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# Localised malignant pleural mesothelioma: a separate clinical entity requiring aggressive local surgery☆

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**Abstract**

**Objective:** Localised malignant pleural mesotheliomas are very rare and although there are sporadic reports in the literature showing that they have a different biological behaviour compared to diffuse MPM there is no major series published demonstrating results of surgical treatment. We present our experience in treating these tumours. **Methods:** Over an 8-year period we performed radical or debulking surgery in 218 patients with MPM. Ten of these patients had localised chest wall tumours and a biopsy either highly suspicious or confirming malignant pleural mesothelioma. They were all male with an average age of 65.9 (56—80) years. Three of the tumours were epithelioid, three biphasic and three sarcomatoid. They all had chest wall resections, with limited lung resections where the tumours were infiltrating the lung and reconstruction using a double prolene mesh and orthopaedic cement. Perioperative events and long-term survival were analysed and survival was compared to survival following operations for diffuse malignant pleural mesothelioma. **Results:** There was no 30-day mortality with only two patients suffering from pleural collections that required ultrasound guided drainage 2 and 8 weeks after the operation. Two patients died from disease progression 3 and 10 months after the operation. Using Kaplan—Meier analysis the mean survival was 56 months. **Conclusion:** Our results suggest that surgery is indicated in treating localised MPM even in T4 (diffuse chest wall involvement) tumours but pleuropneumonectomy is not necessary. These tumours seem to have a different biological behaviour compared to diffuse MPM but further research, including identification of possibly different biological markers is necessary.


*Keywords:* Malignant pleural mesothelioma; Localised; Surgery

## 1. Introduction

Malignant mesothelioma (MM) is the most common primary tumour of the serosal membranes and diffuse malignant mesothelioma by definition is characterised by a pattern of diffuse spread across the serosal surface [1]. A small number of sharply circumscribed localised tumours demonstrating histological characteristics identical to diffuse malignant pleural mesothelioma (MPM) have been described in the literature. These tumours have been given the designation 'localised malignant mesothelioma' [1,2]. The small number of reported cases makes it difficult to determine whether localised MM is a separate clinical entity or whether it is diffuse MM diagnosed at an early stage or with a variant pathologic presentation [1].

We have managed 10 cases of localised malignant pleural mesothelioma (localised MPM) in our department and our experience is presented here.

## 2. Patients and methods

### 2.1. Patients

Over an 8-year period we performed surgery with therapeutic intent to 218 patients with biopsy confirmed or highly suspicious of malignant pleural mesothelioma (MPM). Ten patients, all male, age 65.9 (56—80) years had undergone chest wall resection for localised MPM.

The presenting symptom was pain in seven patients, a palpable chest wall tumour in two and cough and dyspnoea in one. In eight patients a diagnosis of MPM was confirmed and in the remaining two a malignancy highly suspicious of MPM was diagnosed with CT guided biopsy. Nine patients had occupational exposure to asbestos and two patients had preoperative chemotherapy before being referred to surgery.

### 2.2. Operative technique

#### 2.2.1. Chest wall resection

In six patients with localised MPM the tumour was on the right hemithorax and in four on the left. In one patient with

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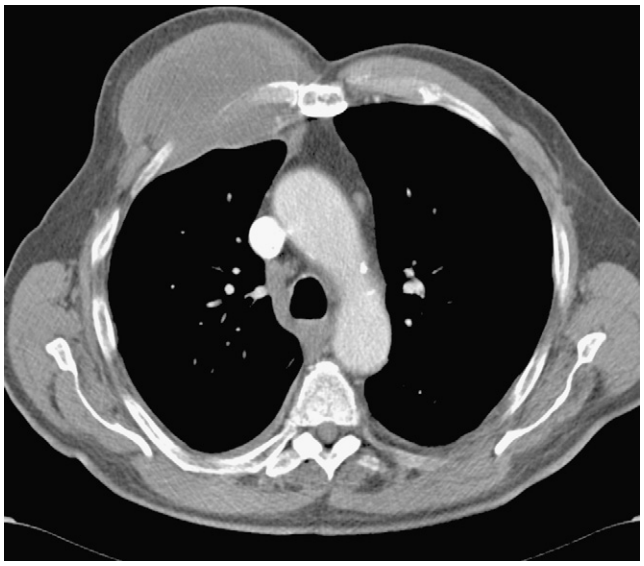

Fig. 1. Infiltration of the sternum by localised epithelioid MPM (patient 6).

right-sided disease there was involvement of the sternum (Fig. 1) and the resection included a hemisternotomy. In another case an anterior and a lateral approach were combined in order to mobilise a tumour that was involving the ribs 1 to 4.

All other cases were approached with an anterolateral or posterolateral thoracotomy. The tumour was resected en bloc with the involved ribs (3—4 in all cases) and a limited lung resection was performed in six cases where the lung was infiltrated. Subtotal parietal pleurectomy was performed in seven cases and total in three. The chest wall was reconstructed using a composite patch constructed from orthopaedic cement sandwiched between two layers of polypropylene mesh. The mesh outline was reinforced using a running No. 1 polypropylene suture and the patch was secured to the rib stumps using interrupted No. 1 polypropylene sutures. The chest was routinely drained using 2

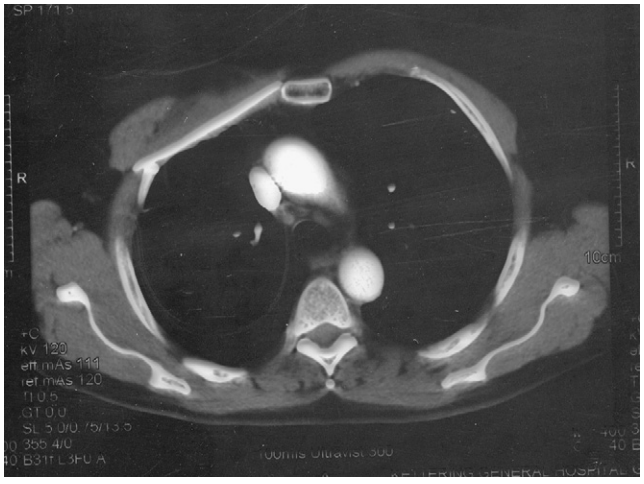

Fig. 2. Chest wall reconstruction on CT 2 years after sarcomatoid localised MPM resection (patient 9).

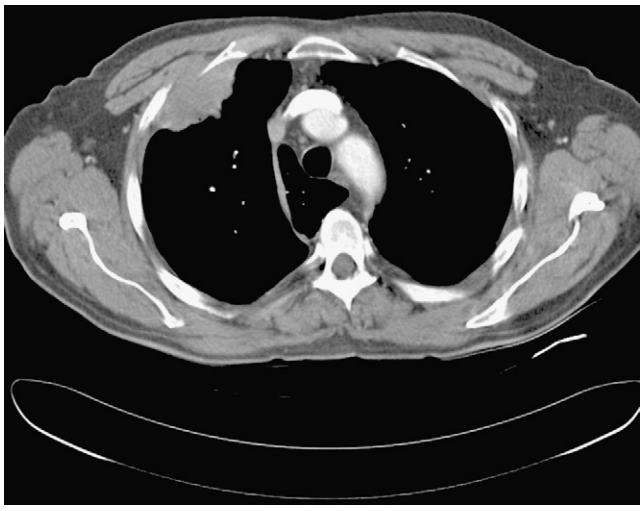

Fig. 3. Sarcomatoid localised MPM (patient 8).

28F chest drains and the space between the patch and the muscles was drained using 1—2 large bore vacuum suction drains. All the patients received epidural analgesia intra- and postoperatively, were extubated in theatre and transferred to the Thoracic High Dependency Unit for postoperative recovery (Figs. 2—4).

### 2.3. Data acquisition and statistical methods

Data for all the patients were obtained from the prospective mesothelioma database held in our institution. Medical notes were reviewed retrospectively to retrieve data that was not immediately available from the database. Up-to-date survival data were obtained from the hospital's patient information system and from the patient's General Practitioners. Statistical analysis was carried out using the software application SPSS for Windows version 12, SPSS Inc., Chicago, USA. Survival curves were estimated using the Kaplan—Meier method.

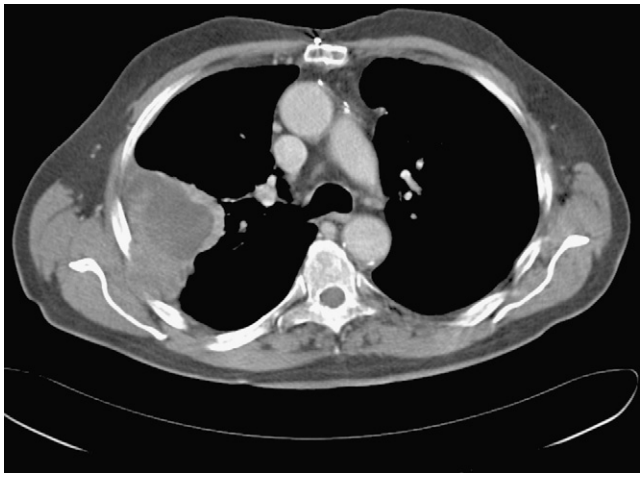

Fig. 4. Biphasic localised MPM (patient 5).

Table 1
Size of tumour and cell type

| Patient | Tumour size (mm) | Cell type |
|---|---|---|
| 1 | 140 × 90 × 35 | Epithelial |
| 2 | 190 × 80 × 30 | Epithelial |
| 3 | 180 × 100 × 70 | Epithelial |
| 4 | 150 × 110 × 60 | Sarcomatoid |
| 5 | 145 × 110 × 55 | Biphasic |
| 6 | 135 × 140 × 170 | Epithelial |
| 7 | 66 × 50 × 60 | Biphasic |
| 8 | 60 × 30 × 70 | Sarcomatoid |
| 9 | 110 × 70 × 30 | Sarcomatoid |
| 10 | 70 × 70 × 45 | Sarcomatoid |

## 3. Results

### *3.1. Patients, perioperative events and adjuvant treatment*

There were no early (30 days) deaths. Two patients needed CT and U/S guided drainage for loculated pleural effusions following the operation.

Microscopic complete resection (R0) was reported in two patients and macroscopic complete resection (R1) in eight. In one case the tumour was extending to the cervical tissues (T4), in a second one the tumour was necrotic and the remaining eight were staged as T3. The mean postoperative stay was 10.4 days (7–14).

Histological examination confirmed malignant pleural mesothelioma in all 10 cases. Immunohistochemistry was performed in nine specimens to confirm the diagnosis of MPM. The size of the tumours resected and the cell type are presented in Table 1. Two of the patients received preoperative chemotherapy, six postoperative chemotherapy and seven postoperative radiotherapy. The duration of follow-up was 1–74 (median 15) months.

### *3.2. Survival*

Two patients in the localised group died from disease progression 3 and 10 months after the operation and a further 2 developed disease progression but were still alive at the time that data was updated. In all four patients, disease progression was in the site of surgery, not in the pleura distant to it or in the form of metastasis. Mean actuarial survival was estimated at 56 months (SE 9). It is of note that the longest survivor in the series remains disease-free 70 months after the operation.

## 4. Discussion

The first accurate pathologic description of mesothelioma was published in 1931 by Klemperer and Rabin [3]. The authors classified the disease as either localised or diffused. The diffuse form was assumed to be derived from the mesothelial cells and the localised tumours were derived from the submesothelial layer [4,5]. This started a dispute that lasted for decades over the origin of the tumours. In the first large review series of solitary fibrous tumours of the pleura published in 1981, Brisseli et al. pointed out that the localised primary tumours of the pleura have received a variety of names, including localised mesothelioma [6]. A few years later, in 1989, England et al. suggested that the term localised fibrous tumour of the pleura should be used instead of localised mesothelioma to describe these tumours because they did not express epithelial differentiation [7]. Nomenclature in the area has been a historic problem because the term localised mesothelioma was used to describe a variety of primary localised pleural tumours [1] such as solitary fibrous tumours of the pleura [2,7], diffuse malignant pleural mesothelioma [8] and haemangiopericytomas [9]. It appears that the first series of 'true' localised malignant mesotheliomas is the one published by Crotty et al. in 1994 [2] and the largest the one published by Allen et al. in 2005 [1]. Exposure to asbestos was positive in 3 out of 6 patients in the Crotty and 4 out of 23 in the Allen series. Nine out of the 10 patients in our series had occupational exposure to asbestos. Mean age at presentation was similar in our series as it was in the others (between 60 and 65 years of age) but there were no females amongst our patients (40–60% in the other series) [1,2].

Chemotherapy and radiotherapy in our series were used on the rationale that since trimodality treatment (surgery, chemotherapy, radiotherapy) is associated with the best results when treating diffuse MPM [10,11], the same logic should be applied when treating the localised variant. It is our institutional policy to refer all patients that undergo therapeutic resection for mesothelioma for adjuvant chemotherapy and radiotherapy. Some of the patients will not get adjuvant treatment because of suboptimal postoperative recovery, individual oncologist's preferences and local policies. There does not appear to be any published evidence for or against the use of adjuvant treatment for localised MPM.

Our long-term results are similar to the ones published by Allen et al. [1] and Crotty et al. [2]: encouraging medium- and long-term survival in our series are similar to the result reported by others [1,2]. The disease recurrences in our series occurred locally with no patients demonstrating the metastatic pattern that Allen et al. reported [1].

The limitations of our report are evident. The number of cases is small and the follow-up period in the majority of the cases is short. We cannot assess the effect that adjuvant chemotherapy and radiotherapy had on the survival and quality of life of the patients. Nevertheless we feel that our results justify our policy to perform less radical surgery in patients with the localised variant.

In conclusion, we agree with most of the reports in the literature that localised MPM demonstrates a different biological behaviour compared to MPM. Locally aggressive surgery is justified in these patients who may not be considered suitable for EPP due to 'diffuse' chest wall invasion and who may not tolerate the combined physiological insult of EPP and chest wall resection. Adjuvant chemotherapy and radiotherapy might have a role to play in the management of localised MPM but further studies are required to assess its efficacy. Most definitely, further research regarding the origin and biological behaviour of these rare tumours is needed.

## References

[1] Allen TC, Cagle PT, Churg AM, Colby TV, Gibbs AR, Hammar SP, Corson JM, Grimes MM, Ordonez NG, Roggli V, Travis WD, Wick MR.

Localized malignant mesothelioma. Am J Surg Pathol 2005;29(7): 866—73.
[2] Crotty TB, Myers JL, Katzenstein AL, Tazelaar HD, Swensen SJ, Churg A. Localized malignant mesothelioma. A clinicopathologic and flow cytometric study. Am J Surg Pathol 1994;18(4):357—63.
[3] Klemperer P, Rabin CB. Primary neoplasms of the pleura. A report of five cases. Arch Pathol 1931;11:385—412.
[4] Suter M, Gebhard S, Boumghar M, Peloponisios N, Genton CY. Localized fibrous tumours of the pleura: 15 new cases and review of the literature. Eur J Cardiothorac Surg 1998;14(5):453—9.
[5] Robinson LA, Reilly RB. Localized pleural mesothelioma. The clinical spectrum. Chest 1994;106(5):1611—5.
[6] Briselli M, Mark EJ, Dickersin GR. Solitary fibrous tumors of the pleura: eight new cases and review of 360 cases in the literature. Cancer 1981;47(11):2678—89.
[7] England DM, Hochholzer L, McCarthy MJ. Localized benign and malignant fibrous tumors of the pleura. A clinicopathologic review of 223 cases. Am J Surg Pathol 1989;13(8):640—58.
[8] Okike N, Bernatz PE, Woolner LB. Localized mesothelioma of the pleura: benign and malignant variants. J Thorac Cardiovasc Surg 1978;75(3): 363—72.
[9] Gengler C, Guillou L. Solitary fibrous tumour and haemangiopericytoma: evolution of a concept. Histopathology 2006;48(1):63—74.
[10] Sugarbaker DJ, Garcia JP. Multimodality therapy for malignant pleural mesothelioma. Chest 1997;112(4 Suppl.):272S—5S.
[11] Sugarbaker DJ, Flores RM, Jaklitsch MT, Richards WG, Strauss GM, Corson JM, DeCamp Jr MM, Swanson SJ, Bueno R, Lukanich JM, Baldini EH, Mentzer SJ. 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;117(1):54—63.

## Appendix A. Conference discussion

***Dr G. Friedel*** (*Stuttgart, Germany*): Did I understand it correctly that you have 80% R1 resection? What was the cause to do so much incomplete resections?

***Dr A. Nakas***: Yes. The cause was that we were fairly close to macroscopic tumour. All resections were macroscopically complete. It just happened. All these tumours were big tumours; we didn't resect any small tumours in this group so we could not really be very generous with the margins. We tried to stay at least 1 cm from the margins, but in all the cases it was actually the pleura which was infiltrated and came back as positive.

***Dr J. Pilling*** (*London, U.K.*): In a number of reports of these localised tumours there has been a strong lymphocytic plasma cell infiltration from the tumour. Was that your experience in the tumour you have resected?

***Dr A. Nakas***: I cannot answer that, because I didn't look at the pathology specifically for this. But I will look at it.

***Dr T.W. Rice*** (*Cleveland, OH*): I am a little confused about what you are describing. Are these fibrous tumours of the pleura which arise from the subpleural fibrous tissue or are they mesothelioma? You should separate these two. What is a localised mesothelioma? Do you think what you are describing is the malignant variant of fibrous tumours of the pleura or are you describing some form of a pleural mesothelioma? You should be able to tell the difference! Have you mixed two entities in these 9 cases? It is confusing!

***Dr A. Nakas***: I do get your point. What was reported in the literature as the malignant variety of the solitary fibrous tumours of the pleura has been described as localised malignant mesothelioma.

***Dr T.W. Rice***: Is this a malignant variant of a pleural fibroma, a sarcoma? These are not mesotheliomas.

***Dr A. Nakas***: No, we are not talking about sarcomas, we are talking about the tumours that they have been described arising from mesothelial cells. These tumours have been described by the pathologists as malignant fibrous tumours of the pleura. Which one is mesothelioma? It is the one arising from mesothelial cells and it is malignant. This is what I am talking about.

***Dr T.W. Rice***: There is a malignant variant of benign fibrous tumour of the pleura, and I think that is what you are describing.

***Dr A. Nakas***: What I am talking about was these 9 cases, who were all malignant pleural mesotheliomas, our pathologists reported them as malignant pleural mesothelioma.

***Dr T.W. Rice***: Maybe they got it wrong. Certainly your 4 sarcomatous tumours could be malignant fibrous tumours of the pleura. They are different entities, one is a diffuse mesothelioma and the other is a sarcoma of fibrous tissue.

***Dr A. Nakas***: There is a localised process which has been reported in the series that I just mentioned as localised mesothelioma before.

***Dr T.W. Rice***: I think you may have two different things mixed together and you have 9 unrelated tumours.

***Dr A. Nakas***: I think that some of the tumours are referred to as malignant fibrous tumours of the pleura, whereas they are actually malignant mesotheliomas and have been reported as mesotheliomas.

Now if pathologists in the past or even now are wrong and we are talking about two different entities that we grouped together, we don't know, but people have been reporting isolated mesothelioma of the pleura as malignant variety.

***Dr T.W. Rice***: Have they reported benign fibrous tumours as benign mesothelioma? There have been advances in pathology. They should be able to separate benign fibrous tumours of the pleura from mesotheliomas.

***Dr L. Molins*** (*Barcelona, Spain*): It looks that it is a pretty controversial issue. The fact is that you did show that all your cases were arising from parietal pleura, not from visceral pleura.

Were perhaps those tumours from visceral pleura? The one which Dr Rice is talking about, is the malignant version of localised fibrous mesothelioma, which are very different because they are long standing tumours.

The question will be: did you find parietal pleura mesothelioma and not visceral ones?

***Dr A. Nakas***: Well 6 of these tumours were infiltrating the lung, so we can't really tell if they were rising from the parietal and they were going to the visceral pleura, or the other way round, because they were all invading the chest wall obviously. All these tumours have been tested for markers and have been reported as mesotheliomas by our pathologists. This is why I refer to these tumours as mesotheliomas.

***Dr W.H. Warren*** (*Chicago, IL*): When you say 'these were tested from markers', were they tested for grade? What is a good marker for these solitary fibrous mesotheliomas?

***Dr A. Nakas***: I cannot answer that question. I am not sure about this. I don't think they were tested for grade. I haven't looked specifically for that.