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NON-PALPABLE INVASIVE BREAST CARCINOMAS FROM THE STOCKHOLM SCREENING PROJECT

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Abstract

Sixty-six non-palpable, invasive mammary adenocarcinomas from the Stockholm mammography screening project were studied with respect to histopathology. In 53 of these tumors estrogen receptor (ER) content was estimated and in 30 of them also the DNA distribution pattern. The tumors were predominantly of low or intermediate histological malignancy grade and ER-rich, whereas the distribution of DNA ploidy equalled that found in a non-selected tumor material. Only 2 tumors recurred during follow-up (median 51 months), indicating that non-palpable breast carcinomas represent a prognostically favourable subset in spite of a relatively high proportion of aneuploid tumors.

Key words: Breast cancer; screening detected, non-palpable, histology, ER content, DNA pattern.

One of the early arguments against screening projects was that mammography would primarily detect indolent, slowly growing carcinomas whose early detection would seemingly prolong patient survival time (lead time effect) without influencing breast cancer mortality. This concept has since been challenged by results from screening centers showing a reduction in breast cancer mortality in the screened population (1–3) and a lower incidence of more advanced breast cancer in the study groups compared with the controls (2, 4). The detection of small, clinically occult carcinomas as a result of screening (5–7) has lead to discussions regarding the optimal treatment of this subgroup and an increasing interest in characterizing these tumors.

Histological grade, ER content and DNA distribution pattern are important parameters when identifying high-risk patients within a given clinical stage (8–12). Controversy exists regarding the value of ER and DNA as independant predictors of prognosis, but there is evidence that both are indicators of growth rate (13–18). The present study was carried out to assess the malignant potential of a series of screening-detected, non-palpable mammary carcinomas through analysis of these tumor characteristics.

Material and Methods

The study comprised 66 consecutive patients with mammographically detected, clinically occult invasive breast cancer who were operated between 1981 and 1985. The patients participated in the Stockholm screening project started in 1981, where women aged 40 to 64 were selected at random for single view mammography. The project and the first round results have been described in detail by Frisell et al. (6). Thirty-five non-palpable invasive carcinomas were detected during the first screening round and 31 during the second. Type of operation and the various procedures utilized for diagnosis are shown in Table 1. Thirty-four (52%) patients were operated with partial mastectomy and axillary dissection. These patients received local postoperative irradiation with 50 Gy. In one patient with pulmonary metastates at the time of diagnosis, the primary tumor was removed by local excision and chemotherapy was given. Patients with pathological stage II tumors (pTpNM) (19) were offered adjuvant therapy according to the guidelines published by the Stockholm Breast Cancer Group (20). The median follow-up time was 51 months (range 25–76).

Tumor sampling. The tumor was defined as non-palpable if physical examination by at least 2 experienced

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Table 1

Diagnostic procedure

Type of operation	No.	Fine-needle biopsy	Frozen section analysis	Examination of paraffin embedded sections	Specimen mammography
Modified radical mastectomy	30	10	17	3	21
Simple mastectomy	1	–	1	–	1
Partial mastectomy and axillary dissection	34	7	17	10	34
Local excision	1	1	–	–	–
Total	66	18	35	13	56

clinicians (one oncologist and one surgeon) did not reveal a palpable lump. A fine-needle biopsy was performed by means of a stereotaxic device (21). If the aspirated material was not conclusive, the tumor was excised under general anesthesia after preoperative indication carried out in collaboration with the responsible roentgenologist and with guidance of the mammogram. The position of the lesion was indicated on the breast with waterproof ink according to its position on the cranio-caudal and latero--medial projections on the mammogram. The surgical specimen was radiographed peroperatively to ensure that the mammographically suspicious lesion had been removed. The carcinoma was indicated with a needle to guide the pathologist. If the diagnosis of carcinoma was established cytologically, the operation was performed without further diagnostic procedures.

Histology. The original histological slides were reexamined by an experienced histopathologist (RN). The tumors were classified according to the WHO nomenclature (22). Tumor grade was determined using a modification of the Bloom & Richardson grading system (9).

Mammography. A single oblique view ad modum Lundgren & Jakobsson was used for screening (23). If malignancy was suspected, the patient was subjected to a conventional 3-view mammography as described previously (6).

Estrogen receptor assay. The ER content was analyzed in 53 tumors by measuring the specific binding capacity of labelled extradiol to cytosols of thawed tumors as described by Wrange et al. (24). The ER value was expressed as femtomoles (fmol) per μg DNA. Tumors with ER values less than 0.1 fmol/μg DNA were considered receptor-poor, and levels equal to or above this limit were considered receptor-rich.

DNA measurements. DNA analysis was performed on a fine-needle aspirate from the thawed tumor specimen. The material was stained according to the Feulgen technique (acid hydrolysis, 5 N HCL, 22°C, 60 min) (25), and DNA measurements were done on morphologically identified tumor cells using a rapid scanning and integrating microspectrophotometer (26). Generally, 100 tumor cells were measured in each slide preparation. Admixed leukocytes or lymphocytes were used as internal controls to establish the 2 c value, i.e. the modal value of normal, diploid cells. The DNA distribution patterns of the various breast carcinomas were grouped into 4 different types according to a previously reported cytochemical classification system (27) where type I corresponds to a diploid, type II to a diploid-tetraploid and types III and IV to an aneuploid DNA distribution. Neither ER nor DNA analysis was performed in 13 tumors due to insufficient tumor material or because the diagnosis was not made until the paraffin-embedded sections were examined. Furthermore, DNA measurements were not performed routinely until the end of 1982, which is one reason why information about DNA content was lacking in the majority of the tumors diagnosed at the first screening. Only 30 tumors could thus be analyzed for nuclear DNA content.

Table 2

Histopathological classification

Histologic type	
Invasive ductal carcinoma	
Grade 1	15
Grade 2	35
Grade 3	4
Tubular carcinoma	4
Mucinous carcinoma	2
Invasive lobular carcinoma	4
Invasive ductal and lobular carcinoma	2
Total	66

Results

The mean tumor diameter was 8.6 mm (range 3–21) as measured on the fresh surgical specimen. Fifty-two (78%)

Table 3

Characteristics of 30 non-palpable breast carcinomas diagnosed at the first (A) and second (B) screening round. a) Axillary lymph nodes not examined

Tumor size (mm)	Axillary lymph node metastases	Histologic type	Histologic grade	ER (fmol/μg DNA)	DNA histogram type
A					
6	0	Ductal	I	0.20	I
6	0	Ductal	II	0.23	I
6	0	Ductal	II	0.94	II
6	0	Ductal	II	0.27	III
7	+	Ductal	II	4.1	III
7	0	Ductal	II	0.18	IV
8	0	Ductal	II	0.38	I
8	0	Ductal	II	2.0	III
8	0	Ductal	II	0.03	IV
9	0	Ductal	II	0.38	II
10	0	Ductal	II	1.4	III
11	0	Ductal	II	0.39	II
12	0	Tubular	–	0.42	II
21	0	Ductal	III	0.06	III
B					
5	0	Ductal	II	0.81	II
7	+	Ductal	I	0.76	I
7	0	Lobular	–	0.48	IV
8	– a)	Lobular	–	1.5	I
8	0	Ductal	I	2.3	II
8	0	Ductal	I	0.62	III
9	0	Ductal	II	0.28	III
9	0	Ductal	II	0	IV
9	+	Ductal	II	0.01	IV
10	0	Ductal	II	0.87	II
10	0	Ductal	II	0.03	IV
12	0	Ductal	II	0.25	I
12	0	Ductal	II	0	III
14	0	Ductal	I	0.68	III
14	0	Ductal + Lobular	–	0.28	III
15	– a)	Ductal	II	1.1	III

tumors measured 10 mm or less. Of the 63 patients where information about axillary lymph node status was available, 56 (89%) were node-negative and the remaining 7 node-positive. Histopathological data are given in Table 2.

Fifty-three tumors were analyzed for ER content; 43 of these (81%) were considered ER-rich, i.e. exhibited values equal to or above 0.1 fmol/μg DNA, and 10 tumors with ER values below this limit were classified as ER-poor. The mean diameter of the 30 tumors, where DNA measurements was performed, was 9.4 mm compared to 7.9 mm of the remaining tumors. Forty-three % of the former group exhibited DNA histograms type I and II and were classified as euploid, whereas 57% contained a high proportion of cells with increased and scattered DNA values and were considered aneuploid (Table 3).

Two tumors recurred locally during follow-up. One of these recurrences occurred in a patient initially treated with partial mastectomy, the other in a patient with distant disease at presentation and where the primary tumor had been removed by local excision. Both patients were subsequently treated with mastectomy. With exception of the last mentioned patient no distant metastases were observed during follow-up of this series.

Discussion

One presupposition for the introduction of screening programs is that treatment of early breast cancer will improve patient survival. A reduced breast cancer mortality has been obtained in screened populations (1–3) by a reduction of the proportion of more advanced tumors (2, 4). Tumor stage has a well established association to the prognosis, and stage I disease, particularly if the tumor is not larger than 1 cm, is associated with very low recurrence and death rates (28). However, even very small tumors have metastatic capacity, and axillary lymph node metastases have been found in as many as 35% of non-

palpable mammary carcinomas (29). In the present study, all 6 tumors with axillary metastases measured less than 1 cm.

The findings of 81% ER-rich tumors, and 93% ductal carcinomas of low or intermediate malignancy grade, in addition to 4 tubular carcinomas, denote an overrepresentation (9, 30) of presumably slowly proliferating tumors in the present series. This, however, is not in accordance with the relatively high proportion of aneuploid tumors, equal to that found in a non-selected material of breast cancer (11). Although previous studies have shown a relationship between tumor size and ploidy, small tumors being predominantly euploid (11, 31), the present finding of 57% aneuploid tumors is not surprising. Breast neoplasias in general seem to express a rather uniform DNA distribution pattern during tumor progression (32, 33). However, DNA analysis was performed in only 45% of the series which might have influenced the results. Technical difficulties in obtaining representative and sufficient cellular material from small non-palpable tumors limited the number of carcinomas analyzed for DNA content. Routine sampling of cytologic material for DNA measurements either by stereotaxic fine-needle biopsy, as described previously (34), or fine-needle aspiration of fresh surgical specimens would increase the number of tumors eligible for cytochemical malignancy grading.

Fallenius et al. reported 90% euploid tumors among non-palpable mammographically detected mammary carcinomas (34), but the patients were self-selected, and one-third were 70 years of age or above. This could in part account for the discrepancy, since advanced age seems to be associated with a high proportion of euploid tumors (35).

The present study does not uniformly support the concept that screening mammography mainly detects carcinomas of low malignancy, while more malignant tumors are less likely to be detected at scheduled screenings (length bias). Extensive use of screening mammography increases the proportion of node-negative breast carcinomas (2, 4–7), and thus axillary sampling provides no additional prognostic information. This emphasizes the need for other prognostic markers. Even if the majority of non-palpable screening detected carcinomas have low histologic malignancy grade and are ER-rich, DNA measurements indicate the presence of a subset of highly malignant tumors. Although a general agreement on the prognostic value of nuclear DNA content in mammary carcinoma is still lacking, there is ample evidence for aneuploid tumors being associated with early relapse as demonstrated in clinical breast cancer materials (11, 27, 36–39). The subordinate role of DNA ploidy in predicting the outcome of patients with non-palpable carcinomas can probably be attributed to the favorable effect of screening mammography, which allows early diagnosis and subsequent adequate treatment of clinically occult aneuploid mammary carcinomas.

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