

Editorial

Histological classification of lung cancer

In 1924, when lung cancer was an uncommon disease, Marchesani proposed a classification of lung cancer into four histological groups. This was later expanded in the World Health Organisation's histological classification of lung tumours of 1967.¹ Further modification was found necessary and a second edition was produced by the WHO in 1981.² This includes, under the heading "Malignant epithelial tumours," eight major groups, 12 variants or subtypes, and additional recommended sub-groups based on the degree of differentiation. Whimster in a volume reviewed on page 178 of this issue refers to some 70 tumours or tumour like conditions which have been reported as occurring in the lungs or pleura.³

How can we reconcile such apparent pathological complexity with the need for a histological classification of lung tumours appropriate for day to day clinical practice? Most clinicians and some pathologists ignore the extended pathological classifications and manage with a condensed version of four headings: squamous carcinoma, adenocarcinoma, small cell undifferentiated carcinoma, and large cell undifferentiated carcinoma without further subdivision—shades of Marchesani. Such a shorthand summary of lung cancer classification is valuable for day to day discussion but is it valid as a serious classification given the complexity of the latest WHO classification? Is there evidence that the numerous subtypes detailed in this classification have any clinical significance?

There are some features in the natural history of tumours which appear to be related to their histological type. The rapid growth and early metastasis of small cell carcinoma is well recognised. Squamous carcinomas tend to grow slowly and metastasise late and a large proportion have not extended beyond the thorax at the time of death, whereas adenocarcinomas and large cell undifferentiated carcinomas fall in between these two extremes. When groups of tumours of comparable stage are compared, differences in prognosis can be shown to be related to the cell type.⁴ Differences in tumour behaviour are also revealed by response to treatment. For example,

among patients undergoing resection who had diseased but resectable mediastinal nodes, those whose tumours had a squamous pattern of differentiation had a significantly better prognosis than those with either adenocarcinomas or large cell undifferentiated carcinomas⁵ and similar, better results for squamous carcinoma are seen for radiotherapy.⁶ When adenocarcinomas and squamous carcinomas are subdivided by degree of differentiation the better differentiated tumours have a less aggressive natural history than the poorly differentiated.⁷

The response of small cell carcinoma to chemotherapy is well known and there are chemotherapeutic regimens which appear to have a preferential effect on adenocarcinomas.⁸ Evidence is accumulating that the subgroups of small carcinoma detailed in the WHO 1981 classification have clinical significance. It has been reported that the untreated classical oat cell carcinoma (the WHO 1981 subgroup a) is associated with longer survival than untreated non-classical oat cell carcinoma (subgroup b),⁹ while varying responses with chemotherapeutic regimens have been reported.¹⁰ Large cell undifferentiated carcinoma with stratification appears to be associated with a better prognosis than large cell carcinoma without stratification (WHO, 1967) after surgery.¹¹

The natural history and behaviour of some of the minor variants are known—for example, the giant cell variant of large undifferentiated carcinoma,¹² which has a fulminant course—whereas in the case of other tumours—for example, the spindle cell variant of squamous cell carcinoma—the natural history and response to treatment are unknown.³

It is clear that there are links between major and minor histological groups of lung cancer and the natural history and response to treatment. At present, where new therapeutic regimens are being tried on groups of tumours other than small cell it appears essential to keep the options open with a wide range of histological groups so that any factor which might select a group of particular response pattern may be identified. At the same time we need a simple form of classification which can be used without confusion. The ideal is a two tier system in which the major headings for day to day use reflect homogeneous groups of the more complicated classification. For example, squamous carcinoma

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would be used to refer to a group of tumours which are further subdivided on the basis of differentiation, but variants would be excluded; large cell undifferentiated carcinoma would refer to a specific group of tumours rather than a rag bag of variants and poorly diagnosed cases as at present. Such simplicity of concept is not seen in the current WHO classification, where variants as well as subgroups based on differentiation are all placed under major headings. The removal of the numerically small variant groups to a common group of unusual tumours would tidy up the classification and clarify problems of allocation when the diagnosis is based on cytology or small biopsy specimens.

The current use of four major headings without further qualification is probably inadequate if we are to get the most from clinicopathological correlations. There are two further particularly insidious dangers in this simplified usage: firstly, those who use such an abbreviated list of the classification may come to believe that all malignant lung tumours fall within these four groups; and, secondly, they may come to believe they are all talking about the same entities, the use of a common language seeming to confer comparability.

The proportions of malignant epithelial tumours which fall under the four main headings depends on how the cases are selected and on whether only surgical cases with adequate material prepared for histological classification are studied or all cases are considered, however diagnosed. Using the WHO 1981 classification on surgically resected material we find in Edinburgh that about 5–7% of lung tumours are of the mixed or adenosquamous variety, 2–3% are carcinoid or atypical carcinoid tumours, 1–2% are rare types, and about 2% are of such unusual pattern that they are difficult to classify into any of the defined groups (D Lamb and DJL Maloney, unpublished observations). This gives a group of around 12% of tumours which do not fit under the four major headings. If we consider cases diagnosed at presentation by cytology or by fibroptic bronchoscopic biopsy then a further group of perhaps 10–20% will not have cell types available (see below).

Many clinicians would comment that they exclude the rare variants from discussion or from the results of a therapeutic trial. That is only possible retrospectively once the diagnosis has been made. At the time of the first diagnosis, when decisions about the patient's management are being made, all groups of tumours must be considered. The minor groups detailed above include tumours of widely varying behaviour and are potentially confused, when biopsy material is used, with one or more of the "usual" carcinomas.

When the four main headings are used alone they should represent a summary or shorthand way of describing the main groups of the lung cancer classification being employed. There are five main classifications: the WHO classifications of 1967 and 1981,^{1,2} the classification of the Veterans Administration Lung Cancer Chemotherapy Study Group (VALG),¹³ that of the Working Party for Therapy of Lung Cancer (WP-L),¹³ and that described in the Armed Forces Institute of Pathology Fascicle by Carter and Eggleston.⁷ In addition, two further classifications are in use—those provided by the International Classification of Diseases (ICD-O) and by the Systematised Nomenclature of Medicine (SNOMED). These latter are really lists of headings with numerical codings intended for easy handling of medical data rather than true classifications and both are based on the first edition of the WHO classification. The five main classifications have been described and discussed elsewhere.^{3 13 14 15}

It is important to realise that these classifications differ significantly in the allocation of cases even between the main groups. For example, the VALG classification includes tumours which do not show keratin or intercellular bridges but which are of squamous pattern as a poorly differentiated version of squamous cell carcinoma. This group of cases would be included under "large cell carcinoma with stratification" in the WP-L scheme and under "large cell carcinoma, solid tumours without mucin" in the WHO 1967 classification. This is an important group of tumours, probably amounting to some 10% of all lung cancers. Poorly differentiated tumours showing the production of mucus by special stains but not showing acinar differentiation are variably listed under large cell undifferentiated carcinoma (WHO, 1967; WP-L) and as poorly differentiated adenocarcinoma by WHO (1981), VALG, and Carter and Eggleston. This group of tumours probably accounts for about 30% of adenocarcinomas¹⁶ or about 5–7% of all lung tumours. The variation between classification mainly affects poorly differentiated tumours and particularly the group of large cell undifferentiated carcinoma. The varied significance of this group of tumours has led to its being used as a repository for all odd or poorly diagnosed tumours in addition to those more formally allocated. This is unfortunate as there is a group of pure large cell carcinomas, perhaps 7–8% of all lung tumours, about which remarkably little is known.

Apart from the quite large variation in the proportions of lung cancer allocated to histological subgroups by the design of the classification, there is the problem of how accurately tumours are allocated to the different groups by different pathologists. The

reproducibility of a classification is largely dependent on the quality and specificity of the criteria provided and the willingness of pathologists to apply them. Regrettably, this aspect of lung cancer classification leaves much room for improvement. In particular, there is little guidance in the "grey areas," where there may be histological doubt between two similar groups of tumours—for example, between poorly differentiated squamous carcinoma and large cell undifferentiated carcinoma. This lack of specific criteria allows different pathologists to interpret the guidelines differently.

Individual pathologists may show good reproducibility in their use of a classification, but when more than one pathologist is concerned the interobserver variation becomes a problem.^{10 17 18} We may get some idea of the size of the problem by considering the diagnosis of small cell carcinoma, believed by many to be simple and reproducible. In a recent review of over 850 lung tumours coming to thoracotomy from 1968 to 1972 we reviewed the histological material from all cases originally diagnosed by several pathologists and identified 123 cases of small cell carcinoma.¹⁹ To come to the final total of 123 small cell cases we had to change the original diagnosis from large cell to small cell in 13 cases and from small cell to large cell in eight. This gives a figure for the "grey area" between small cell carcinoma and large cell undifferentiated of some 17%. In addition, five examples of atypical carcinoid tumour had to be removed from the small cell carcinoma group.¹⁹ The problem is greater in the case of carcinomas other than small cell, particularly when classification is based on fiberoptic bronchoscopic biopsy. Chuang *et al*, comparing preoperative fiberoptic biopsy cell typing with the final diagnosis based on the resected specimen, found that 38% of the patients undergoing resection had incorrect preoperative cell typing and that only three of 24 large cell undifferentiated carcinomas were confirmed after surgery²⁰ (p 175 of this issue).

In the two WHO classifications the small cell carcinomas are subdivided into three subgroups. Hirsch *et al*¹⁰ investigated the interobserver variation in the diagnosis of small cell carcinoma and of the subtypes. The main diagnosis of small cell carcinoma was agreed by all three pathologists in just over 90% of cases, but in the diagnosis of the morphological subtypes unanimity between the three pathologists was achieved in only 38% of cases according to the WHO 1967 classification and in 54% on the basis of the 1981 classification. They concluded that these three experienced pathologists were applying different criteria in identifying the subtypes of small cell carcinoma and suggested that this could explain the contradictory results of clinical studies concerning

such subtypes. These results reflect the inadequacies of the general guidelines provided by the WHO classification. These authors propose further helpful diagnostic features to aid in the diagnosis of small cell carcinoma.

When we come to cytological diagnosis of lung tumours the histological typing becomes an even greater problem. Here the pathologist is attempting to identify a histological pattern of tumour using cytological criteria which were not designed necessarily to match the histological classification in use. Most cytologists refer to the classical work of Koss, which gives a simple grouping of tumour types and the criteria for identifying them.²¹ Since these criteria were first described, however, the histological classifications have changed significantly—the change between the 1967 and 1981 WHO classifications being a striking example. There have been no attempts to match up the cytological criteria with altered histological classification. A major factor affecting classification is the wide observer variation in the application of cytological criteria. This is in part due to the variation in technical quality of preparation in different departments but, even when this is allowed for, any comparison between cytopathologists shows wide variation.²² In comparisons between cytology and subsequent histopathology some 80% of cytologically diagnosable neoplasms are found to be correctly typed.²³ The proportions of cases correctly typed by cytology vary appreciably between the different histological groups, well differentiated squamous carcinomas and small cell undifferentiated carcinomas being correctly diagnosed in over 90% of cases in some series; whereas in most series the poorly differentiated adenocarcinomas, poorly differentiated squamous carcinomas, and large cell undifferentiated carcinomas are correctly diagnosed in around 50% and sometimes in a lower proportion of cases.^{23 24} Some publications show better results than others and these usually concern studies in which individual pathologists have worked closely with individual cytopathologists or have carried out the cytological diagnosis themselves. Here again, we must not confuse reproducibility by one pathologist, or within a group, with comparability between groups.

In comparisons of the diagnostic accuracy achieved in cell typing cytology, biopsy sample, or resected specimen it is usually assumed that the final histological diagnosis is an absolute and that all the "errors" (or perhaps deviations would be a better term) are on the cytological side. This ignores the problems of histological classification already referred to. The cytological features, as opposed to the tissue pattern, may be of more value than many his-

topathologists realise and could with advantage be incorporated into criteria applied to histological classification. This might lead to a fusion of the currently disparate criteria for cytology and for tissue diagnosis.

Accepting that there are problems in the histological typing of tumours when cytology or small biopsy specimens are used, how should we approach this problem? Chuang *et al*²⁰ (p 175) suggest that if no clearcut evidence of differentiation is seen tumours should be classified as "carcinoma, non-small cell type" but this infers that the tumour, whatever it is, is not a small cell carcinoma, which is not necessarily true. Yesner and Carter¹⁶ emphasise the importance of not overdiagnosing cases in which cytological or small biopsy material failed to show clear evidence of squamous, glandular, or small cell differentiation. They suggest that these cases should be included in the undifferentiated large cell carcinoma group. It is unfortunate that the large cell carcinoma group should again be used as a rag bag; there is much to be said for keeping it as a specific defined entity. There is, of course, a significant proportion of tumours which cytologically or in a small biopsy specimen do not show specific differentiation—which may, however, be seen after subsequent biopsy or resection. It seems preferable that at the time of their original diagnosis these cases should be put in the separate group "not showing evidence of adenocarcinoma or squamous or small cell differentiation on fiberoptic biopsy or cytology" until further evidence becomes available. The problem is one of sample size or sample quality or both and it seems unlikely that this can be overcome by applying more sophisticated techniques such as electron microscopy or any of the specific diagnostic monoclonal antibody techniques currently being developed. If in future with improved chemotherapeutic agents it proves advantageous to subdivide this group then it may be necessary, as a routine, to proceed to more invasive diagnostic techniques.

Those interested in assessing the effects of changes in management such as new techniques of staging or new forms of chemotherapy need to take into account those aspects which may independently affect the natural history of the tumour and the response to treatment. The most important of these factors at present is the histological classification. A major ethical consideration when a clinical trial is being set up is that the trial should be carried out in a proper scientific manner so that as much information as possible is gained from the procedures undertaken and made available for publication. Careful choice of histological classification and some form of quality control of its use are as essential as the clinical

controls built into the selection of cases in the comparison of therapeutic regimens. It is inadequate for a trial to appoint a referee, or even a small group of referees, to enter cases based on histological appearances unless there is a basis of specific and detailed agreed criteria. This point requires emphasis as it is easy to pay lip service to the principle and say that tumours were classified "according to the WHO classification" when all the pathologist is doing is using the same headings. Such agreed criteria should have been published and shown to work both reproducibly by single pathologists and compatibly by different pathologists. If one pathologist acts as a referee or a small committee acts by consensus without such criteria the consequence is a result which may or may not be comparable to the results of other groups. The aim of clinical trials is to provide information by which all may benefit, not just the centre concerned.

There are problems in the histological classification of lung tumours. The aim should surely be—at least nationally, and under ideal conditions internationally—to develop the use of a common classification with defined histological criteria and with sufficient knowledge of intraobserver and interobserver variation to be able to assess how meaningful the groupings are. The differences between histological classifications are not fundamental in the sense that they recognise different histological groups, but rather interpretive in that they make different decisions about where such groups should be fitted into the classification or where to draw the line between related or similar groups. Perhaps the final decision on which classification is to be used should be based empirically on which classification provides the most reproducible results in use for histological diagnosis when large or small amounts of tissue are available and for cytological diagnosis.

The inadequacies of pathological classification and its application are recognised by pathologists and they should be recognised and understood by clinicians. The responsibility for improving classification must be shared between those who provide the data and those who use the data.

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