	3
David Rice[e]	80	30	180	Y	Y	N	3 percent	+/-	Y	Stage dependent	3
Larry Robinson[f]	~20	~10	~120	Y	Rare	Y	<3 percent	N	Y	Stage dependent	2
Eric Vallieres[g]	20	15	~150	Y	Y Rare	Y	4 percent	Y	Rad.	~24	~5

* "Always as advocate and treating physician," Dr. Harpole

The following surgeons did not respond to the survey: Raphael Bueno, Robert Caccavale, Joseph Friedberg, Daniel M. Labow, David P. Mason, Daniel L. Miller, Valerie Rusch, David Sugarbaker, Stephen C. Yang. PubMed data for Drs. Sugarbaker and Bueno showed median survival for EPP at 19 months and surgical mortality between 3.4 and 3.8 percent.

Chart J1-J2 Footnotes

[a] Surgical Criteria: Disease limited to predominantly epithelioid histology in one hemithorax, adequate cardiac and pulmonary function Surgeon's comments: "Each patient must be looked at individually. Surgical procedure should be tailored to the patients' functional status, extent of disease and type of meso. And must take into consideration patients' goals."

[b] Surgical criteria: Able to accomplish a maximum cytoreduction with a mortality <= 5 percent; independent of age and histology; dependent on functional status. Surgeon's comments: "Survival rates are stage dependent."

[c] Surgical criteria: [for EPP] epithelial or mixed histology verified by Roggli; adequate PFT's with differential ventilation-perfusion scan; normal dobutamine echo without evidence of pericardial involvement; mesothelioma protocol CT with 3-D reconstruction; PET without distant disease; no significant co-morbidity. [for PD] verified pathology, can include sarcomatoid; either significant co-morbidity or T4 disease. Surgeon's comments: "Duke University sees most of the mesothelioma cases in the southeastern U.S."

[d] Surgical criteria: Stage I-II, (occasionally Stage III node neg.), physiologically fit for surgery

[e] Surgical criteria: non-sarcomatoid; confined to ipsalateral hemithorax; not N3; no trans-diaphragmatic involvement; estimated post-pneumonectomy FEV ≥ 1.0 1/min/sec; cardiac status healthy. Website: www.mdanderson.org/diseases/mesothelioma. Surgeon's comments: "The above comments apply to extra-pleural pneumonectomy, not pleurectomy. Comparing survival rates for this disease is MEANINGLESS unless one compares stage-specific survival."

[f] Surgical criteria: Predominantly epithelial histology with disease limited to the hemithorax and no obvious nodal involvement. Website: www.mychestsurgeon.com. Surgeon's comments: "With maintenance interferon therapy median survival exceeds 3 years."

[g] Surgical criteria: Fit, early stage, good cardiorespiratory reserves

[1] Review of 328 patients who underwent EPP, "Prevention, early detection, and management of complications after 328 consecutive extrapleural pneumonectomies," J Thorac Cardiovasc Surg. 2004 Jul;128(1):138-46

[2] Review of tri-modal EPP in 183 patients, "Resection margins, extrapleural nodal status, and cell type determine postoperative long-term survival in trimodality therapy of malignant pleural mesothelioma: results in 183 patients," J Thorac Cardiovasc Surg. 1999 Jan;117(1):54-63; discussion 63-5. Patients with epithelial, margin-negative, extrapleural node-negative resection had extended survival.