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*EDITORIAL*

# Prognostic factors in malignant mesothelioma: where do we go from here?

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One of the characteristics of mankind is its desire to know before or prognosticate. This explains the popularity of oracles and astrologers in ancient times. Foreknowledge about the outcome of a battle or the yield of a harvest could be of obvious importance to a ruler. In earlier days there was no concept of chance, for this developed only recently in the history of man. Since the birth of the idea of chance, however, predictions of the scientific future have fallen into the hands of statisticians.

In medicine, identification of prognostic factors is the present-day equivalent of predicting the future. This is true for most malignancies and mesothelioma is no exception. Several variables are known to influence the outcome of a cancer in an individual patient. Different classifications of them are appropriate depending on one's interests. A natural classification reflects the biological meaning of prognostic factors. It includes a) host factors like sex, age and race, b) tumour characteristics like morphology, size and extent, and c) the effects of tumour on the host *e.g.* performance status and weight loss. Knowledge of these factors is important and useful for the physician, the patient and his/her family for several reasons [1, 2]. The most obvious one is that it allows physicians who care for cancer patients to be able to answer questions from the patient and his/her family concerning the probable outcome of the disease. Secondly, the recognition of prognostic variables is of particular importance in the design of clinical trials of cancer therapy. Since the effects of these variables are frequently stronger than many cancer treatments, ignoring their influence in the conduct and analysis of clinical trials may conceal small but important effects of treatment. If, on the other hand, prognostic factors are not equally distributed between treatment groups, a difference in outcome may be mistakenly attributed to therapy. Furthermore, treatments may have different effects in patients with different prognostic characteristics. This is called treatment-covariate interaction. Hence, the need to take account of prognostic factors when reporting and comparing the results of a treatment. Knowledge of prognostic variables also helps in determining the necessary sample size and predicting the necessary duration of a study to obtain reasonable statistical power. Finally, when considering randomized studies, it is crucial to determine those prognostic variables for which to stratify at allocation of treatment or at retrospective analysis [3].

Recognition of the important influence of prognostic factors on the outcome of cancer patients has led to the development of methods of classifying cancer. Tumour size (T), node involvement (N) and metastatic disease (M) are strong prognostic attributes of many cancers. Thus, the widely used TNM-system of staging cancers is primarily a way of grouping together patients with the same anatomic extent of their cancer and a widely similar outcome.

Although it is common place to speak of the "natural history" of a tumour, the clinical course of untreated patients is seldom adequately known, since there are few opportunities for their observation. Even if no effective therapy is available, the administration of palliative treatment for complications such as pain or infection may favourably influence the patient's survival, even when the primary disease remains unaffected. A clinician's knowledge about prognosis then comes from personal recollections about similar patients, and from reports in the literature. The former may impair or distort his ability to use past experience as a guide to making predictions about present patients. Examples include a sharply limited capacity to retain items of quantitative information, a predilection to generalize from recent patients, and the undue influence exerted by the recollection of unusual or atypical cases. Thus, literature reports are more likely to be reliable sources of information about prognosis. Studies on prognostic factors examine the association between characteristics of patients or their diseases, and health outcomes, which in cancer usually means recurrence of disease or death.

In non-small cell lung cancer (NSCLC), experts have reached agreement on general criteria regarding the importance of different prognostic variables [4]. As it is felt that these statements also apply to malignant mesothelioma, they are included here:

1. It is fundamental to use both univariate and multivariate analyses to determine significant prognostic factors;
2. It is recommended that prospective collection of data be carried out during studies with analyses of pretreatment factors only;
3. Post-treatment factors, such as response to treatment, should only be used if corrections such as "landmark" and "transient state" analysis are included. The effects of response may relate to the host factors only, and not to the effects of treatment;

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4. Since they correct for unknown prognostic factors, randomized studies are ideal for defining significant new prognostic factors. These require large patient numbers, but only studies of this magnitude will actually identify new factors and clarify the value of old factors.

Therefore, the importance and validity of a certain prognostic factor will be much greater when it has been identified in a prospective randomized study with uni- and multivariate analysis, rather than in a retrospective review. On the other hand, complete follow-up data are necessary in these prospective studies, as patients who are lost to follow-up are unlikely to have experienced the same outcome as those who remain, introducing a considerable bias.

According to these criteria, only performance status and disease extent have been identified as of definite importance in the prognosis of NSCLC [4].

## Malignant mesothelioma

Malignant mesothelioma is a cancer usually originating from the parietal pleura and less frequently from the peritoneum or pericardium. There is ample epidemiological and experimental evidence pointing towards a causal association with previous asbestos exposure, besides a very low "background" incidence [5]. The increasing use of asbestos in society is reflected, with a 20 year delay, in a similarly increasing incidence of malignant mesothelioma. Besides mining areas like Western Australia, incidence rates of mesothelioma are highest in districts that harbour ship building and repair industries, *e.g.* the Rotterdam, Marseilles and Antwerp areas.

In spite of, or perhaps because of, its histogenesis, malignant mesothelioma is a very difficult tumour to diagnose early. The symptoms are quite diverse, although almost all patients present with either chest pain, dyspnoea or cough due to the presence of pleural fluid and invasion of the thoracic wall. Most cases require an open or closed pleural biopsy as pleural fluid analysis has a low sensitivity. Treatment of mesothelioma has proven disappointing, regardless of the modality used [6]. Median survival is less than 1 yr (7–10 months) with less than 5% 5-yr survivors.

In 1976, BUTCHART *et al*. stressed the prognostic importance of disease extent and histological subtype [7]. It is, however, unclear whether a multivariate analysis was applied in their analysis. Nevertheless, their experience laid the base for a staging system that is still widely in use, although it involves surgical and pathological techniques. Recent refinements in staging techniques using thoracoscopy, computed tomography (CT) and magnetic resonance image (MRI) scan have led to a new TNM-staging system for malignant pleural mesothelioma [8]. Its obvious advantage is that, being clinical, it can be used outside the surgical context. Its importance as a prognostic factor has until now not been validated, although through its analogy with Butchart's classification, this may soon be available. Since 1976, various other variables have been proposed as of prognostic importance [9–24]. However, only a few have met the criterium of randomization [9, 13]. In these studies good performance status (PS) 0 and 1, and absence of prior treatment were each associated with a longer survival duration. As the latter is a so-called "treatment factor", its importance has to be validated by a "transient state" analysis. In one of the randomized studies, there was a trend toward a longer survival for cases classified as epithelial [9]. In neither study did tumour stage turn out to be an independent prognostic variable. However, in several prospective non-randomized series Butchart's stage I/IIA, pleural site and epithelial subtype are associated with a less unfavourable prognosis [10–12, 15]. The latter two reflect the observation that nearly all cases of long survival have been reported in patients with epithelial subtype and pleural localization. In the only prospective study in which no survival differences were found for these different factors, it is unclear whether a multivariate analysis was performed [14]. Most retrospective series confirm the importance of the above mentioned prognostic factors: disease extent, PS and histological subtype [16–22]. The study by VAN GELDER *et al*. [23], published in this issue of the Journal, reports the Rotterdam experience in a population with a high asbestos-related mesothelioma incidence. All other parameters, possibly connected with a favourable prognosis, are doubtful and none of them has ever repeatedly been identified. This is the case for age, race, sex, site, duration and type of initial symptoms and presence of asbestos exposure. Some studies even gave contradictory results [24].

As yet, no single biological factor has unequivocally been isolated as prognostic. Studies with flow cytometric analysis of DNA-content and cytogenetic changes have spurred research into the molecular biological background of the tumour [11, 19]. Unlike in NSCLC, no single gene point mutation or oncogene product has been prospectively identified as an independent prognostic variable. Only the presence of *p21*-ras immunoreactivity in tumour tissue appears to bear a less unfavourable prognosis compared to its absence [25]. Further research in this field is needed.

Nearly 20 yrs after BUTCHART *et al.* [7] wrote that "stage I cases of pure epithelial histological type appear to carry a better prognosis", we still have not identified any new valid prognostic factors in a disease that badly needs new prospects in therapy. As in NSCLC, disease extent and PS are of definite prognostic importance. Unlike in NSCLC, histological subtype seems to influence survival. However, the relative difficulty of exact histological subtyping on small biopsies or cytological specimens, compared to larger thoracoscopic or necropsy samples, must be taken into consideration. In this regard, it seems unlikely that tumour histology can be used as a stratification factor when comparing results from different centres using different diagnostic modalities. All other variables appear to have no clear clinical value.

Regrettably, as long as no randomized clinical studies are conducted in which a stratification for these factors is made, their use will be restricted to modulate the prediction of outcome for an individual mesothelioma patient. The design of such studies depends on the identification, by several phase 2 studies, of a treatment active in more than 15–20% of patients. Most authors still feel that

this is not yet the case and advocate further (randomized) phase 2 studies in malignant mesothelioma [7, 26].

Thus, in what directions should the study of prognostic factors proceed, keeping in mind the aforementioned statements?

1. To validate the new TNM staging system, its importance as a prognostic factor requires rapid confirmation. This can easily be done by combining and analyzing data of all available phase 2 studies.
2. New prospective studies should preferably use this TNM classification. This will make clinicians more experienced with its use. As a transition, both Butchart's and TNM staging systems can be used. A conversion table between both has been published [10].
3. As long as no active treatment is available, further identification of "post-treatment factors" is futile, as their only possible use could be in studies which include a second therapeutic intervention.
4. In the design of all future phase 2 studies, a major emphasis should be placed on prospective collection of data relating to biological factors. These should be collected from laboratory tests performed on patient samples of tumour and/or normal tissues. Efforts should concentrate particularly on molecular biological changes as studies in patients with NSCLC have shown that a point mutation can have a tremendous impact on survival [27]. Besides conferring a possible prognostic factor, these studies can provide us with a lever, useful in the future (gene-) therapy of malignant mesothelioma.

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