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 patients¹ 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 up³ 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 analysis³ (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 screening⁶ 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 factor⁸ 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.

- 1 Baak JPA, van Dop H, Kurver PHJ, Hermans JO. The value of morphometry to classic prognosticators in breast cancer. *Cancer* 1985;56:374-82.
- 2 van der Linden JC, Baak JPA, Lindeman J, *et al.* Prospective evaluation of prognostic value of morphometry in patients with primary breast cancer. *J Clin Pathol* 1987;40:302-6.
- 3 van der Linden JC, Lindeman J, Baak JPA, *et al.* The multivariate prognostic index and nuclear DNA content are independent prognostic factors in primary-breast-cancer patients. *Cytometry* 1989;10:56-61.
- 4 Uterlinde AM, Baak JPA, Schipper NW, *et al.* Further evaluation of the prognostic value of morphometric and flow cytometric parameters in breast-cancer patients with long follow-up. *Int J Cancer* 1990;45:1-7.
- 5 van Diest PJ, Baak JPA. The morphometric prognostic index is the strongest prognosticator in premenopausal lymph node-negative and lymph node-positive breast cancer patients. *Hum Pathol* 1991;22:326-30.

- 6 Uterlinde AM. Malignant behaviour of breast cancer. A morphometric and DNA flow cytometric study on hospital and population screening patients (Thesis). Free University Press, Amsterdam, 1988.
- 7 Tosi P, Luzi P, Sforza V, *et al.* Correlation between morphometrical parameters and disease-free-survival in ductal breast cancer treated only by surgery. *Appl Pathol* 1986;4:33-42.
- 8 Meyer JS, Bauer WC, Rao BR. Subpopulations of breast carcinoma defined by S-phase fraction, morphology, and estrogen receptor content. *Lab Invest* 1978;39:225-35.
- 9 Silvestrini R, Daidone MG, Gasparini G. Cell kinetics as a prognostic marker in node-negative breast cancer. *Cancer* 1985;56:1982-7.
- 10 Baak JPA, van Diest PJ, Ariens ATh, *et al.* The multicenter morphometric mammary carcinoma project (MMMCP). A nationwide prospective study on reproducibility and prognostic power of routine quantitative assessments in The Netherlands. *Path Res Pract* 1989;185:664-70.

Role of aluminium sensitivity in delayed persistent immunisation reactions

We read with interest the report of angio-lymphoid 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 immunisation⁴ or hyposensitisation injections⁴ 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

aluminium, plain vaccines should also be submitted for absorbent vaccines to prevent further immunisation reactions.

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- 1 Hallam LA, Mackinlay GA, Wright AMA. Angiolymphoid hyperplasia with eosinophilia: possible aetiological role for immunisation. *J Clin Pathol* 1989;42:944-9.
- 2 Fawcett HA, Smith NP. Injection-site granuloma due to aluminium. *Arch Dermatol* 1984;120:1318-22.
- 3 Tosti A, Vincenzi C, Peluso AM. Accidental diagnosis of aluminium sensitivity with Finn Chambers. *Contact Dermatitis* 1990;48:48-9.
- 4 Clemmensen O, Knudsen HE. Contact sensitivity to aluminium in a patient hypersensitized with aluminium precipitated grass pollen. *Contact Dermatitis* 1980;6:305-8.

Dr Hallam comments:

The histological changes described by Fawcett and Smith certainly seem to bear a striking resemblance to the appearances we described. We did not see clinically remarkable necrosis or vacuoles surrounded by multinucleated giant cells, however. It is also interesting that Fawcett and Smith note the resemblance between their cases and the lesions of angiolymphoid hyperplasia and related disorders, known as the "inflammatory angiomatoses" reported by Wilson.¹

We did not stain for aluminium or test for aluminium hypersensitivity in our cases, but agree this would be a worthwhile exercise.

- 1 Wilson Jones E. Malignant vascular tumours. *Clin Exp Dermatol* 1976;1:287-310.

Locally organised medical audit in histopathology

We read the paper by Ramsay on local pathology audit with interest as this department has been engaged in the internal audit of necropsies and surgical pathology for over 18 months.¹ The necropsy audit has been invaluable in achieving greater uniformity in the standard and timeliness of our reports as well as providing data on clinicopathological discrepancies with which to stimulate clinicians' interest in the necropsy.

Our surgical pathology audit covers similar ground to that of Ramsay and makes use of the dedicated McDonnell-Douglas system described by others for timing the laboratory procedures.² Monthly discussions involving all the pathologists and representatives of the MLSO and clerical staff have been beneficial in harmonising our approach to diagnostic problems and appreciating others' difficulties. These meetings also serve as a focus to address current problems as well as those shown up by the retrospective audit. We rapidly abandoned anonymity in the review process, partly because cases were easily traceable through the computer, and also because it inhibited the discussion when the original pathologist was not able to justify his or her approach to a case.

Two problems have concerned us: firstly, maintaining enthusiasm for the audit process once it became "routine"; and secondly, we felt that we could not audit our overall performance without considering whether we provided the information that clinicians

required. Both problems have been resolved by inviting a surgeon or physician with a particular interest to a pathology audit meeting at which we discuss a group of cases selected on the basis of SNOMED codes to provide a range of specimen types and diagnoses. By a judicious choice of clinicians, these meetings have been of greatest value in modifying our practice to ensure that our reports are clinically useful. They also help clinicians to appreciate some of the problems of providing a service and give them a greater understanding of some of the subtleties of the wording of pathology reports.

Although a random audit of cases is still necessary to maintain the internal standards of a department, we would commend the use of periodic specialty based meetings, involving the interested clinicians, as a means of entering the "audit loop" for the clinically relevant performance of a department.

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- 1 Ramsay AD. Locally organised medical audit histopathology. *J Clin Pathol* 1991;44:353-7.
- 2 Zuk JA, Kenyon WE, Mysckow MW. Audit in histopathology: description of an internal quality assessment scheme with analysis of preliminary results. *J Clin Pathol* 1991;44:10-16.

Dr Ramsay comments:

I thank Helliwell and Smith for their comments. Since first presenting the Southampton audit scheme at the Pathological Society meeting in Aberdeen in 1989,¹ it has been used as a basis for local audit in histopathology departments throughout Britain and on the continent, frequently with modifications to accommodate local circumstances. From their letter it seems clear that the University Department of Pathology at Liverpool has established a useful audit system that includes an assessment of their necropsy performance.

Like the authors, at Southampton we abandoned anonymity early in our program. Although the department was not computerised

at the time (late 1988), cases could still be readily traced, and individuals were often recognisable by their reporting style. We are also aware of the two problem areas detailed in the letter. The maintenance of enthusiasm for any regular task is always difficult. At Southampton we encountered this problem after 18 months of audit, and went through a period in 1990 when the system was in "abeyance", although we now manage to run it on a regular basis.

The clinical importance of the information provided by pathologists is an area where audit is difficult, but can be of vital importance. I am pleased that the clinicians in Liverpool are sufficiently "broad-minded" to attend pathology audit meetings, and feel that this cooperation should be encouraged. At Southampton we adopted a rather more formal approach to this problem and are in the process of writing up a study based around the clinicopathological meeting, an established forum for interaction between clinician and pathologist. Over a three month period 56 meetings covering eight specialties were attended, and all diagnostic amendments noted, together with information from the clinicians as to how these would affect patient management. The reasons for diagnostic change were also determined, and all clinicians were questioned about the role and value of specialist clinicopathological meetings. The study reviewed 416 cases, and found that 81% of the diagnoses were unchanged, 10% were refined, and 9% were changed. In only 4% of the cases, however, did the diagnostic change result in a significant (as defined by the clinician) change in patient management.

I therefore agree that a random audit is not the only means of assessing performance and that an input from the clinicians is valuable, particularly with regard to selected specialist cases.

- 1 Ramsay AD, Gallagher PJ. Quality control of surgical pathology by peer review—the Southampton Experience. *J Pathol* 1989; 158:343A.

Declining necropsy rate

We read with interest the recent paper by Benbow on medical students' views on necropsies.¹ In common with many other hospitals around the world our own district general hospital has suffered a steady decline in the hospital necropsy rate,^{2,3} in our case from over 50% in 1960 to 10% in 1990 (excluding coroners' necropsies). In an attempt to address this we sent a questionnaire to 120 of our clinical colleagues to canvass their opinions on the current situation and the reasons behind it.

Replies were received from 37 consultant

and 43 junior clinical staff. It was interesting to compare the replies of consultant and junior respondents. When asked if the falling necropsy rate worried them, 79% of consultant but only 37% of junior clinical staff stated that they were concerned by it (table). Furthermore, most consultants (51%) felt that for patients dying in hospital a necropsy was desirable in most cases; most junior staff (64%) considered necropsy desirable in only a few cases.

When asked about reasons for the declining necropsy rate, decreased emphasis on necropsy in medical education was considered an important factor by the highest

Replies of consultant and junior clinical staff to necropsy questionnaire

	Consultant (%)	Junior (%)
Are you worried by the declining hospital necropsy rate?		
Yes	79	33
No	16	52
Don't know	5	15
For patients dying in hospital necropsy is desirable in:		
All cases	19	7
Most cases	51	29
A few cases	30	64
No cases	0	0