Introduction: Histological subtype is an established prognostic factor in malignant pleural mesothelioma (MPM). We retrospectively investigated the accuracy of classifying histological subtype on diagnostic biopsies and examined the impact of different diagnostic procedures on the outcome.

Methods: Consecutive patients with histologically confirmed MPM who underwent extrapleural pneumonectomy (EPP) from 1994 to 2009 were included. Patient records were reviewed, and the initial diagnoses of histological subtype were obtained. The archival EPP specimens were reviewed by a panel of pathologists. The histological subtype obtained at review was compared with the initial diagnosis.

Results: Eighty-five patients underwent EPP. Two patients achieved a pathological complete response after neoadjuvant chemotherapy, leaving 83 patients to be included in this review. Different diagnostic methods were used before EPP: 81% thoracoscopy; 7% thoracotomy; 11% computed tomography-guided procedure; and 1% other. Patients determined to have an epithelial subtype (n = 64) at EPP were diagnosed correctly at initial diagnostic biopsy in 84% of cases, whereas patients considered to have a biphasic subtype (n = 19) at EPP were diagnosed correctly at diagnostic biopsy in 26% of cases. The sensitivity and specificity of diagnostic biopsy for epithelial MPM was 93% and 31%, respectively. The overall subtype misclassification rate was 20%. Biopsy by thoracotomy was most accurate in subtype classification (83%) compared with radiological-guided biopsies. Of the long latency period between asbestos exposure and development of MPM,2 and the continued widespread use of asbestos in industrializing countries in Asia,3 MPM will remain a worldwide health issue for many decades to come.

Despite suspicious clinical symptoms, a typical chest x-ray appearance, or computed tomography (CT) findings suggestive of a unilateral pleural effusion or pleural thickening, even when accompanied by a history of asbestos exposure, the definitive diagnosis of MPM cannot be made without a tissue diagnosis. At times, MPM may be diagnosed by cytologic examination of the pleural effusion in combination with characteristic radiological appearances and appropriate follow-up; however, the results are often equivocal, or insufficient material is obtained to provide a definitive diagnosis. Therefore, definitive histologic diagnosis by radiological-guided core biopsy, video-assisted thoracoscopic biopsy, or open pleural biopsy is often required. The World Health Organization classification of tumors of the lung and pleura recognizes three major subtypes of MPM: epithelial, sarcomatoid, and biphasic. Accurate histological subtyping is important, as histological subtype is a validated prognostic factor. Survival of patients with epithelial tumors is better than that of patients with nonepithelial tumors.5-7

Some clinicians believe that only patients with epithelial subtype should be eligible for extrapleural pneumonectomy (EPP), as the natural history of the disease does not seem to be altered by radical surgery in patients with biphasic or sarcomatoid mesothelioma.8,9 Hence, accurate subtyping before radical surgery is paramount. Nevertheless, because of heterogeneity of MPM, sampling errors can affect relatively small diagnostic biopsies, and accurate subtyping may not be achieved by diagnostic biopsy alone.

Conclusions: The determination of histological subtype from a diagnostic biopsy is difficult due to sampling error, but an adequate specimen obtained from surgical biopsy increases the accuracy of subtype classification compared with radiological-guided biopsies.

Key Words: Malignant pleural mesothelioma, Epithelial mesothelioma, Biphasic mesothelioma, Diagnosis.

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always be feasible, even when the biopsies are obtained by thoracoscopy.\textsuperscript{10,11}

Although it is widely accepted that diagnostic biopsies by video-assisted thoracoscopy or thoracotomy are more likely to provide sufficient material for accurate histological diagnosis of mesothelioma than core or closed pleural biopsies on fine needle aspirate,\textsuperscript{12} it is not known whether this approach provides greater accuracy in ascertaining the histological subtype compared with other less invasive procedures.

The experience of our group with EPP since 1994 has allowed a comparison between subtyping of the initial diagnostic biopsy and that of the final EPP specimen.\textsuperscript{13} In this study, we have examined the accuracy of subtyping on biopsy samples obtained by thoracoscopy, thoracotomy, or a CT-guided approach using the final diagnosis by a review panel as the gold standard. In addition, we have explored the accuracy of different biopsy procedures on the diagnosis.

MATERIALS AND METHODS

Eighty-five consecutive patients with MPM who underwent EPP at Royal Prince Alfred and Strathfield Private Hospitals, Sydney, Australia, were included in the study. For each patient, the operative notes, outpatient records, and pathology reports from the medical charts and electronic records were reviewed in full. The initial assessment of the subtype was derived from the diagnostic pathology report. Seventy-eight archival EPP specimens were resected, stained with calretinin (Invitrogen), D2-40 (Signet), BG-8 (Signet), and CD15 (Dako), and reviewed by pathologists with substantial experience in MPM (K.L. and S.K.) independently. The total number of sections had not been recorded for all EPP specimens, but where data were available ($n = 66$), the median number of sections that resulted from each EPP procedure was 23, with a range from 12 to 57. Pathologists were blinded to the original subtype diagnosis, and discrepancy in assessment between the pathologists was reviewed by the most senior pathologist (D.W.H.).

Histological Subtype Assignment

The histological subtypes were assigned in accordance with World Health Organization criteria and recommendations. The presence of an epithelial component was assessed by the presence of an “epithelioid” cytology in terms of rounded to polygonal neoplastic cells, usually with at least focal tubular, papillary, or trabecular patterns for the cells, or their disposition as sheets of cells, whereas a sarcomatoid component was assessed by the presence of nonepithelioid spindle-cell tissue, usually resembling fibrosarcoma or malignant fibrous histiocytoma. On rare occasions, it may be difficult to ascertain whether the cells are epithelial or mesenchymal (histiocytes) in character, and such mesotheliomas have been designated as “transitional”: in this circumstance, classification as either epithelioid or sarcomatoid tissue may be facilitated by a transition to adjacent more obvious epithelioid or sarcomatoid tissue, and by immunohistochemistry (with absent or restricted labeling for/with mesothelial markers). There were no true “transitional” mesotheliomas in our series of cases.

A biphasic histological subtype was assigned only if both subtypes (epithelial and sarcomatoid) were accounted for more than 10% of cross-sectional area. The archival tissue for the remaining five EPP specimens was unable to be located, and the histological subtype was determined from the pathology report.

This study was approved by the Human Research Ethics Committees at the Sydney South West Area Health Service—Concord Repatriation General Hospital Zone.

Statistical Analysis

Using the final histological subtype of the EPP specimen as the gold standard, the sensitivity, specificity, positive predictive value, and negative predictive value were determined for the accuracy of the initial biopsy histological subtype diagnosis. This analysis comprised only patients with a pre-EPP diagnosis of an epithelial or a nonepithelial (biphasic and sarcomatoid) subtype and excluded patients without an initial subtype or a negative initial biopsy.

RESULTS

Patient Cohort

The median age of the 85 patients in the EPP cohort was 58 years (range: 22–74). Eighty percent of patients were men. Fifty-eight percent of patients had a right-sided EPP.

The initial pathological diagnoses were based on histology in 91% of patients and in 9% on cytological examination of the pleural effusion or from the fine needle biopsy. The diagnostic procedures that resulted in the diagnosis for all 85 patients included thoracoscopy (81%), thoracotomy (7%), CT-guided procedure (11%), and biopsy of a chest wall nodule (1%). All 9% of cytological examination of the pleural effusion resulted from a CT-guided procedure.

All but two patients had definitive pathological diagnosis of MPM before EPP. The two remaining patients proceeded to EPP based on a highly suspicious pleural aspirate (obtained by CT-guided needle).

Nineteen patients (22%) had preoperative therapy: 18 were treated with neoadjuvant chemotherapy, whereas one was treated with concurrent chemoradiation. Two patients attained a pathological complete response with the combination of a platinum and pemetrexed, limiting our study series to 83 patients. Figure 1 demonstrates the flow diagram of our study.

Comparison between Initial and Final Histological Subtype

Table 1 demonstrates the relationship between the initial and final histological subtype diagnoses of resected MPM. Of the 83 patients with MPM with residual tumor at EPP, 64 (77%) had an epithelial MPM, whereas 19 (23%) were found on review to have a biphasic MPM.

Among those 64 patients with an epithelial subtype at EPP, 54 (84%) had been classified as epithelial on the basis of the pre-EPP diagnosis, three (5%) were classified as biphasic, one (2%) was classified as sarcomatoid, whereas classification was not possible in six (9%) including the two patients with suspicious cytology mentioned earlier in the text.
A biphasic MPM was found after EPP in 17% of patients initially diagnosed with an epithelial subtype, while 3% of patients with a nonepithelial classification on the final specimen failed to show any sarcomatoid component. Therefore, the accuracy of subtype classification and the adequacy of tissue sampling is likely to be important to obtain an accurate histological subtype classification.

A consideration of the diagnostic accuracy of the histological subtyping is better in biopsies obtained by thoracoscopy (83%) than thoracotomy (74%), although we acknowledge the limitation of the small number of patients in the subset who had thoracotomy procedures (n = 9), which may limit the interpretation of these results. Thus, the adequacy of tissue sampling is likely to be important to obtain an accurate histological subtype classification. If an initial nonepithelial subtype diagnosis had served as an exclusion criterion, four patients would have been excluded from EPP due to sampling error. Conversely, 17% of patients with an epithelial subtype on initial biopsy had nonepithelial classification on the final specimen. Misclassification rate is relatively high, and on the basis of low negative predictive value seen in our study, we caution using subtype as a selection criterion for EPP, unless a large diagnostic biopsy specimen was obtained and the histological subtype assignment was deemed accurate.

In conclusion, an adequate pleural biopsy increases the accuracy of histological subtyping. In addition, this series underscores the inherent problems of sampling errors and inaccurate histological subtyping due to inadequacy of samples.

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