Prognostic value of measurement of elastosis in breast carcinoma

AJ ROBERTSON, RA BROWN,* IA CREE, JB MACGILLIVRAY, W SLIDERS, J SWANSON BECK

From the Departments of Pathology and *Mathematics, University of Dundee

SUMMARY The extent of elastosis in the stroma within the anatomical “tumour” in 80 patients with breast carcinoma was assessed by observational microscopy using a 4-point grading system, and measured by semiautomated histometry as an area percentage with a Quantimet 720 image-analysing computer. In this retrospective study, measurement of elastosis in tissue removed at time of initial diagnosis was shown to have little value for prediction of duration of survival.

The presence of elastosis or elastic tissue in the stroma of sections from breast carcinoma was first described by Cheatle and Cutler. Shivas and Douglas used this early observation to develop an “elastica index” which they claimed had prognostic value in a group of patients treated by local mastectomy and radiotherapy since the patients with moderate or large amounts of elastosis had a significantly greater duration of survival. Wallgren et al. in an analysis of breast carcinoma prognostic factors also found that moderate or massive elastosis was related to a good 5-year survival rate but, interestingly, this trend was not confirmed when the 10-year survival rate was considered. Mitchell et al. showed that those patients with more marked elastosis tended to have a better prognosis, but this difference was not statistically significant.

Several methods for visual grading of elastosis have been proposed but all are at best semi-quantitative and, being subjective, they are dependent on the experience of the observer. Such measurements can be made more rapidly and precisely by use of a Quantimet 720 image-analysing computer, since elastin fibres can be stained sharply to contrast well with the background stroma. In this paper we report our assessment of the accuracy of visual grading of elastosis and the prognostic value of measurement of elastosis by a Quantimet 720.

Material and methods

Patients
The study was based on 100 women indexed consecutively in the records of the Department of Pathology, University of Dundee, between 1967 and 1969 as having presented for the first time with breast carcinoma: 20 patients had to be excluded, either because they had been lost to follow-up (4), or because insufficient material was available for the present study (16). Observations were made on the surgical specimens from the remaining 80 patients, who were aged between 33 and 86 yr (mean 58.6 yr) at the time of operation. Surgical treatment consisted of local mastectomy and radiotherapy in 57 cases; the remainder were treated by mastectomy alone. Follow-up for the purposes of this study was stopped in December 1979, at which time 40 patients had died from breast carcinoma, 17 had died from other causes and 23 were still alive. The post-operative survival time was recorded for each patient.

Light microscopy
The original paraffin-embedded blocks of tissue were recut at a micrometer setting of 7 μm: A surfometre (Planer Products Ltd, Sunbury-on-Thames; Type SF 100) was used to measure accurately the section thickness of random slides. Consecutive sections were stained with Mayer’s haemalum and eosin for general observational microscopy and with the modified Weigert-Sheridan technique for visual and automated assessment of the degree of elastosis. All the sections used in the study were stained in a single session with the same batch of dye to minimise differences in staining quality. The sections were assessed by two observers, one of whom (JB MacG) had more experience than the other (AJR): neither histopathologist had knowledge of the clinical or pathological details when they examined the sections and they assessed the amount of elastosis according...
to the illustrations in the paper by Shivas and Douglas: on this 4-point scale, 0 indicated that elastosis was absent and grades 1-3 an increasing amount of elastosis.

**Automated Histometry**

The Quantimet 720 image-analysing computer has previously been described in detail. The Weigert-Sheridan stain for elastin was selected since it gives good contrast in optical density between the very intense staining of the elastin fibres and very weak staining of the remainder of the stroma: this allows precise measurement of the area of elastin fibres in the section.

To allow assessment of the degree of elastosis, the Quantimet 1-D detector and standard computer modules were set to measure the area in each microscope field occupied by elastosis and non-elastotic tissue. A final magnification of × 160 was used throughout the study. The automatic stage X-Y control was used to scan the section in as many non-overlapping consecutive fields as possible, with visual control to ensure that no area with a major cutting or processing artefact was included in the final assessment: at least 12 fields and usually more than 20 fields were examined in each case. The Quantimet 720 was interfaced with a Hewlett-Packard 9810A desk-top calculator which had been programmed to calculate the mean percentage of elastosis, the standard deviation and the coefficient of variation for each section.

**Results**

The Table shows a comparison of the visual gradings of "elastica index" obtained from the two histopathologists. As is the case for any such subjective assessment, some disagreement was found between the observers, but in only two cases did this amount to a difference of more than one grade and there was complete agreement in 55 of the 80 cases. The relation between the visual grading and the Quantimet measurements of elastosis is shown in Fig. 1: in both cases there is a clear relation between the visual grading and the Quantimet assessment.

### Correlation between visual gradings of "elastica index" by two observers in 80 cases of breast carcinoma

<table>
<thead>
<tr>
<th>Grade</th>
<th>Observer 1</th>
<th>Observer 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10 4 0 0</td>
<td>14</td>
</tr>
<tr>
<td>1</td>
<td>2 19 5 0</td>
<td>26</td>
</tr>
<tr>
<td>2</td>
<td>1 6 14 3</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>0 1 3 12</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>13 30 22 15</td>
<td>80</td>
</tr>
</tbody>
</table>

Grade 0 = elastosis absent.
Grade 1 < 2 < 3 = increasing amounts of elastosis.

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Fig. 1  Comparison between visual estimates of elastosis grade on a 4-point scale and Quantimet 720 measurement of percentage of field occupied by Weigert-Sheridan stained elastin fibres: a more experienced observer and b less experienced observer.
In general those neoplasms graded visually as 0 had less than 1% elastosis, grades 1 or 2 had between 1 and 10% and grade 3 had usually in excess of 10%, but there was a considerable spread of Quantimet values among the neoplasms in each visual grade and some overlap between the grades. It is interesting to note that the less experienced observer produced visual gradings in which there was a greater spread of Quantimet values and consequently a greater overlap between grades. Fig. 2 is a scatter diagram showing the relation of mean percentage of elastosis determined on the Quantimet to the postoperative survival of the total group of 80 patients; note that a considerable number of patients with a high Quantimet value had a short survival time, while a low Quantimet value did not preclude a long survival. In an attempt to confirm the original finding that assessment of the degree of elastosis alone is a good prognostic indicator, two methods of data analysis were adopted.

(a) Experimental survival curves were calculated for the subgroup of 36 patients who had died from metastatic carcinoma and had been treated by both mastectomy and radiotherapy since this subgroup was directly comparable to that studied by Shivas and Douglas. The curves, derived from the assessments by the more experienced observer, are shown in Fig. 3: the data obtained from the less experienced observer was essentially similar. The difference between the survival curve of those patients graded 3 and the curve for those graded 0 just attained significance at the 5% level using a one-sided two-sample Kolmogorov-Smirnov test. Although there was some suggestion of a slight shift towards greater survival periods for those neoplasms graded 1 or 2, the differences between them and the grade 0 curve were not significant.

(b) The second method of analysis attempted to exploit the Quantimet data by assuming that the survival curve for patients with any chosen percentage of elastosis was exponential and of the type suggested by other workers in survival analysis. We have used this standard approach because the exponential survival curves of those patients who died are compatible with the exponential distribution. With this assumption, namely the percentage (P) of patients with x% elastosis who survive for at least t months

$$P = 100 e^{-t/(\alpha + \beta x)}$$

the expected survival time is (\(\alpha + \beta x\)) months. This method of fitting a curve to the survival data was applied to patients who had received both mastectomy and radiotherapy, and the estimates of the survival parameters (\(\alpha\) and \(\beta\)) were determined by standard maximum likelihood methods. For the group of 36 patients who had died from metastatic disease the estimate of \(\alpha\) was 39.3 months (SE 9.5) and \(\beta\) was 1.98 months/percentage elastosis (SE 1.92); for the larger group of 57 patients which included those patients who had died from metastatic cancer or any other cause or were still alive, \(\alpha\) was 89.3 months (SE 20.0) and \(\beta\) was 3.16 months/percentage elastosis (SE 3.88). Figs. 4a and b show the 5% and 10% contours of the likelihood surfaces for the smaller and larger of the subgroups, respectively: sets of survival curves are shown in Figs. 5a and b. The very large differences between the values of \(\alpha\) in the two groups is a reflection of the obvious fact that survival experience in the smaller group will, of necessity, be much shorter since death is a necessary qualification for inclusion in the group.
Prognostic value of measurement of elastosis in breast carcinoma

Fig. 4 Contours of the likelihood surfaces (10%, solid and 5%, hatched) of the estimates of the survival parameters, $\alpha$ and $\beta$, for patients who had radiotherapy after mastectomy, with the maximum likelihood value indicated by an X. 

a Subgroup of patients dying from metastatic carcinoma and b the whole group of patients.

Fig. 5 Computer-fitted curves showing the influence of extent of elastosis on the survival (on a logarithmic scale) for patients who had radiotherapy after mastectomy with 0% elastosis (lowest curve) and 20% elastosis (upper curve): the 5%, 10%, and 15% elastosis curves occupy intermediate positions. a Patients who died of metastatic breast carcinoma and b all patients, whether living or dead at the end of the period of study.
Two important points are to be recognised:

(a) $\beta$, the parameter associated with percentage elastosis, has in both subgroups a standard error of the same size as the parameter estimate and

(b) the likelihood contours include regions where $\beta = 0$.

Thus the data do not confirm the prognostic value of elastosis estimation, and furthermore, it would appear that knowledge of this factor alone does not substantially improve the histopathologist’s ability to predict the survival period of specific groups of patients.

Discussion

A grading system, if it is to be of value to the histopathologist, must be both rapid and easy to perform and have a good degree of reproducibility. Our study, however, has demonstrated that the assessment of “elastica index,” in common with most other such systems based on observational microscopy, has a not inconsiderable level of observer error, although admittedly this becomes less with increasing experience. We have been unable to attain the 80-100% reproducibility described by Masters et al. Many of the inherent disadvantages of visual grading can be overcome by use of our new semiautomated method of image analysis on the Quantimet 720 and this system provides a simple and precise estimation of the percentage area of a breast cancer tissue section occupied by elastosis.

When the survival curve data derived from the Quantimet were examined it was found that there was a marginally better survival in patients with massive elastosis when compared with those who had none, but that the difference was so small as to be of little consequence to the overall duration of survival. Similar results were obtained by visual grading: a difference, just significant at the 5% level, was found between patients with grade 3 when compared with grade 0 but no significant difference was found in comparisons amongst the other grades. Although this discrepancy between our study and that of Shivas and Douglas could possibly be explained partly by the relatively small number of patients in our series that were directly comparable to those in the original study, it is clear that elastosis has a much smaller effect on survival than was previously thought. Moreover, our findings are in agreement with those of Mitchell et al. who found that minor differences in elastosis had no significance, but that there was a trend towards a better prognosis in those patients with marked elastosis; they concluded that elastosis did not have a great influence on survival time. Wallgren et al. in a sophisticated multivariate analysis of various prognostic factors in breast carcinoma, also reported that extent of elastosis had no effect on the 10-year survival figures, although interestingly, in their study, moderate or massive elastosis did seem to have an effect on 5-year survival levels.

It is possible that some of the variation in published reports has arisen because of differences in what has been assessed. Elastosis occurs in two main forms—focally around ducts, and also in a more diffuse form within the stroma: we have measured the total elastosis content of the lesions. Anastassiades et al. assessed periductal elastosis and, rather surprisingly, claimed that it has an unfavourable influence on long-term survival so a more detailed study of the microanatomical distribution of elastosis is still required.

Another factor which may explain the discrepancy in results, is the nature of the groups of women who have been studied. In Shivas and Douglas’s original study all the patients had died from metastatic disease and inevitably this had resulted in preselection of the cases since the remainder with include some patients who have survived and others who have died of unrelated causes. Any analysis of the value of a prognostic factor must take account of the other subgroups since the ultimate fate of the individual patient cannot be known at the time of initial diagnosis. The absolute requirement of prediction of those patients that are going to die of metastases precludes the “elastica index” along with having any practical clinical use in prognosis of the individual patient. It may still, however, prove to be of value when incorporated into more extensive multivariate analysis.

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Requests for reprints to: Professor J Swanson Beck, Department of Pathology, University of Dundee, Ninewells Hospital and Medical School, Dundee DD1 4HN, Scotland.