Well, good morning everyone, I’ve been asked to speak today about the issues we face with the management of malignant mesothelioma and again the title of this presentation would be Treatment Challenges in Malignant Mesothelioma. This obviously is a very important problem here in this area of the country and our country overall, and worldwide due to the chronic industrial exposure to asbestos, particularly in the middle of the 20th Century that was not recognized however into the 19th Century but not until the latter third of the 20th Century were regulations related to asbestos exposure implemented in Europe and subsequently in the United States.

If we look mesothelioma distribution in the United States today you can see a strong clustering of, of case identification in areas where industrial activity is and particularly construction, ship building industry is focused in the upper east coast around the basin of the Mississippi River and out east around San Francisco and the Seattle area. And with incidents and death per million somewhere in the range of greater than 10 individuals per million in, in those areas but less so in other areas where those activities are less of a occupational risk.

If we look at the background of mesothelioma there is a strong association with industrial asbestos exposure, as mentioned shipbuilding industries, insulation and construction. There is a long latent period of 20 to 50 years after the chronic exposure to asbestos fibers. Additionally asbestos is identified within the specimens of patients with mesothelioma at about 60 to 70% of patients, 30% of patients is not identified and may be related to some other genetic or other environmental exposures.
It’s commonly a disease of older white male patients and presentation is usually in the advanced stage in greater than 80% of patient cases.

But what about malignant mesothelioma? It commonly presents with dyspnea, a patient with dyspnea and chest pain and is the hallmark of this disease is an encompassing of the pulmonary parenchyma and the mediastinum by a fibrosing aggressive process involving the visceral and parietal pleura, going within the fissures, invasion with the mediastinum, crossing the diaphragm and also involving the abdominal cavity, and there can be metastatic disease identified on ultimately at death in 20 to 50% of patients.

The reasons for frustration in the management of this disease is the poor response to systemic therapy, radiation in-effectivity in relationship to the exquisite sensitivity of local intrathoracic and abdominal organs associated with the disease, therefore even though focally mesothelioma can have sensitivity to radiation in the 50 grade range many of the organs at risk such as the heart, the lung, the liver, kidney, esophagus have sensitivities and tolerances of much less than 30 grade overall. The surgery for mesothelioma is extensive and morbid, with great frustration to all of us who have dealt with this process, and recurrences are high and there are high fatality associated with the disease overall.

Well what about the natural history? Again, this is a process presenting with pleural effusion encasement of the lung and progression across the mediastinum with progressive inanition and tumor
cachexia it being the primary causes of death in these individuals; and a local growth being the primary manifestation, although metastasis can be seen such as this in the contralateral lung on autopsy studies in up to 50% of cases.

The malignant mesothelioma survival untreated has a very dismal prognosis with an average survival of around 7 months as demonstrated here in the workup presented by Merritt, et al.

It’s important when we deal with mesothelioma and suggest therapy that we work through a proper staging system to direct the most appropriate treatment to the most patients. The first effort was that of Butchart staging system, which is really a system that began right at the infancy of CT imaging and was primarily a clinical staging system based upon chest Roentgenography of standard AP and lateral films and physical exam, and by that Stage I process was a – and also surgical exploration and the finding of surgery. Stage I according to this, this staging system which began in 19 – in the early 1970s, was Stage I, that was a tumor involved within the capsule of the parietal pleura, ipsilateral lung, pleura pericardium and diaphragm; Stage II invading the chest wall, the mediastinum, esophagus, opposite pleura, positive nodes within the chest; Stage III through the diaphragm or peritoneum, peritoneum excuse me, opposite pleura, positive nodes and full resistant metastasis. And this was again right at the beginning when the role of surgery was being explored for mesothelioma and were very clinically gross undertaking.
The Brigham group based upon their experiences which began in the 1970s and flourished in the 1990s looked at the staging system based upon their surgical intervention and really this is a staging system which was in use up until the early ‘90s where again the primary staging modality was that which was seen at the time of surgical intervention and again Stage I very similar to the Butchart system where diseases combined within the capsule parietal pleura and without mediastinal lymph node involvement, Stage II was defined by the presence of intrathoracic nodes, Stage III was locally advanced disease which may or may not be resectable particularly if there’s contralateral disease present and Stage IV which is distant metastatic disease. And the focus of their surgical intervention was that for Stage I disease overall except for surprise identification of intrathoracic nodule processes. The avoidance of Stage III and IV was obviously the goal to avoid unnecessary exploratory thoracotomy without total debulking of the tumor mass.

The present staging system was basically the idea of Val Rusch and the international mesothelioma interest group which tried to mimic the circumstances associated with the TNM classifications of other solid tumors. And that would be, a T1 lesion would be a lesion, T1a that limited the parietal pleura, T1b a lesion involving the ipsilateral pleura and the mediastinum, diaphragmatic surfaces with scattered focuses on the visceral pleura. Stage II would involve both pleural surfaces, Stage III locally advanced but potential resectable and Stage IV was advanced, unresectable disease. The same nodal staging would be as applied to other intrathoracic malignances, Stage I be highest, I’m sorry M1 being hilar, M2 meaning mediastinal, M3 contralateral mediastinal and the Stage IV, T4 would be a lesion crossing into the opposite hemithorax of the celomic cavity. This gave us a staging
system which is presently used today very similar to what we stage esophageal and lung cancer, colon cancer, other solid organs we, we face clinically.

Well, what about the clinical assessment of mesothelioma? It begins with the standard chest roentgenogram, the patient on the left has — does have chest pain and an occult presence of mesothelioma minus an effusion. The patient on the right has a bulky mass at presentation associated with significant chest pain, and of course the intermediate circumstance is that of an associated pleural effusion with dyspnea. These are — so the chest roentgenogram is our first, first point of inspection, the clinical history obviously is very important and the demographic profile that I mentioned earlier.

Computer tomography really is the hallmark of our evaluation of patients and you can see a normal CT scan on the left but on the right a patient who is affected by mesothelioma with the characteristic findings of pleural thickening, parietal thickening along with growth within the fissures and involvement of the mediastinal structures. The obvious issue is identification by those, those means of stage IV, III and IV disease where surgical resection and debulking is not possible as illustrated here where the tumor mass is extending across the diaphragm invading into the liver and you can see the surface implants upon the dome of the liver here at the time of attempted extrapleural pneumonectomy. Obviously this patient is one where section intervention of local control would not be accomplished.
Today we rely heavily on PET CT imaging with mesothelioma and you can see the involvement in the posterior gutter in this patient suggestive of extensive involvement into the retroperitoneum and also anteriorly into the abdominal cavity. And this patient would thus be staged at Stage IV and unresectable. Experience with this has been illustrated by Flores and his group at Memorial and presented in 2003 where in 6 of 63 patients were found to have occult M1 metastatic disease or M3 disease with PET imaging. The sensitivity of the tumor extent was 19% and the mediastinal node involvement was identified occultly in 11% of the patients.

MD Anderson’s experience is also similar where PET CT correctly assigned a stage in 72% of patients, it overstaged in about 20% of patients and thus with clinical evaluation and intraoperative evaluation is important in those – in some patients, and under-staging occurred in 10% of patients. Unsuspected metastasis was found in 24% of patients thus avoiding unnecessary surgery.

Here is a couple of examples of that where you can see a metastasis to the humeral head and the obvious involvement within the left hemithorax. There is a patient with a metastasis to the adrenal gland with extensive mediastinal and local mesothelioma involvement within the left hemithorax, you can see it crossing into the contralateral right sided posterior aspect of the pleura. And you can see also identified foci of metastatic disease within the abdomen. With the advent of PET, as mentioned, many patients thought otherwise not to have metastatic disease are being identified and this concept of mesothelioma being commonly confined to the hemithorax and being a locally aggressive disease only is no longer being supported.
With regard to chemotherapy, systemic therapy we have had some improvements in the opportunities to apply systemic therapy for this disease. If we look at the overall Phase I and II trial responses to single agents with non-platinum based agents the single agent response is around 10%, Anthracycline similarly and platinum based agents around 10 to 20%. Interestingly the advent of Pemetrexed and Antifolate is – has significantly improved our overall systemic management of this disease in that it is known that mesothelioma has a significant folate utilization and its antifolate pathways appear to improve our overall local and systemic response. In that Cisplatinum alone you can see on the dotted line had versus the combination therapy was significantly improved with the medial survival greater than – improvement of over 3 months, and an actual response rate, local response or local control rate of 41% versus 17% when single agent therapy was utilized.

This is how that was evaluated and how this is systemically – the systemic response is evaluated under local control and otherwise, and by definition of Volgelzang and his group have led the way and this standard has been established that an objective response is estimated at a 30% reduction in the pleural involvement utilizing it up to 9 points on average on CT examination of the pleural involvement.

So other agents also have activity against mesothelioma, most interestingly again this group of drugs that are antifolate and activities similar to 5FU and Methotrexate, this is Vogelzang’s work I just presented to you and also some work more recently by von Meerbeck et al who looked at
Pemetrexed plus Cisplatinum and found a similar response, so there are on the horizon other drugs that will be coming into play with regard to the management of mesothelioma. Other drugs – Gemcitabine is also an active agent that is commonly utilized when – after Alimta has been exhausted as an agent, primary agent with Cisplatinum.

We worry about surgical management of mesothelioma, the options and the work of the surgeon in the management of this disease involves these areas of activity and that would be diagnostic through VATS and open biopsy to determine what the pleural thickening of the pleural effusion is associated with. Symptom control such as pleurectomy and decortication and cytoreductive therapies such as extrapleural pneumonectomy and pleurectomy decortication, we’ll go over these in further detail.

With a world to cytoreductive surgery, the issues to be considered is should a complete – that we always need to move toward an R1 or microscopic only residual disease or 0 disease in the management of mesothelioma is very uncommon. We should also consider the availability of adjuvant therapy such as chemotherapy and focused radiotherapy depending upon the resective cytoreductive therapy utilized, be it pleurectomy decortication, decortication pleurectomy or extrapleural pneumonectomy, and then we should also weight the surgical benefits versus tumor in patient factors such as the performance status, histology and grade of the tumor and stage when contemplating extensive resection such as an extrapleural pneumonectomy or falling back to pleurodesis alone or decortication or partial decortication with subsequent palliative systemic and local therapy.
Well what about surgical staging? This is how we would work through the process of a patient presenting to us with mesothelioma and that would be look at the demographics, make sure the patient has a non-sarcomatoid process. We believe that aggressive resection should be applied primarily to those individuals that are less than 70, and non-sarcomatoid involvement and a performance status of a ECOG 0 to 1. If that’s not the case then palliative therapy with chemotherapy as mentioned or palliative radiation therapy which has an effect, a local effectiveness in controlling pain and reduction in mass with focal postage stamp type therapy around 60 to 70%. So there is some benefit there with – in the palliation of this disease with the use of chemo and radiation.

A physiologic assessment obviously standard spirometry for major resection, we certainly want to have a postoperative FE1 of greater than a liter. Cardiac evaluation is important and we must rule out pulmonary hypertension during the course of this process if pneumonectomy is going to be considered.

In the radiographic assessment that I showed to you, mentioned to you earlier particularly with the PET fusion CT scanning and also MRI scanning to assess extensive chest wall or mediastinal involvement, in those cases where extensive chest wall involvement is identified we do not recommend extensive debulking procedures as the, the prognosis in those cases is not very good.
Potentially resectable, we begin with surgical staging and that would be thoracoscopy plus or minus laparoscopy with peritoneal lavage and EBUS or mediastinoscopy to evaluate the mediastinum for node positivity. If all that is negative then we attempt to consider cytoreductive surgery by extrapleural pneumonectomy or pleurectomy decortication.

Thoracentesis alone, is it adequate in making a diagnosis and also helping us to move forward with therapy? And I would say no, it’s only positive in about 35% of patients for malignant disease and also there is a great consternation in the differentiating metastatic adenocarcinoma from a variety of different primary sites from mesothelioma, so it is very much recommended that a larger tissue sample be obtained by thoracoscopy which has a 98% accuracy in determining the etiology of this process as being mesothelioma – primary mesothelioma and also getting a histologic identification of epithelioid which is our goal, and the avoidance of sarcomatoid or in some pleomorphic or mixed varieties depending on patient’s functional status when we consider extirpative surgery. Also look into these larger tissue samples will more definitively identify metastatic disease from another primary versus primary pleural mesothelioma.

This is a typical appearance at thoracoscopic intervention where you see these elevated hyperemic nodules within a background of fibrosis, they are quite – they can be quite varied in their presentation and then sometimes the pleural mass can be thick and very fibrotic, more consistent with a sarcomatoid primary etiology or it can be more inflammatory in presentation which is more
commonly seen with the epithelial variety or a primary metastatic focus of a malignancy within the chest.

Interesting when you look at the thoracoscopic examination and the presence of normal visceral pleura versus invasion of the visceral pleura you can see that, that when dealing with epithelioid malignancies as shown Boutin and others reported in 1993 a significant improvement in survival in the Stage I variety of tumors where it was limited only to the parietal pleura as shown in these two varied survival patterns between these, these presentations. We also again remember that we need to evaluate the abdominal cavity radiographically and sometimes directly with laparoscopy prior to attempted thoracoscopic, excuse me prior to thoracotomy and resective therapy because of the – this would represent an advanced stage of the disease where such cytoreductive therapy does not have a benefit.

What types of cytoreductive surgery do we have in mind, and that would be extrapleural pneumonectomy is the, is one option and this would be directed primarily at the node negative disease patients where the entire ipsilateral pleural envelope is removed along with the lung, the pericardium and the diaphragm. The pericardium ipsilateral aspect of the pericardium replaced with Gore-Tex fenestrated so as to prevent important obstructive pleural effusion and also the diaphragm is replaced with Gore-Tex as shown here, and the specimen is again encompasses all of the tissues be that diaphragm, lung, mediastinal structures, mediastinal lymph adducts and pericardium along with the primary pleura.
What is the rationale for extrapleural pneumonectomy? We can go back to the work of Sugarbaker which was presented in 1999 where he found with Stage I disease, again that node negative disease and this was per their association, this was before the, the more recent T&M classification, this includes T1a and 1b, Stage I by their definition would be those that had node negativity with, and the histology in this case was epithelioid node negative and clear margins are meaning that there was no gross disease present. And those patients in addition had trimodality therapy including adjuvant chemotherapy and radiotherapy, the 5 year survival among individuals with Stage I disease approached 50%.

Significant morbidity was associated with their experience and in 2004 Sugarbaker looked at these experience in those patients resected and atrial fibrillation and the other forms of – other postoperative problems were commonly seen. The mortality was gratifying in this series with less than 4% overall, however this must be kept in mind that this is a group of patients with a high postoperative complication rate.

Well what about radiotherapy after extrapleural pneumonectomy, and it appears that this has some advantages, but it does require expert radiotherapy management, Rusch and colleagues in 2001 looked at a Phase II trial perspective evaluation with extrapleural pneumonectomy of the hemithorax with radiation, used 54 Gy in 30 fractions and this was again after total extirpation of the lung. The opportunity to improve things with radiotherapy following decortication pleurectomy – pleurectomy
decortication is not equivalent to this because of the risk of injury to the underlying lung and mediastinal structures. But when extrapleural pneumonectomy is performed it appears that this does have some value, particularly when it is focused to and directed to shield the organs at risk. She looked at 54 patients with no adjuvant chemotherapy and interesting that survival was quite improved over historically seen. And again with a very good response to local control and survival particularly in Stage I and II disease paralleling if not superior to that reported by the Brigham group.

The new focus now is on intensity modulated radiation therapy, again we are very focused, the radiation beams are delivered at 10 degrees separation in the calculation of the dosimetry so that you can really pair in on the extrapleural plane, avoid the heart, avoid the spinal column - the spinal cord, esophagus, liver, stomach and the kidney. And this is the type of radiotherapy that needs to be utilized post-extrapleural pneumonectomy when – in an adjuvant fashion to avoid complications and improve overall control.

The M D Anderson experience is quite gratifying in this extent also and Rice et al reported their experience in 2007 with this, and were there with 100 patients that they had undergone – excuse me, performed extrapleural pneumonectomy, most of those as seen in most series with Stage III disease and if you look at their survival again it parallels what was seen by Rusch and Sugarbaker when you had an epithelioid node negative in a circumstance of extrapleural pneumonectomy and IMRT gratifying overall survival in this disease when node positive obviously the survival fell off and then
non-epithelioid node negative and node positive you can see it really follows the natural history of that disease and in this circumstance such aggressive cytoreductive therapy probably is not indicated.

Interestingly if you look at the role of radiation therapy in this setting the first, the Baldini group report is really an evaluation of the Sugarbaker Brigham group. You can see that the radiation therapy that they used in that tri-modality setting reported by Sugarbaker had a significant local failure rate of nearly 50%, but a distant failure rate of a third or so. With the combination of – this was less focal radiotherapy, more conventional therapy and not the focused therapy I described using IMRT that Rusch and the Rice, Rusch did in New York City and Rice in Houston where with that association they have a significant reduction in, in the local recurrence rate and in that setting you can see because of better local control the presentation of disease, subsequent presentation of disease was primarily systemic in over 50% of patients in both series. And this is, you can see the experiences of other groups with conventional radiotherapy and their recurrence pattern versus those two groups which have led the way with more focal directed precise radiotherapy.

What about pleurectomy decortication, and I think that this is gaining traction internationally as a means of managing the disease but for the very select patients with node negativity and very good performance status as seen in the lower right column. The idea is to remove all disease along the diaphragm, pleural mediastinum, in the fissures and to debulk the disease as much as possible. And in this setting good control of the disease can commonly be seen. A very large tumor debulking can be accomplished as demonstrated here and over time you can see that in selected patients that there
can be good control out several months following this approach of pleurectomy decortication. Again you have to be diligent in removing all visceral pleural nodules to have the greatest success with this approach along with the removing of all the parietal pleura involved with disease.

Intrapleural immunotherapy is chemotherapy in addition to the pleurectomy decortication is an approach which has been looked at and utilized over the years. Several studies have looked at this with an idea of intrapleural therapy at the time of resection but – and Rusch and Harvey Pass and those have utilized this along with the not only chemotherapy but with photodynamic therapy and also immunotherapy in the case of Pass’s work in 1997, but again the local failure was not improved in this setting although there is some interesting results from Friedberg’s group at the University of Pennsylvania with his very aggressive decortication and pleurectomy approach and photodynamic therapy. It’s questionable if that control is related to the photodynamic therapy since it really didn’t show benefit elsewhere and more of a factor of his very aggressive intraoperative debulking of the disease.

We and others across the world really have been very interested in hyperthermic intrapleural chemotherapy, we used Cisplatinum 60/90 minutes post resection or pleurectomy. The temperature of the patient is up to 39/40 degrees during the course of this and we know that the penetration of Cisplatinum is 20 to 50 times greater than intravenous installation of the drug for systemic use in this setting. The standard dose is 200 to 250 mg of Cisplatinum given during the course of this therapy
and the results are early but encouraging, not much can be said other than this is a primary approach that we are using particularly after pleurectomy decortication.

Finally I’d like to go into the issue of extrapleural pneumonectomy versus pleurectomy decortication for mesothelioma. And it’s interesting when we look at the compared results of pleurectomy decortication versus extrapleural pneumonectomy of the years and going back to Valerie Rusch’s experience in 1996, you can see that she had a more favorable outcome in those patients she could get a good pleurectomy decortication versus the results long term with extrapleural pneumonectomy. Similarly Pass, his groups in 1997 reported a similar advantage to just extrapleural – good extrapleural pneumonectomy, excuse me pleurectomy decortication as compared to extrapleural pneumonectomy with a doubling of the survival time in that setting. Stewart conversely to this argued that extrapleural pneumonectomy had an improved survival pattern within his patient population. So I think patient selection obviously goes – comes into play here and the degree and the extent of which you are diligent in performing the pleurectomy decortication in those patients selected for that intervention.

Interestingly in 2008 Flores combined his work with Harvey Pass and looked at over 300 patients that had extrapleural pneumonectomy versus pleurectomy decortication and again with the – I believe the influence of Pass’s efforts and also their local work they identified again that the significant trend for improvement in long term survival with pleurectomy decortication versus extrapleural pneumonectomy, so I think the jury is out with regard to what should be applied for
which group of patients. These are – when we look at the recurrence pattern it’s important to recognize that that local failure is more common with pleurectomy as opposed to extrapleural pneumonectomy, with distant recurrence being more commonly the presentation or a combination of distant pleural – distant recurrence along with local pleural involvement. Less commonly seen on the left where with the pleurectomy population, pleurectomy decortication, you have a much more common presentation of aggressive local disease being at play.

When we look at operative mortality however pleurectomy appears to win out in the management of these patients and we tend to select pleurectomy for our poorer risk patients with limited disease with an overall mortality rate certainly less than 10%, usually less than 5; whereas extrapleural pneumonectomy has a much higher mortality rate, the best of which is similar around less than 4% as seen in the Sugarbaker experience which was reported in 1999 but continues to be less than 3% today. Our experience is somewhere around 4 or 5% here at the University of Pittsburgh.

Complications are also less common with the extrapleural pneumonectomy, excuse me with the pleurectomy versus the extrapleural pneumonectomy group, but again in both populations complications are relatively common, the most commonly seen problem being that of supraventricular tachycardia.

So what are the pros and cons of these extrapleural approaches? Well pleurectomy has a higher local recurrence rate, 70 to 100% extrapleural pneumonectomy, depending upon the circumstances and the
adjuvant therapies somewhere around 30%. Certainly pleurectomy is less cytoreduction than extrapleural pneumonectomy. The advantages are a lower mortality and lower morbidity, and adjuvant – however adjuvant radiation therapy is quite difficult in the pleurectomy decortication circumstance but adjuvant radiotherapy is much easier but still a substantial undertaking when extrapleural pneumonectomy is utilized. So I think that if we look at an algorithm of management or a clinical flow chart I think we begin with adequate surgical staging of the patients if there is no nodal involvement, then intraoperative staging is accomplished; if there is no nodal involvement at intraoperative staging then consideration for the good risk patient for extrapleural pneumonectomy. In I, particularly in II but particularly – and possibly in I disease pleurectomy decortication with intraoperative chemo-profusion would be an important option. If II disease is indentified clinically and you have a good risk patient then you might consider induction chemotherapy followed by pleurectomy decortication with subsequent further intraoperative chemotherapy. And for a metastatic or N3 disease we would recommend primary nonoperative therapy with systemic therapy with a Pemetrexed based regimen with Cisplatinum and with supplemental radiation therapy to treat symptoms.

So as a conclusion today we have these and that is optimal management is controversial between extrapleural pneumonectomy and decortication pleurectomy in the management of regionally limited disease; however for the good risk patient with node negative disease the bias continues to be toward extrapleural pneumonectomy when possible because of the opportunities associated with adjuvant chemotherapy and adjuvant radiotherapy improving local control. And so in fit patients with
epithelioid node negative tumors multiple modality therapy may improve survival but yet this isn’t proven internationally. Cytoreductive surgery should remove all macroscopic disease, this is our goal as surgeons if we take this, these patients on. And hemithoracic radiation greater than 45 Gy after extrapleural pneumonectomy lessens the risk of local recurrence, unfortunately distant failure limits survival in these patients and improved systemic therapy is what we need to also strive for and get in addition to improve local control. So thank you for your time, any questions the time is now.

A quick question for you. (inaudible)

Well I think that is a good idea, the last – or the International Lung Cancer Conference just – or presently is underway actually in Amsterdam and the one two years ago in San Francisco really led many of us to believe this is a good approach for individuals that, that have regionally advanced not very bulky disease that could be, be managed with extrapleural pneumonectomy that don’t appear to be good candidates for decortication pleurectomy. And so I think that’s an approach we should try to move to utilize more commonly. It also weeds out those individuals that are going to have progression through systemic therapy that – and where our regional efforts are probably going to not be of value. So I’m tending to consider that much more commonly in those individuals where you can’t really debulk the disease effectively in the beginning, but the jury is still out on that. But I know that there is you know much greater enthusiasm in Europe to utilize that in Italy and Switzerland and Germany than what we’ve done here in North America.
(Inaudible)

We have our hypothermic perfusion protocol, otherwise we and national are still just relying upon the adjuvant therapy with – or induction therapy with Platinum and Alimta. There really isn’t anything afoot nationally or locally behind those efforts because of the enthusiasm with Cisplatinum and Alimta at that time which was really a step ahead of what was seen you know just before the new millennium in the systemic management of the disease.

Anyone else? All right, thank you for your time.