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Malignant Pleural Diseases

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Pleuro-peritoneal Shunt for Malignant Pleural Effusions

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The prognosis of patients who have a malignant pleural effusion (MPE) is poor, with a median survival of 4 months¹. The presence of a malignant effusion significantly impairs quality of life due to dyspnea (96%), pain (57%) and cough (44%)². The management remains controversial for recurrent MPE in the presence of a trapped lung that fails to completely re-expand after drainage of the effusion.

The pleuro-peritoneal shunt allows continuous drainage of pleural fluid into the peritoneal cavity. This allows the lung to expand to its maximal possible extent and the mediastinum to shift back towards the affected side, thus improving dyspnea. Pleuro-peritoneal shunts are more commonly used for intractable aseptic MPE, when a trapped lung is present. The shunt has also been used for the treatment of chylothorax in both adults and children.

The pleuro-peritoneal shunt (see figure, courtesy of Cardinal Health, Inc.) is made of silicone and consists of a double-valved pumping chamber with a catheter at either end. These peritoneal and pleural catheters are both fenestrated to facilitate drainage.



Operative technique. The shunt is normally inserted under general anesthesia with the patient in a supine position or with the operative side slightly

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elevated. We perform bronchoscopy to exclude endobronchial obstruction. Thoracoscopic assessment is then performed. If the lung is trapped, we proceed with shunt insertion. The VATS port site is extended to 4-5 cm in length and a subcutaneous pocket is created in a position to allow fixation of the pumping chamber over a rib for ease of palpation and compression. The shorter of the two catheters is inserted into the pleural space. Fluid should be left in the pleural space or normal saline instilled to allow flushing of the shunt in the early post-operative period. A separate 3-4cm transverse, sub-costal incision is made and purse-string sutures are placed in either the posterior rectus sheath or transversalis fascia and the peritoneum.

We then verify, visually and digitally, that the peritoneal space is free of adhesions. The peritoneal catheter is passed through the pocket and tunneled to the sub-costal incision using long Robert's forceps. The catheter is then passed through the purse-strings into the peritoneal cavity. The pumping chamber is secured within the pocket using non-absorbable sutures. It is then primed by pressing until fluid flows though from the pleural cavity.

In the next 24 hours the pumping chamber is pressed 25-30 times every 3 to 4 hours. After the first day the patient is encouraged to press the chamber for 5 to 10 minutes, three to four times a day. Regular pumping of the shunt reduces the likelihood of occlusion. Port-site radiotherapy is considered after recovery from surgery³. The intra-operative use of a single VATS port limits the radiation field.

Results. Over a 15 year period, 360 patients with a MPE were treated in our unit, 160 (44%) of which had a trapped lung at operation and underwent pleuro-peritoneal shunt insertion. Good palliation was achieved in 95% of patients⁴. There were no operative deaths, although three patients died in hospital from progressive respiratory failure. Twelve patients (8.5%) developed shunt occlusion requiring revision or replacement (we prefer the latter). 4% of the shunts had to be removed because of infection and one patient developed tumor seeding along the tract. Peritoneal seeding was not a problem, even in longer term survivors (>6 years in one case). The patients' relatively short life expectancy means that any peritoneal seeding that develops is unlikely to impact significantly on their quality of life.

Pleuro-peritoneal shunts have been used in many cancers, including breast carcinoma (36%), malignant mesothelioma (23%) and lung carcinomas (22%).

Discussion. The majority of patients with MPEs suffer from dyspnea. In most cases, dyspnea can be relieved or improved by talc pleurodesis if the lung re-expands, or by pleuro-peritoneal shunt insertion if it remains trapped. Other treatment modalities include the use of a permanent indwelling catheter, decortication or pleurectomy. The former has been associated with infection and empyema, and also has the drawback of external tubing and requiring training of the patient or carer. Decortication and pleurectomy are more major surgical procedures unsuitable for palliative purposes.

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Prophylactic Drain Site Radiotherapy for Mesothelioma: Does it Make Sense?

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Diagnosis of pleural mesothelioma can be made by cytology of pleural effusion, closed pleural biopsy or video-assisted thoracoscopy. Many patients require repeated drainage of effusions and both the original and subsequent drain sites are at risk of subcutaneous tumor growth from direct seeding outwards from the pleural surface. Estimates of the incidence of tumor seeding ranged from 5 to 48%¹⁻⁴. Prophylactic radiotherapy to drain sites has been offered by an increasing number of centers over recent years² to reduce the incidence of tumor seeding based on the premise that such tumor deposits are common, painful and resistant to treatment.

The table at the end of the article lists seven published series addressing this topic of which only three are randomised controlled trials. The Boutin trial, based on which prophylactic radiotherapy was first promoted, was published in 1995¹. None of the 20 patients treated with prophylactic radiotherapy developed drain site metastasis whereas 8/20 (40%) who did not receive radiotherapy had tumor seeding. The radiotherapy delivered was 21 Gy in three fractions on consecutive days. In those patients who did develop subcutaneous tumour deposits, the mean interval between intervention and appearance of nodule was 6 months (range 1-13). This study

stimulated other investigators to publish retrospective case series. A Dutch Belgian survey in 2002 found that prophylactic irradiation of intervention sites was offered in 32 of 38 responding centers (84%)².

In Glasgow, having adopted the Boutin regimen, we observed that in spite of prophylactic radiotherapy some patients still developed subcutaneous tumor. We also noted that for many patients these nodules were not symptomatic and in those who did have discomfort, further radiotherapy appeared to be effective in reducing the size and tenderness of the mass. We designed a study to assess the efficacy of radiotherapy in preventing tumor seeding and to determine if tumor nodules were painful or troublesome to patients³. Patients (n=61) were randomised to immediate drain site radiotherapy 21 Gy in three fractions given within 21 days of intervention, or to best supportive care, and followed up for 12 months. Subcutaneous tumor deposits developed in 10 patients: 7/31 (23%) in the treated arm and 3/30 (10%) in the best supportive care arm p<0.05). Median time to development of subcutaneous tumor was six months. The one other published RCT by Bydder⁴ randomised 43 patients with 58 drain sites between single fraction (10 Gy) prophylactic radiotherapy and no treatment. The rate of subcutaneous tumor development was 7% in the radiotherapy arm compared to 10% in the control arm. Given the short survival of patients with mesothelioma and that subcutaneous tumor deposits may take months to develop and may not cause symptoms, prophylactic radiotherapy is not justified.

Published series on radiotherapy to mesothelioma drain sites

Year	First author	design	Patients (nr)	RT Mets	no RT Mets
1995	<i>Boutin</i>	RCT	40	0%	40%
1995	<i>Low</i>	RS	20	0%	NA
2004	<i>Bydder</i>	RCT	43	7%	10%
2004	<i>Cellerin</i>	RS	33	22%	48%
2005	<i>Pinto</i>	RS	85	NA*	0%
2006	<i>West</i>	RS	37	5%	NA
2007	<i>O'Rourke</i>	RCT	61	23%	10%

RCT= randomized controlled trial; RS=retrospective series; mets = metastasis*. All patients in this trial received chemotherapy but no drain site radiotherapy

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Pleural Biopsy for Patients with Suspected Malignant Effusions

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Malignant pleural effusions (MPE) result from infiltration of the pleura by malignant cells¹. Cytological examination of pleural fluid is diagnostic in 60-90%, depending on the volume and frequency of aspirations. Pleural biopsy offers excellent specificity, but sensitivity varies among different methods and whether or not an image-guided procedure is performed.

Closed pleural biopsy needles with either Abrams (guillotine) or Cope (hook) devices were developed over 50 years ago. Yields of >90% have been reported in pleural tuberculosis (TB). Malignant pleural disease is less homogeneously distributed over the pleura than TB, which predisposes blind biopsies to sampling errors. Furthermore, only 70-90% of all pleural biopsy specimens contain pleural tissue. It is therefore no surprise that unguided pleural biopsies are only diagnostic in approximately half of all MPEs². Among patient with negative cytology for malignant disease only an additional 7% will have diagnostic unguided biopsies¹.

Utilizing imaging to assist pleural biopsy increases the diagnostic yield, particularly if a pleural based tumor or focal nodular pleural thickening can be identified. Ultrasound (US)-assisted Tru-cut needle biopsies have higher sensitivity and specificity in the diagnosis of pleural malignancy than unaided biopsies. Diacon *et al*³ found that US-assisted cutting needle biopsy (CNB) had 85% sensitivity for malignant neoplasms in general and 100% for mesothelioma in tumors over 2cm in diameter³. The same authors showed that the less traumatic US-assisted transthoracic fine needle aspiration (TTFNA) with rapid on-site evaluation was diagnostic in 87% of cases while avoiding the increased risk of bleeding with CNB in the vicinity of intercostals arteries⁴. Compared to CNB, US-guided TTFNA had a superior yield for bronchial carcinoma whereas CNB was superior in the minority of cases with non-carcinomatous tumors and non-malignant lesions. CT-guided pleural biopsies with CNB have the highest diagnostic yield and can be performed in lesions as small as 5mm. Maskell *et al* reported a

sensitivity of 87% in patients with suspected MPEs but negative pleural fluid cytology⁵.

A suspected MPE that remains undiagnosed on cytology and transthoracic biopsy is an indication for either medical thoracoscopy or video-assisted thoracoscopic surgery (VATS). Local expertise and availability often dictate the choice between the procedures. Both allow for wide inspection of the pleura and harvesting large biopsy specimens which results in sensitivities of >90% in MPE¹. Medical thoracoscopy is usually performed under local anesthesia and conscious sedation, whereas VATS requires general anesthesia, which can put patients with impaired pulmonary reserve at increased risk. Semi-rigid pleuroscopy was recently introduced⁶. The technique is similar to medical thoracoscopy, but uses devices derived from bronchoscopes, which should make medical thoracoscopy more affordable and technically accessible to practicing interventional pulmonologists. Recent studies have reported sensitivities of 62-90% for MPE.

In conclusion, patients with a suspected MPE and negative cytology should undergo transthoracic pleural biopsy, preferably using US or CT guidance. Patients who remain undiagnosed should be referred for medical thoracoscopy, and if non-diagnostic or unavailable, VATS. Very rarely open surgical biopsy may be required.

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Mesothelin for Diagnosis of Mesothelioma: Enough evidence for clinical use?

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Malignant mesothelioma (MM) is a cancer with poor survival, mainly induced by past asbestos exposure. MM incidence is rising in many countries worldwide. The possible use of serum or pleural fluid proteins to establish an early diagnosis or assess response to treatment and disease progression has been recently evaluated. Finding a biomarker for these purposes is extremely challenging, given the biologic features of

MM, and the need to differentiate MM from benign pleural diseases and metastatic pleural malignancies¹.

Mesothelin is a glycoprotein expressed on the cell surface of normal mesothelial cells and highly overexpressed in mesothelioma and various carcinomas. Soluble mesothelin (SM) or soluble mesothelin-related peptides, have emerged as a promising biomarker for MM. SM levels were significantly increased in serum and in pleural effusion of patients with MM compared to healthy asbestos-exposed subjects or patients with benign pleural lesions or pleural metastasis. Serum and pleural fluid SM showed excellent sensitivity (70-80%) and specificity (80-100%) as diagnostic markers for MM¹⁻³. However, SM does not capture sarcomatoid (and some of the biphasic) mesotheliomas which hampers its use as a sole diagnostic (or screening) marker. Combining osteopontin or CA125 with SM was not helpful towards this goal^{4,5}.

It has been suggested that elevated serum SM in asbestos-exposed subjects may predict the development of MM long before it becomes clinically apparent, reflecting the presence of yet undetectable small foci of MM. It could be thus suggested that invasive diagnostic methods should be used in subjects with pleural abnormalities and high SMRP levels to exclude mesothelioma or metastatic malignancies though such a strategy requires validation by prospective trials. Presently mesothelioma cannot meet the essential criteria for cancer screening programs: there is no validated screening tool or effective cure for MM, and no evidence that early detection alters outcome. However, detecting mesothelioma years before its clinical presentation may allow the investigation of new treatment modalities in early-stage patients. Studies assessing SM alone or combined with other potential biomarkers for MM diagnosis or screening are underway.

Serum SM levels were higher in patients with larger tumor load². Preliminary data suggested that serum SMRP may be helpful in monitoring patient response to therapy. In those who underwent tumor debulking surgery for peritoneal MM (or ovarian carcinomas), serum SMRP levels decrease dramatically within days. Our (unpublished) data from patients subjected to chemotherapy or gene therapy support this hypothesis. Reports on SM value as a prognostic marker in patients with MM are discordant^{2,4}.

In conclusion, there is not enough evidence yet to justify clinical applications of serum or pleural fluid SM determination in all MM patients. SM alone has probably insufficient specificity and sensitivity for MM screening, but may help clinicians in the diagnosis of epithelioid MM. In the meantime, histopathologic diagnosis should remain the “gold standard” given the important therapeutic and medical-legal implications of mesothelioma. SM may be also used to assess MM patients’ outcome and response to treatment, but this needs to be tested in prospective studies.

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CASE REPORT

Epithelioid Hemangioendothelioma/ Angiosarcoma of the Pleura

Epithelioid hemangioendothelioma (EHE)-angiosarcoma, first described in 1975¹, is a rare malignant tumor of vascular origin usually arising in bone, liver, soft tissue, or lung but rarely the pleura². We describe a case of EHE with bilateral pleural, lung and bone manifestations.

A 71 years old asbestos-exposed ex-smoker was evaluated for persistent low back pain and a left-sided pleural effusion. The pleural fluid was a serosanguinous, lymphocytic (lymphocytes 75% of total leukocytes) exudate with a low ADA level (22 IU/L). Blood tests showed anemia (Hct 31%), raised serum CA125 (2135 U/ml) and ESR (105). Bone scintigraphy revealed increased osteoblastic activity



Figure 1

of the vertebral body of T12. Medical thoracoscopy on the left pleural cavity revealed diffuse irregular thickening of visceral and parietal pleura and scarce white nodules on the parietal pleura (figure 1).

Histologic studies failed to establish a specific diagnosis. Cytology revealed clusters of atypical cells with hyperchromatic nuclei and well visible nucleolus. Immunostaining was negative for keratin

5/6, 7, 20, TTF1, calretinin, thrombomodulin, PAS/AB and Perls. No staining for vascular markers were performed.

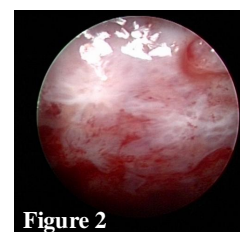


Figure 2

Two months later the patient developed bilateral pleural effusions together with multiple pulmonary nodules. Thoracoscopy was performed again, this time on the right side, and revealed diffuse white-gray nodules and plaques on the parietal pleura (figure 2).

The pleural biopsies showed thickening with large epithelial-like malignant cells with abundant eosinophilic cytoplasm and large nuclei with discrete nucleolus, moderate cellular atypia and rare mitotic figures (figure 3).

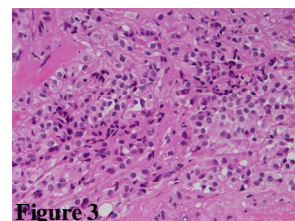


Figure 3

The tumor cells were surrounded by cellular fibrous stroma. Intense mesothelial hyperplasia was observed. Tumor cells were positive for CD31, factor VIII, CEA and vimentin confirming the diagnosis of EHE/pleural angiosarcoma. The patient received four courses of carboplatin/etoposide, and had an initial partial response before he deteriorated and died 12 months after diagnosis.

Pleural angiosarcoma is a multi-organ, aggressive malignancy that is difficult to characterize. Prognosis is poor, though sensitivity to cisplatin/etoposide has been reported^{3,4}. High suspicion and thorough pathologic investigation are needed for its diagnosis. Malignant cells are cytokeratin negative but vimentin positive. Immunoreactivity to CD31, CD34 and factor VIII is further diagnostic.

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The 2008 Congress of the International Mesothelioma Interest Group will be held in Amsterdam from Sept 25th to 27th. For details, see www.imig.org.