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Report

Size of breast carcinomas at operation related to tumour growth rate

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Abstract

The mean nuclear area (MNA) of breast carcinoma cells, previously shown to be related to prognosis, is here presented as a potential overall measure of tumour growth rate prior to operation. Recording of tumour diameter and MNA in 340 infiltrating breast carcinomas demonstrated that tumours of low MNA tended to present at a lower diameter that those of high MNA. The former have thus remained 'small' over a longer period, giving the woman more time to report them at this stage. It is suggested that mass screening from breast carcinoma may pick up these slow growing tumours, missing those of high growth rate unless the screening interval is correspondingly short.

Introduction

The size of a breast carcinoma at operation is an important clinical milestone in its life history. It provides a measure of stage, i.e. how far the tumour has come, but gives no indication of the time it has taken to get there.

The terms 'anaplastic' and 'dedifferentiated' are commonly used to describe tumours that show features we have learned to associate with rapid growth. Both are vague and ill-defined. Both include subjective evaluation of nuclear size. The latter is also an important feature in histological grading [1], a measure that gives at best a group prognosis that may be wildly inaccurate in the individual case. The advent of computerised morphometric apparatus has led to more objective methods. These have demonstrated that the mean nuclear area (MNA) is also of prognostic significance, and that it, in this respect, parallels the findings on histological grading [2]. It thus seems to provide a measure of growth rate, one that ignores the biological ups and downs of tumour kinetics, but in the long run gives a rough overall estimate based on survival studies.

The use of multiple variants in the assessment of prognosis in breast cancer has become commonplace in recent years [3, 4]. Choice of variants is important, and it has been shown that tumour diameter and the tumour growth rate are key factors in this respect [5]. The present work describes the distribution of MNA relative to tumour diameter at operation in 340 infiltrating breast carcinomas, 238 of which were node-negative.

Material and methods

The 340 infiltrating breast carcinomas studied were consecutive cases treated by modified radical mastectomy with axillary node dissection over the 5 yrs 1970–72 and 1977–78. No preoperative treatment had been given. Nodal metastases were present in 102 cases. The greatest diameter of the primary tumours had been measured by the pathologist. Slides stained with haematoxylin and eosin from formalin-fixed parrafin-embedded material were available in all cases.

The MNA of the tumour cells (100 nuclei) in the node-positive cases had been measured previously

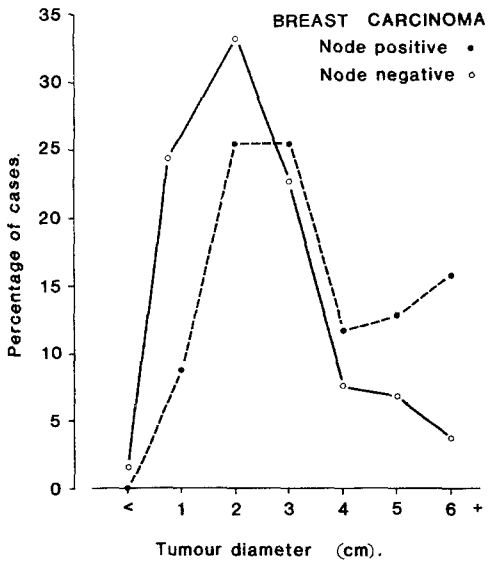

Fig. 1. The percentage distribution of 340 cases of breast carcinoma relative to tumour diameter and nodal state.

using photomicrographs projected onto a digitizer attached to a computer [2]. In the node-negative cases the tumour cells were viewed directly in a Leitz microscope instead of from photomicrographs. A trial run using 100 nuclei per case in 22 node-positive cases showed no significant difference between these two methods. Further, the number of nuclei measured was reduced to 20, in keeping with that used in other studies [6], as here again no significant difference was found on comparison with the results of using 100 nuclei per case.

Statictical evaluation was based on the Chi-square test.

Results

The percentage distribution of tumour diameter in node-negative and node-positive cases is compared in Fig. 1. Over half of the node-negative cases had tumours of under 3 cm in diameter compared to 1/3 of the node-positive. The actual difference is statistically significant, 141 cases under 3 cm in the node-negative and 35 in the node-positive, compared to 97 and 67 for tumours of 3 cm and over ($\chi^2 = 18$, $p<0.0005$).

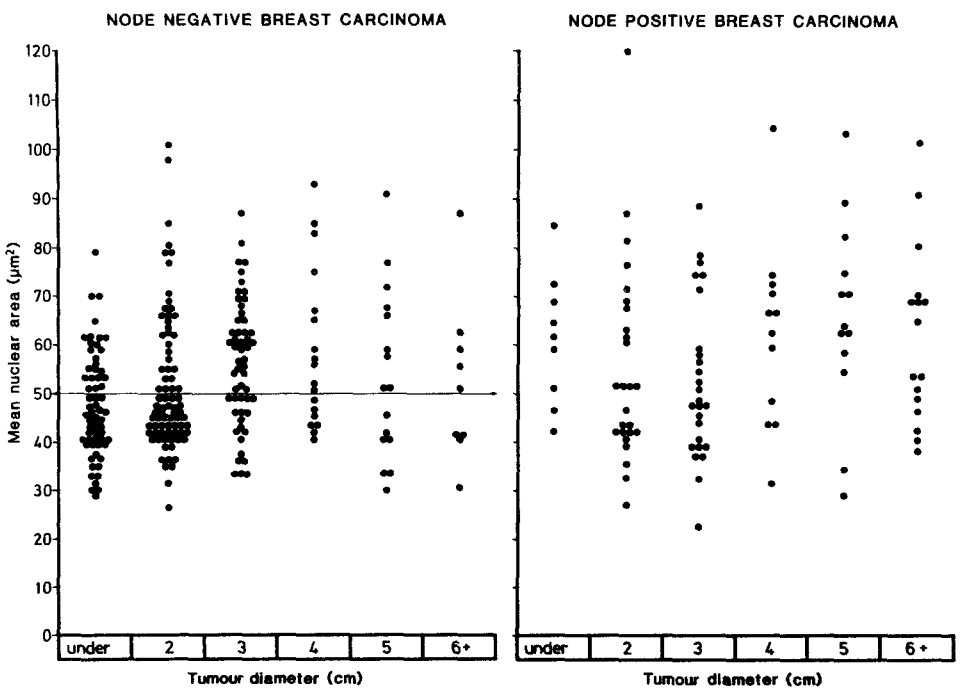

Fig. 2. Scatter diagram showing the mean nuclear area (MNA) of 340 breast carcinomas related to tumour diameter and nodal state. The line at 50 μm^2 in the node-negative divides those of high from those of low MNA, see text.

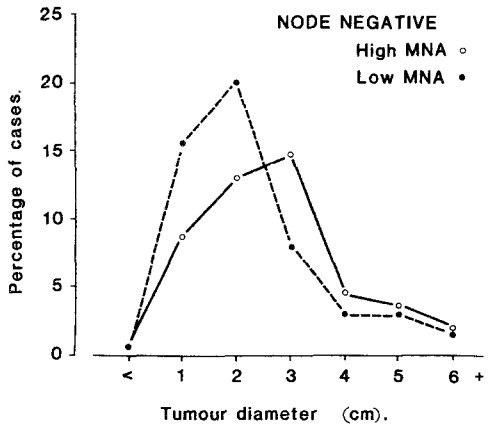

Fig. 3. The percentage distribution of tumour diameter in node-negative breast carcinoma (238 cases) of high and low mean nuclear area (MNA).

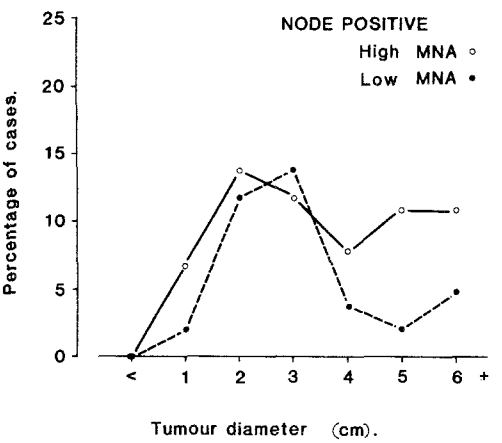

Fig. 4. The percentage distribution of tumour diameter in node-positive breast carcinoma (102 cases) of high and low mean nuclear area (MNA).

The range in diameter of node-negative and node-positive tumours was great (Fig. 2). The node-positive were from 1 cm upwards in diameter. Each size class covered a wide spectrum of MNA.

Inspection of Fig.2 shows that in node-negative cases a line drawn at the MNA 50 μm^2 level divides the series approximately equally: 114 cases above this line, 124 below. The two major groups (2 and 3 cm in diameter) were divided at 66:67. Values of 50 μm^2 and over were thus termed high MNA, those under low MNA. Just over half (125) of the node-negative tumours were of low MNA, compared to approximately one third (29) of the node-positive ($\chi^2 = 5$, $p<0.02$).

In node-negative cases (Fig. 3) a low MNA was more common than high for tumours under 3 cm, while the reverse was the case in those of 3 cm or more. This difference is statistically significant ($\chi^2 = 13$, $p<0.0005$), as is that between tumours of 2 versus 3 cm in diameter ($\chi^2 = 8$, $p<0.005$). The corresponding pattern for node-positive tumours (Fig. 4) shows that the distribution of high and low MNA was similar for tumours under 4 cm in diameter, but there were more with high MNA in those of 4 cm or more in diameter. Division of the series between 3 and 4 cm shows that this difference is statistically significant ($\chi^2 = 3.8$, $p<0.05$).

Discussion

In the clinical situation different patients present with tumours of different size. A great many factors may be involved. Among these are the patient's awareness of her own body and the physical state of her breasts, which will determine the time it takes her to find a lump in her breast. Next she must acknowledge to herself that there really is a lump there, get an appointment, and have it removed. All these factors will contribute to the time that passes before operation. The majority are difficult to measure and their importance will vary from patient to patient. The time available for the patient to pass through all the above phases, from awareness to removal, is however determined by the tumour growth rate. As demonstrated in this present work this influences the tumour diameter at operation.

The key here is that a tumour with a slow growth rate will remain 'small' over a longer period than one that is fast growing. There will thus be more time available for the patient to discover it while it is still small. In keeping with this, over 70% of the node-negative cases with low MNA presented with tumours under 3 cm in diameter, and few reached 4 cm or more. The shift to a greater diameter (3 cm) in the node-positive with low MNA could be due to the individual variable factors mentioned above. It

is here of note that women in this district have a threshold diameter for palpation of benign breast tumours of about 2 cm [7].

In tumours with a high MNA, the peak value in the node-negative was at 3 cm. These tumours thus reached a greater diameter in the time available than those with a lower growth rate. The node-positive with high MNA showed little difference in distribution from the node-negative for those under 4 cm, but over this the majority were node-positive.

Recording of the tumour diameter at operation and measurement of the MNA of the tumour cells can thus be used to give an estimate of the time a tumour has taken to reach a given stage. Such a measure has not been readily available from routine specimens previously. Paradoxically a small tumour may well be older, i.e. have been present longer, than a larger one. The concept of early diagnosis [8] should be modified to include this reality (see also [9]). It is not unlikely that repeated screening will primarily bring to light small tumours of slow growth rate, while small tumours of rapid growth rate may well be missed unless the screening interval is short. This may tend to bring such schemes into disrepute, unless there is general awareness of this possibility.

Acknowledgement

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