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Editorial Comment

Prognostic factors in head and neck cancer

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Prognostic factors are necessary to categorise head and neck cancer patients into well-defined groups, to optimally inform patients, select the most appropriate treatment and to be able to compare treatment results. In this issue of the *European Journal of Cancer*, Rodrigo and co-authors [1] describe a well-performed restrospective immunohistochemical study on the prognostic significance of E-cadherin expression in supraglottic laryngeal cancer. Until recently, research on this topic focused on clinical and morphological features such as tumour location and extent, number and level of lymph node metastases, extranodal tumour spread, as well as patient factors such as nutritional status and age [2,3]. As these clinical features have proven to be unreliable predictors for individual patients and several features can only be investigated after surgical resection, an extensive effort has started to identify features of the primary tumour that predict treatment response and prognosis. So far, most research relating to prognostic tumour features focused on protein expression of proteins involved in cell cycle regulation, signal transduction, apoptosis, cell adhesion and cell–extracellular matrix interaction [4–9]. Recently, apart from protein expression, genetic alterations have been correlated to prognosis as well [10–12]. Many of these studies have come up with markers or combinations of markers with independent prognostic significance for metastasis, treatment response or survival.

It is important to realise that prognostic features depend on the treatment modality as well. Factors predictive for tumour response to radiotherapy may not be important for patients treated with surgery and vice versa. This is certainly true for pure surgical features, such as the status of the resection margins [13], but may be as important for molecular features. Although it is likely that features relating to apoptosis or proliferation are of more importance for patients treated with radiotherapy or chemotherapy than in patients treated surgically, several studies have shown that proteins involved in the cell cycle are predictive for metastases as well [5,14]. It is therefore important to study prognostic factors in a well-defined patient group treated with the same modalities. With respect to this criterion, Rodrigo and colleagues [1] have studied a well-defined large group of patients with laryngeal carcinomas, all treated surgically and half treated with postoperative radiotherapy as well. Apart from their study, it has been shown in several publications that proteins related to invasion or angiogenesis, such as E-cadherin and metalloproteinases are of prognostic significance in head and neck cancer patients and are important for predicting metastases [15–22]. In this respect, the current article confirms the findings of most other studies.

A major difficulty in interpreting the results as presented in this study and the literature is that many authors report conflicting results. With respect to p53 overexpression for example some authors report a favourable prognosis [23], whilst some report a less favourable prognosis [24], and others found no influence at all [25]. The authors of the article in this issue describe the same problem for E-cadherin expression. These differences can be attributed to the fact that single markers are not predictive in all patients and a panel of markers is needed for reliable and reproducible results. However, other possibilities are that the heterogeneity of tumours and representability of the biopsies hampers the reliability of the protein expression analysis in biopsies. Another important bias is that the immunohistochemical scoring system used is not the same in different studies. In fact, scoring systems are often based on the results of the study itself. For example, Rodrigo dichotomised the E-cadherin staining score at the percentile 75 because this yielded optimal results in the univariate analysis in his series, whereas he did not

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validate this dichotomisation. Takes and colleagues on the other hand, dichotomised at 0% for E-cadherin [21]. So far, these problems and the contradictory clinicopathological correlations have prohibited wide acceptance and implementation of immunohistochemical markers to predict response or prognosis into clinical practice.

As the authors state, it is unlikely that one or a few markers will predict the clinical behaviour of a patient. In this respect, micro-array analysis of gene expression has high expectations. With this technique, the expression level of many thousands of genes can be analysed simultaneously [26]. Although the initial experiments are very promising, difficulties in RNA amplification, reproducibility and statistical analysis, as well as the high costs, still need to be resolved [27,28]. It might well be that within a few years, specific prognosis-related DNA-arrays become available at reasonable costs obviating the need for a panel of antibodies for immunohistochemistry.

Even though much work has been done to discover and refine predictive markers in head and neck cancer, much progress still needs to be made. A general conclusion from the available studies is that more than one marker will be needed to assess an individual patient's prognosis as it relates to treatment choices and outcome. Tumour marker profiles may be more valuable if they include at least several markers with unrelated or mutually opposing biological roles so that statistical assessments may divide patients in meaningful therapeutic or prognostic groups. Because immunohistochemistry is hampered by the variable scoring systems and because it is unpractical to test large panels of antibodies, the use of gene expression profiling is more promising. Furthermore, there is a great need to implement the currently available markers into prospective clinical trials to assess their efficacy.

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