J Clin Pathol 1991;44:876–878

CORRESPONDENCE

Prognostic value of morphometry in breast cancer

We completely agree with Dr Laroye and his colleagues that it is dangerous to draw any conclusions at all from the results of a study of only 75 patients with breast cancer. The Multivariate Prognostic Index (MPI) was developed in an initial study of 271 patients[1] and evaluated in two other studies, one retrospective (225 patients with long term follow up)[2] and one prospective (195 patients, with short term follow up[3] and subsequent longer term follow up).[4] In these studies a discrepancy between lymph node response (as negative or positive) and MPI (with 0·60 as the cut off) existed in 14–25% of all cases and the actual outcome of the patients was more in agreement with the MPI than with the lymph node classification. Other groups also found that the MPI offers exceedingly good prognostic value (Dr Collan, Finland; Dr Bathal, Melbourne; Dr Peterse, EORTC Amsterdam, personal communications).

In the meantime, we had the opportunity to discuss their results with Laroye and his colleagues. Their survival data indicate that: (a) lymph node response survival curves are similar to those of our previously published material.[1] This eliminates the possibility of differences in the accuracy of axillary lymph node sampling between our material; (b) that their patients with an MPI of more than 0·60 fared better than their lymph node positive patients.

There is only one explanation for this: that large tumour size and high mitotic rate in their material were associated with a better prognosis than cases without these features. This does not agree with all the reported findings of the past 65 years, and it seems that their findings should be interpreted very carefully.

We do not agree with their statement that a significant arithmetical error exists in our published paper,[2] and we also believe that our original conclusions are not correctly interpreted. We literally said: "in agreement with the results of the previous retrospective study, the prospective use of the index had the strongest predictive prognostic value, followed by the mitotic activity index. Statistical analysis showed that the actual prognoses of 43 of the 195 (22%) patients were more accurately determined by the prognostic index rather than by using the presence of the lymph node metastases as the classifying variable". This statement is true, because as mentioned in our article, the recurrence-free survival curves and Mantel-Cox values of the patients who were lymph node negative and had an MPI of >0·60 were no different from those who were lymph node positive. In fact, the survival curves showed complete overlap; the same was found for those who were lymph node positive with an MPI of less than 0·60 and those who were lymph node negative (figure).

To suggest that of the 13 patients with an MPI of more than 0·60 and without recurrence are "false positives", as Dr Laroye has done with our material, is a "fixed endpoint approach". This is absolutely wrong as in this prospective study the patients had variable and limited follow up. The authors could have used such an approach in our other studies (with long term follow up) or the subsequent paper on the prospective analysis[3] (also with longer term follow up); in all three, the overall predictive value of the MPI greatly exceeded that of lymph node response. The same phenomenon was found in premenopausal women.[5]

The finding that the MPI has such a strong prognostic value is very understandable, as the mitotic activity index is the most important feature in the MPI. That this proliferation marker is prognostically highly significant, more so than lymph node response, in premenopausal breast cancer patients and in carcinomas detected during population screening[6] is biologically acceptable and agrees with the results of Tosi *et al.*[7] It also fits in with the well established value of grading and is in accordance with the finding that the thymidine labelling index is a strong prognostic factor[8] in lymph node negative patients.[9]

Recently we finished a multicentre morphometric prospective study on more than 3500 breast cancer patients.[10] One of the conclusions of that study was that inaccurate mitotic activity index determinations can occur when people lack experience in morphometric assessments. Less easily explained is the lack of the prognostic value of the MPI.

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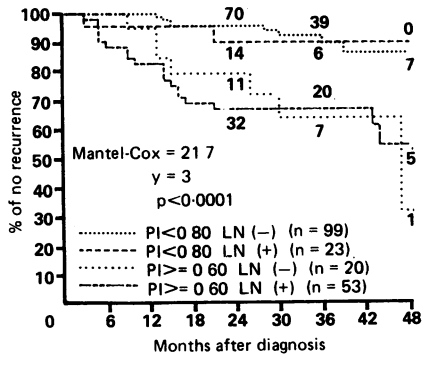

Recurrence-free survival curves.

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Role of aluminium sensitivity in delayed persistent immunisation reactions

We read with interest the report of angiolymphoid hyperplasia with eosinophilia,[1] describing the histology of subcutaneous nodules excised from five children at sites corresponding to previous immunisation injections. The authors suggest that the histological appearance might represent a reactive process to vaccination. The histological features described are similar to those reported by Fawcett and Smith of injection-site granuloma.[2] In their report biopsy specimens from immunisation sites showed focal granulomatous inflammation consisting of lymphoid follicles surrounded by a dense cellular infiltrate that included many eosinophils. Aluminium particles were shown in tissue sections using a solochrome-azurin stain. The authors postulated that the histological appearances were a consequence of a reactive process to the aluminium component of absorbent vaccines.

Aluminium hypersensitivity is recognised in contact dermatitis clinics and may be discovered accidentally during routine patch testing.[3] Aluminium Finn Chambers are used for application of patch test allergens; individuals allergic to aluminium develop eczematous reactions at all patch test sites. Aluminium sensitivity is also recognised as a cause of persistent subcutaneous nodules at sites of immunisation[3] or hyposensitisation injections[4] with aluminium precipitated allergens. When patch tested these subjects can be shown to be allergic to aluminium.

We suggest that the histological findings reported by Hallam *et al*[1] could be explained by an allergic reaction to the aluminium component of vaccines. The role of aluminium sensitivity could be investigated by patch testing their patients with aluminium and identifying aluminium within tissue sections.

Aluminium is widely used in absorbent vaccines and, although allergic reactions are rare, recognising the role of aluminium in persistent immunisation reactions is of practical importance as histology of these lesions may resemble a neoplastic process. An allergic patch test reaction to aluminium in such instances would favour a benign reactive process. In patients known to be allergic to